High-risk sexual behaviour among HIV-negative MSM in England: behavioural data to inform HIV prevention

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Statement of Authorship

I, Sarika Desai, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: _____Date:_____

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Abstract

HIV transmission is ongoing among MSM in the UK; particularly among MSM attending GUM clinics. GUM clinics are where the majority of MSM test for HIV and where effective HIV prevention interventions including condoms, behavioural interventions and HIV testing are freely available. However, the offer of these services is highly varied. This thesis set out to explore whether measures of incidence and sexual behaviours that increase the risk of HIV acquisition could facilitate risk assessments of MSM and objective risk-based triaging of interventions.

A mixed methods approach was used; after a review of the literature on HIV incidence, an analysis of HIV incidence and risk factors for infection was performed among MSM attending GUM clinics. Next, standardised sexual behavioural data were collected from MSM at five GUM clinics and these data were linked to clinical outcomes. Qualitative interviews were undertaken with service providers and users to understand their views on HIV risk assessments in clinical practice. Finally, a risk assessment tool was developed using available clinical and sexual behavioural data to stratify MSM by their HIV risk.

HIV incidence was high and clinical and behavioural risk predictors including previous bacterial STI and numbers of partners men practiced condomless receptive anal intercourse with were identified. A greater proportion of infections were attributed to sexual behaviours than clinical STI history. There were no objections to using behavioural and clinical data to risk assess MSM though MSM were divided about only being offered tiered prevention services. The risk assessment tool performed well even after internal validation. The tool does require extensive validation before it can be recommended for clinical practice.

The key findings are summarised and contextualised in the literature and current sexual health landscape. The study's limitations are addressed and the public health implications and future areas of research discussed.

Impact Statement

In this thesis, surveillance data was used to develop a methodology to calculate national HIV incidence among MSM. The method has been used to annually estimate incidence among MSM, which is particularly important given the recent decline in HIV diagnoses in this population. The method could also be beneficial to the better understanding of incidence in other populations attending GUM clinics in England. The method has been shared with the GUMCAD team to facilitate this activity and has been published in a peer-reviewed journal for further dissemination.

Research on risk stratification of MSM has directly contributed to the development of the eligibility criteria for the PrEP IMPACT trial that was launched in 2017. Further stratification analyses could be undertaken to better understand other populations attending GUM clinics that are also in need of PrEP. These analyses could be of benefit to the PrEP IMPACT trial and can be brought about by sharing the analysis methods with the trial group.

Research conducted into the sexual behaviours of HIV negative MSM has influenced the content of the sexual behavioural data that will be collected nationally from MSM attending GUM clinics. There is considerable overlap

between the questionnaire used in the thesis and the questions MSM will be asked at all GUM attendances.

The work in this thesis could benefit clinical practice in GUM. It provides a new approach to triaging HIV prevention services based on HIV risk. The evidence from the qualitative interviews with service providers and users could be used to advocate for the tool as it was largely found to be acceptable and a useful aid for decision making. The impact can be realised through further research to validate the risk assessment tool developed in the thesis. A future research project could be developed in collaboration with clinics and academic partners to achieve validation in another GUM attending sample of MSM.

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List of Abbreviations

AI	Anal intercourse
ART	Antiretroviral therapy
AUC	Area under the curve
CAI	Condomless anal intercourse
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIAI	Condomless insertive anal intercourse
CRAI	Condomless receptive anal intercourse
EMIS	European MSM Internet Survey
EPV	Event per variable
GMSHS	Gay Men's Sexual Health Survey
GUM	Genitourinary Medicine
GUMCAD	Genitourinary medicine clinic activity dataset
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
HR	Hazard ratio
IAI	Insertive anal intercourse
LA	Local authorities
IQR	Interquartile range
LGV	Lymphogranuloma venereum
MAR	Missing at random
MCAR	Missing completely at random
Min	Motivational interviewing
MI	Multiple imputation
MICE	Multiple Imputation by Chained Equations
MNAR	Missing not at random
MSM	Men who have sex with men
NATSAL	National Survey of Sexual Attitudes and Lifestyles
NGO	Non-governmental organisation
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NPV	Negative predictive value
OR	Odds ratio
PAR	Population attributable risk
PEP	Post-exposure prophylaxis
PHE	Public Health England
PPV	Positive predictive value
PrEP	Pre-exposure prophylaxis
PY	Person years
RAI	Receptive anal intercourse
RCT	Randomised control trial
RDS	Respondent driven sampling
RITA	Recent Infection Testing Algorithm
ROC	Receiver operating characteristic

RR	Risk ratio
SD	Standard deviation
SEM	Social Ecological Model
STI	Sexually transmitted infection
TasP	Treatment as Prevention
TLS	Time location sampling
UCL	University College London
UK	United Kingdom
US	United States
VCT	Voluntary counselling and testing
WHO	World Health Organisation

1 Introduction

1.1 Background and Rationale

Since the first reports of the human immunodeficiency virus (HIV) in the early 1980s, the HIV/AIDS epidemic has emerged as a global challenge and has gone from the 33rd most important cause of disease burden in 1990 to the fifth in 2010 (1). UNAIDS estimated 34 million people (31.4-35.9 million) were living with HIV at the end of 2011(2), which approximates to almost one per cent of adults aged 15-49 years living with HIV worldwide. Another 2.5 million (2.2-2.8) people were newly infected with HIV and 1.7 million died from AIDS-related causes.

In the United Kingdom (UK), men who have sex with men (MSM) make up one of the largest groups living with HIV. In 2011, when the research in this thesis started, HIV prevalence was stable among MSM (3), though the number of new HIV diagnoses had continued to increase year on year so that in 2011, 48% of diagnoses were among MSM (4) despite MSM only representing 3.4% of the UK male population. These data therefore highlighted MSM to be disproportionately affected by HIV. More recently, declines in new diagnoses have been observed among MSM (see section 2.2).

It is unlikely the increase can fully be attributed to increases in HIV testing as HIV incidence estimates available to 2011 did not suggest a downward trend in the prior decade (5-7). The majority of MSM in England test and are diagnosed with HIV in genitourinary medicine (GUM) clinics. Over the same time period, the diagnoses of other sexually transmitted infections (STI) rose among MSM attending GUM clinics (8) and further evidence of ongoing risk in this population

was demonstrated by behavioural surveys where MSM attending GUM clinics reported more risk behaviours than those that did not attend clinics (9).

Given these conditions, the greatest impact on HIV transmission in the UK could be best achieved by focussing on MSM attending GUM clinics. In 2011, a number of interventions that aimed to reduce HIV risk were available for MSM including condoms, behavioural interventions and HIV testing. Though not yet available in the UK, there was emerging evidence that pre-exposure prophylaxis (PrEP) was effective at reducing the risk of HIV acquisition (10) and could potentially be another intervention tool for MSM. However, without any guidance on how these interventions should be triaged and offered to MSM, actual clinical practice in England was highly varied and dependent on where MSM attend (11). For example, there was no clear pathway for offering behavioural interventions to men and though the majority of clinics risk-assessed MSM for HIV to some extent, the behavioural questions used were clinic-specific and not nationally comparable. Stratifying MSM into groups according to HIV risk and triaging HIV prevention interventions based on risk could be one way to uniformly offer services but this would require information on incidence and behaviours that increase the risk of HIV acquisition and transmission, which was relatively limited in this clinical setting in England.

This thesis examines the potential to standardise and collect behavioural information recorded during routine consultations in GUM clinics and to use the data to inform the development of a HIV risk triaging tool that could aid decision making for HIV prevention. It aims to do this by collecting sexual behaviour data and identifying behavioural and clinical risk factors for HIV acquisition.

1.2 Research question

Can standardised and evidence-based sexual behavioural data enhance HIV prevention for MSM attending GUM clinics?

1.3 Aims and Objectives

The aims of this thesis are to investigate the feasibility and clinical utility of standardised sexual behavioural data collection from HIV negative MSM attending GUM clinics in England as a means to enhance HIV prevention for this population. The broad objectives of this research are:

1. To systematically review, appraise and summarise the literature on methods to measure HIV incidence and estimates of HIV incidence and risk factors for HIV infection among MSM
2. To calculate HIV incidence among MSM attending GUM clinics and identify risk factors for HIV acquisition
3. To collect sexual behavioural data from HIV negative MSM attending GUM clinics
4. To estimate prevalence of sexual behaviours and to identify behavioural risk factors for HIV acquisition
5. To derive, performance test and validate a clinical risk assessment tool to stratify MSM by HIV risk
6. To describe the value of collecting standardised behavioural data and specifically the use of a clinical risk assessment tool from the service provider perspective
7. To describe self-perception of HIV risk and the acceptability of being risk assessed among HIV negative MSM

1.4 Thesis Outline

This thesis is based on mixed methods including an empirical study carried out in five GUM clinics in London, Brighton and Manchester, a secondary data analysis of HIV incidence among MSM, qualitative interviews and risk prediction development. The timeline of the work alongside the PhD timeline, including interruptions, is shown in Figure 1.1 and the objectives and outputs are summarised in Figure 1.2.

Chapter two contains a general literature review on HIV epidemiology, behavioural research and HIV prevention measures available for MSM. Chapter **three** details the methodologies used to answer each of the research objectives. There are four sections in the method and each corresponds to one of the four results chapters. Chapter **four** is a systematic review of the current literature on global HIV incidence and risk factors for HIV acquisition among MSM. Chapter **five** is the first of the results chapters and follows on from the systematic literature review by calculating HIV incidence among MSM attending GUM clinics in England using routine national surveillance data. Results are presented for incidence in 2012. The chapter ends with clinical and demographic predictors of HIV acquisition. Chapter **six** describes the results of a behavioural study conducted in five GUM clinics. The results include a description of sexual behaviours among MSM attending GUM clinics, seroadaptive behaviours, HIV incidence and risk predictors for HIV infection including any behaviours associated with HIV infection. Chapter **seven** documents the results of two qualitative studies; the first was semi-structured interviews conducted with clinical staff to understand thoughts on the feasibility and utility of implementing standardised behavioural data collection in GUM clinics. The second examined perceptions and acceptability of using behavioural and clinical data to create risk

scores that stratify MSM by risk and that also determine the set of behavioural interventions they would be offered. Chapter **eight** is the final results chapter and describes the statistical outputs generated from the steps involved in developing a risk assessment tool that stratifies MSM by their risk. The statistical method used was that identified from a literature review of clinical risk tools available for HIV and STIs. This chapter also described how well the model performs at predicting for HIV infection. Finally, chapter **nine** brings the research together and describes the implications on current practice and policy in GUM clinics for HIV prevention for MSM.

Since starting the thesis, the evidence base on HIV prevention for, and sexual behaviours of, MSM has considerably increased. There have also been changes to clinical practice that have facilitated greater access to HIV tests (e.g. self-sampling, online triaging and express services). The use of behavioural data, though, has not appreciatively changed. In the next chapter, I discuss the literature to reflect these developments and I further discuss the implications in the discussion chapter (chapter 9).

Figure 1.1 Timeline of PhD and research activities

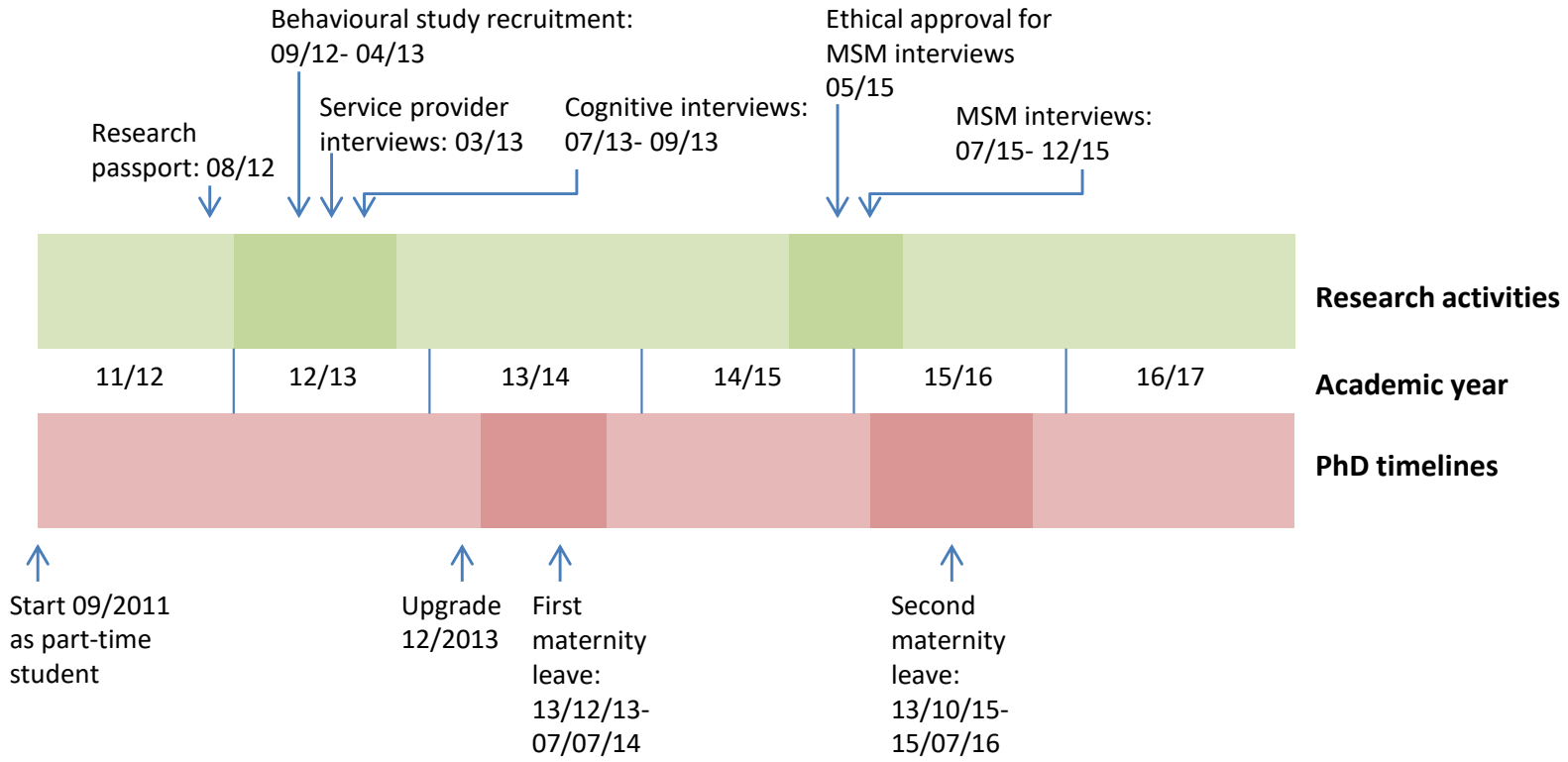
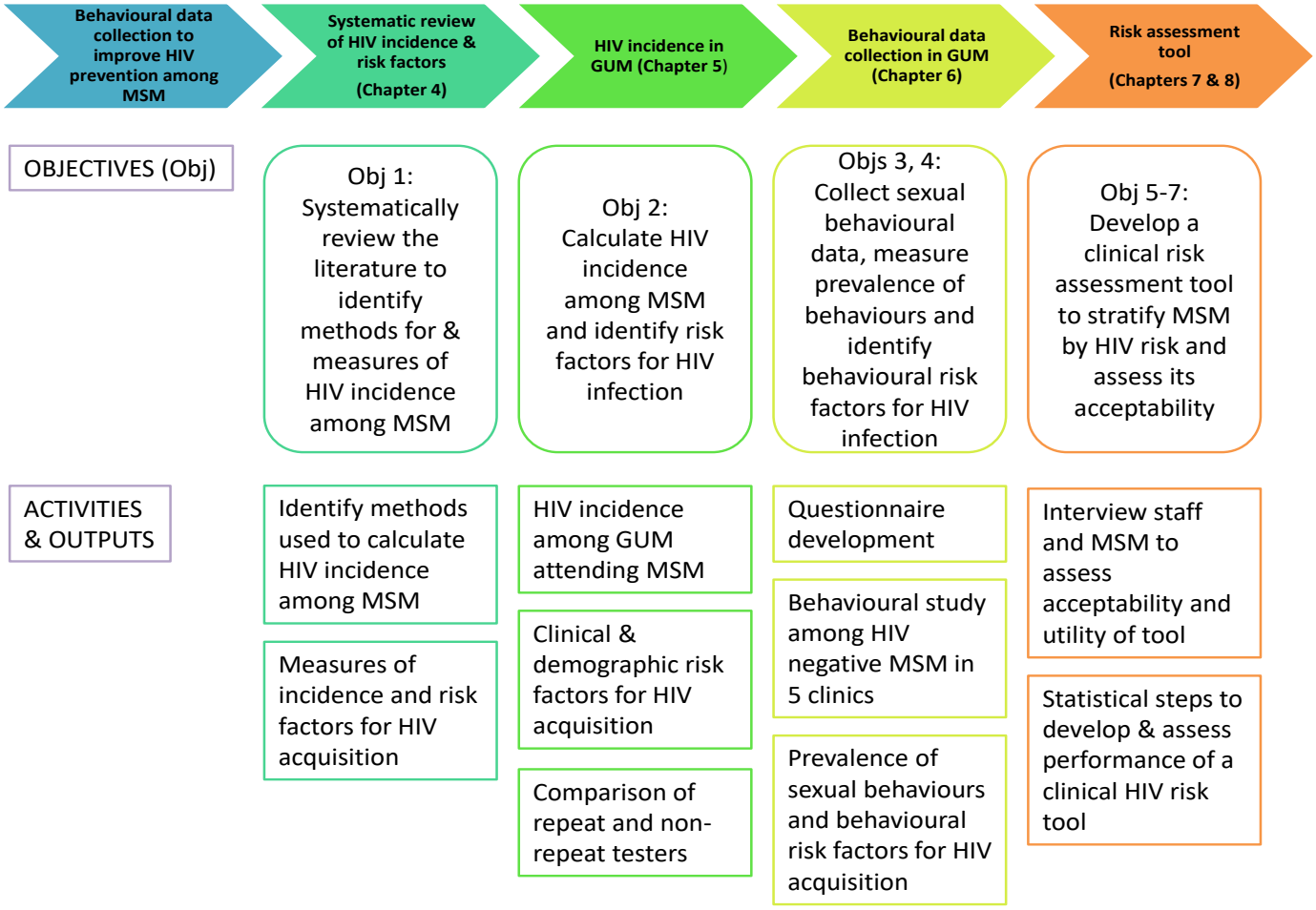


Figure 1.2 Objectives, activities and outputs of the research



2 Background

2.1 Epidemiology of HIV in the UK

At the time when this research began (2011), there were an estimated 96,000 people living with HIV in the UK and approximately 25% of these prevalent infections were undiagnosed with the individual unaware of their infection (4). By 2015, an estimated 101,200 were living with HIV and 13% were undiagnosed (12). Individuals who are unaware of their infection cannot benefit from antiretroviral therapy (ART) initiation and could potentially transmit the virus to uninfected partners if having condomless sex. Of the 6,095 new HIV diagnoses that year, 39% were heterosexually acquired, 54% through sex between men, 3% through injecting drugs, and the remainder were 'other' (e.g. blood products, vertical transmission) or unknown. Almost half of those who heterosexually acquired their infection were of black African ethnicity.

African-born adults (28%) and MSM (46%) made up the two largest groups living with HIV in the UK in 2015. The overall HIV prevalence rate was 22/1,000 population among black African men, 43/1,000 among black African women, and 59/1,000 among MSM adults compared to 1.6/1,000 in the total population (12). The high prevalence rate among Africans was primarily due to high prevalence in the home countries where infection was acquired before migration to the UK (13). However, changes to migration policies during the mid-2000s have incidentally impacted the HIV epidemic in the UK (14). The number of new HIV diagnoses reported among individuals born in Africa has considerably declined since 2006, while diagnoses from other countries have increased and for those born in the UK have remained at around 2,700 a year (Figure 2.1). In comparison, new diagnoses among MSM have continued to increase year on year except in 2015 when numbers remained comparable to 2014.

Figure 2.1* Numbers of new HIV diagnoses by world region of birth, United Kingdom, 2006-2015

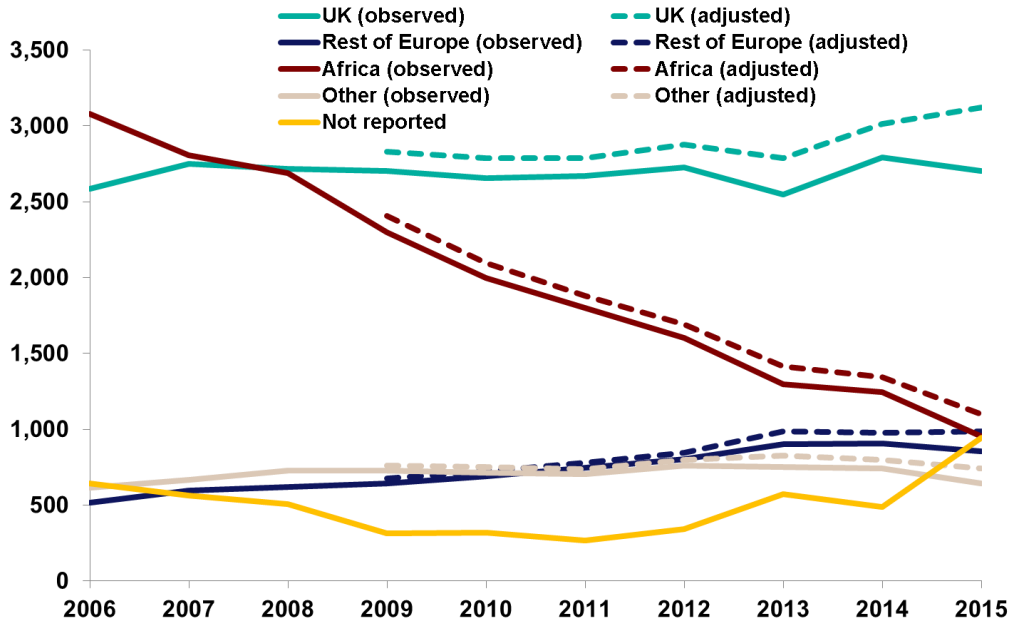


*Figure reproduced from the Public Health England 2016 HIV annual slide set. Values are adjusted for missing country of birth where stated

2.2 Epidemiology of HIV among MSM

Recent estimates of MSM population sizes have allowed diagnosis and prevalence rates to be estimated for MSM in the UK. The size of the MSM population is derived from population surveys where MSM often compose a small proportion of the total population. In the third decennial National Survey of Sexual Attitudes and Lifestyles (Natsal) conducted between 2010 and 2012, 190 men who participated met the definition of MSM (men who reported sex with at least one man in the five years prior to the interview) (15). This information was incorporated into a multiparameter evidence synthesis model, which has been described previously (3) and an output of this model includes an estimation of the MSM population aged 15-44 years in the UK. An estimated 3.3% of men aged

15-44 years have sex between men, which extrapolated to the whole population equates to approximately 880,000 adult (≥15 years) MSM in the UK (using mid-2015 population estimates from the Office of National Statistics and crudely assuming 3.3% of men aged >44 years are also MSM). This estimate is in line with a recent report, which estimated that 3.1% of the English male population was gay and bisexual (16). There is, however, some uncertainty in these estimates as sexual identity, attraction and behaviour can be different at the individual level. While 2.5% of men reported gay and bisexual identity in Natsal, a higher proportion reported same sex attraction and behaviour (17), suggesting the MSM population could be higher than estimated here and is dependent on how the population is defined.

Overall HIV prevalence (diagnosed and undiagnosed) has risen from 4.7% in 2011 to 5.9% in 2015 among MSM in the UK with approximately 12% now living with undiagnosed HIV. The increase in prevalence is likely due to ongoing HIV transmission and stable numbers of annual deaths. Trends in prevalence are not sufficient for understanding the distribution of new infections and those acquired years before. Due to the availability of ART, the cohort of MSM living with diagnosed HIV is growing and with a greater number of prevalent infections, the opportunity for HIV transmission in sero-discordant relationships where the HIV positive partner is not on treatment and/or virally suppressed could potentially also increase. However, in the UK, ART coverage is high and viral suppression within a year of starting treatment is also high (18).

In 2015, the HIV diagnosis rate was 396/100,000 (3,320/838,990[1]) among MSM. Although the epidemic was still concentrated in middle-aged white MSM, the epidemic has diversified in the last decade with large proportional increases among men born in other European countries, Asia and Latin America (19). By age group, diagnoses substantially increased among youngest MSM; a marker of ongoing HIV transmission.

Diagnostic data, which are the mainstay of surveillance, do not estimate HIV incidence. HIV incidence is a measure of newly acquired HIV infections and is a vital parameter to describe the current HIV epidemic and identify sub-groups at greatest risk of infection. New HIV diagnoses will be made at different stages of infection; an early diagnosis could capture a recently acquired infection (e.g. in the last six months) or an infection where the CD4 count at diagnosis is ≥350 cells/µL, while a late HIV diagnosis could have been acquired many years earlier and where the CD4 count is <350 cells/µL. The reported increases in new diagnoses among MSM could be due to changes in HIV testing behaviours and/or ongoing HIV transmission. The proportion of HIV negative MSM testing in the past year (20) and the total number of tests performed in GUM clinics (21) has increased in the last decade. Concurrently, CD4 count at diagnosis has also increased (19), which suggests MSM are being diagnosed at an earlier stage of infection (7) and that, at least in part, the increase in new diagnoses is due to increases in testing. The impact of increased testing was recently observed in a number of GUM clinics when in 2016, these clinics observed a significant drop in new HIV diagnoses. Three factors are considered to have largely contributed to this drop: i) increased numbers of MSM attending clinics, ii) increased HIV testing

[1] HIV negative MSM population was calculated as the total number of MSM in the UK (880,000) minus the number of MSM living with diagnosed HIV infection in 2015 (41,016). Therefore, there were an estimated 838,984 HIV negative adult MSM in the UK in 2015.

among new and repeat testers in recent years and iii) adoption of treatment as prevention (TasP)(22). Increased testing initially led to an increase in new diagnoses in both groups of testers as would be expected but thereafter a decline was observed. The observed increases in HIV testing may have also reduced the undiagnosed prevalence and potentially transmission as undiagnosed infections are significant drivers of HIV transmission. Further, considering the importance of primary HIV infections on HIV transmission, a significant number of infections could be averted by frequent testing and a change in risk behaviour after diagnosis (23).

The proportion of recently acquired infections, while not a measure of HIV incidence, can provide evidence of on-going transmission among newly diagnosed individuals and can be estimated through surveillance programmes. The recent infection testing algorithm (RITA) surveillance programme (24) in England, Wales and Northern Ireland uses an in-house avidity test at Public Health England (PHE) (25) to test for recent HIV infection. Where tested for recent infection, 27% of HIV diagnosed MSM in 2015 had probably acquired their infection recently, higher than for other transmission risk groups. The proportion of recent infections increased with decreasing age so that 32% of 15-24 year olds had a recent infection. Other proxy indicators for HIV incidence, such as increases in new diagnoses among the youngest MSM also suggest HIV transmission is ongoing among MSM. New diagnoses and recent infections among younger men could be used as a proxy of HIV incidence as the time interval between infection and diagnosis is shorter than for older ages.

Between 2001 and 2010, between 2,300 and 2,500 annual new HIV infections were approximated among MSM in England and Wales (7) with no evidence of a

decline (5-7). The last available incidence estimates from MSM attending GUM clinics, which are more than a decade old, also indicated stable incidence (2.5% in 2001 (26) and 3% in 2002 (27)). The increases in HIV testing over the years has contributed to a downturn in new diagnoses among MSM in 2016, though it remains to be seen whether this is a sustained decline and whether these changes have impacted HIV transmission. The availability of direct estimates of HIV incidence would allow better evaluation of these changes. HIV incidence methodologies and estimates from the UK and worldwide are discussed in more detail in the systematic literature review conducted and reported in Chapter 4.

Overall these data highlight that current routinely available data are important for monitoring the HIV epidemic but to understand the current epidemic, incidence estimates and changes in testing/diagnosis practices as well as in behaviours that facilitate HIV transmission could be invaluable.

2.3 The role of sexual health services in the HIV epidemic

The majority of HIV tests and diagnoses (>80%) among MSM are made at GUM clinics (28). Research shows GUM clinics are the preferred sites for HIV testing for a large proportion of MSM and that half had attended a GUM clinic in the previous year (9). This is not surprising as GUM clinics offer a range of sexual health services including testing and treatment STIs, free condoms, HIV testing, advice, and post-exposure prophylaxis (PEP). It is a legal requirement for these clinics to be free, confidential and open access (a referral is not required). Depending on the STI being tested, an individual may give a urine sample, blood sample, a urethral swab and/or rectal swab. Specific guidance from the British Association for Sexual Health and HIV (BASHH) suggests that venous blood

should be taken for HIV tests and urethral, pharyngeal and rectal samples for STI testing among MSM (29).

Since 2013, local authorities (LAs) (administrative body in local government) commission public health services including sexual health as part of the Health and Social Care Act 2012 reforms (30). As well as commissioning GUM, two other sexual health services have transferred commissioning to LAs: contraception and sexual health advice, promotion and prevention, which includes HIV prevention initiatives (31). Services are configured and provided in different ways across the country. GUM services can be provided with HIV services or increasingly GUM is being integrated with sexual and reproductive services to create community-based 'one-stop shops' (32) that could facilitate HIV prevention initiatives. Integrated contraception and sexual health services offer HIV testing, STI screening, treatment, care and sexual health advice in one place. These services are potentially more accessible and located in settings outside GUM (e.g. general practice) but in one study MSM expressed some concerns to One Stop Shops, which included having to wait with women and families, loss of confidentiality and intimacy and potential homophobia(33). In fact, most preferred GUM clinics to the idea of integrated services.

As well as being the preferential testing site, GUM clinics also serve a higher risk MSM population. The available data indicate MSM who attend GUM report higher risk behaviours such as more sexual partners than men that don't attend GUM (9). A clinic notes audit of 598 HIV negative MSM in 2010 indicated that 33% reported condomless anal intercourse (CAI) in the last six months and 10% exclusively practiced receptive CAI (CRAI) (where they are the bottom partner) (11).

2.4 Sexual behaviours among HIV negative MSM

While UK national surveillance systems collect extensive demographic and clinical information on HIV diagnosed MSM and MSM attending GUM clinics (including HIV negative MSM); at the beginning of this research none captured behavioural data. The inclusion of behavioural information into national surveillance systems could help identify those sub-populations at increased risk, the behaviours that put them at risk and the contribution of behavioural changes to changes in the epidemic.

Though the use of sexual behavioural information to inform HIV prevention is the focus of this thesis it is important to recognise that there are other determinants of health, which are also important for HIV risk and health in general. Social determinants include factors that are not controllable by the individual but affect the individual's health. These include the social and physical environment and health services. Social factors such as income and education can be important markers of risk. In the US, black MSM with higher financial hardship are more likely to engage in behaviours that place them at greater of infection (34). Higher education levels and being in a steady relationship were also associated with lower perceived HIV risk among men in the UK (35) Environmental factors such as housing conditions and social networks can equally be key drivers of infection with men in unstable housing more likely to acquire STIs (34). Interventions that supplement behaviour targeting with approaches that address these contributors of disease and underlying factors such as poverty, education, homophobia and stigma are likely to have a greater impact on HIV prevention. Stigma has been shown to be linked to higher engagement in sexual risk behaviour and leading to higher unmet prevention needs among MSM in Europe (36).

Just as the individual and environmental level factors that affect risk change over an individual's life course so do the sexual behaviours men engage in. Sexual behaviour is dynamic and evidence suggests that MSM transition between periods of risk. Men characterised as medium risk had a mean duration of consecutive high-risk intervals 1 year compared to 2 years among the high risk (37). Participants of the iPrEx trial also showed considerable temporal variation in engagement in condomless anal intercourse and very few of the seroconversions occurred among those who reported CRAI every quarter (38). Thus considering the variation in sexual behaviours, the behaviours may identify high risk moments rather than high risk individuals.

2.4.1 Why are sexual behavioural data collected?

In the context of the HIV epidemic, behavioural data can be collected for a number of reasons and purposes. I have identified five themes from the literature: monitoring the HIV epidemic, early warning system, monitoring and evaluation of prevention programmes, policy development and clinical decision making tools.

2.4.1.1 Comprehensive monitoring of the HIV epidemic

The effective tracking and describing of the HIV epidemic over time should include behavioural and biological data components that are collectively analysed. Behavioural data can monitor risks related to HIV transmission and can be used to interpret trends in HIV incidence and prevalence and identify drivers of the epidemic.

In 2008, less than half the European countries reported an established surveillance system that combined biological and behavioural surveillance for HIV and STIs (39) and specifically for MSM, 14 of the 27 countries that returned information on MSM reported a system of behavioural surveillance (40). Even among countries with systems in place to monitor behaviours among MSM, the types of surveillance system and the indicators collected were diverse. These findings show there is still a long way to go to establish behavioural surveillance for MSM across Europe.

The value of combining biological and behavioural surveillance is exemplified by the Gay Men's Sexual Health Survey (GMSHS). This is a community based survey recruiting MSM from social venues such as bars and clubs in London and Scotland. The relatively recent introduction of oral sampling for HIV has enabled undiagnosed HIV prevalence estimates and the combined collection of behavioural data and oral samples has allowed analyses of MSM at risk of transmitting and acquiring HIV (20).

2.4.1.2 Early warning system

Early warning systems are described by the World Health Organisation (WHO) as "timely surveillance systems that collect information on epidemic-prone diseases in order to trigger prompt public health interventions" (41). The incorporation of behavioural data in surveillance systems specifically for early warning of any changes is important for the spread of HIV infection among MSM. Targeted surveys among MSM in 1996, 1997 and 1998 in England were the first to report an increase in unsafe sex as measured by CAI in the past year (42). These seminal surveys strongly influenced the establishment of the GMSHS in London and the use of community- and venue-based surveys to regularly monitor

behaviours among MSM. Since then, this survey has provided considerable insight in the trends of sexual behaviours among HIV negative and positive MSM. Similarly, the Australian Gay Community Periodic Surveys (GCPS) identified an increase in CAI with casual partners among MSM which resulted in mobilisation of resources and prevention measures that reduced CAI with casual partners and new HIV diagnoses (43).

2.4.1.3 Policy development

Greater insights into population behaviours can have an important role to play in policy initiatives and a data-driven approach to policymaking has become widely adopted. Policies to increase HIV testing among MSM are an example of the data-driven approach. In the United States (US) routine screening in certain populations was successful while modelling studies reported testing all but the lowest-risk populations for HIV once every three to five years was cost-effective (44). This led the Centers for Disease Control and Prevention (CDC) to subsequently recommend expanded testing to the general population (45). Concurrently, data from behavioural surveys conducted among MSM in the UK highlighted testing levels were too low to have an impact on the HIV epidemic. Forty-one per cent of HIV positive MSM were unaware of their status and sexual risk in this population was higher than among HIV negative MSM (46). In response to these events, in 2008, national HIV testing guidelines were developed and recommended annual HIV testing for MSM or more frequently if there was evidence of ongoing high risk exposure (47). The policy recognises that annual testing may be sufficient for low risk MSM but for those engaging in risk behaviours such as CAI, more frequent testing would be beneficial.

2.4.1.4 Development, monitoring and evaluation of prevention programmes

Behavioural data are frequently used to inform the development, monitoring and evaluation of prevention campaigns and initiatives. Although the overall aim of a prevention programme is to reduce new HIV infections, some outcomes of programme components may use proxy measures to determine whether new infections have declined. An example is changes in sexual behaviours; a downturn in high risk behaviours may indirectly suggest an impact on HIV transmission and decline in incidence. In the US, HIV prevention indicators were developed to evaluate the effectiveness of prevention efforts. While there were no national behavioural indicators included for MSM due to lack of data, behavioural indicators were included for heterosexuals (48).

A government campaign in Uganda to increase awareness of HIV/AIDS and promote faithfulness to one partner is another example of the value of behavioural data in monitoring prevention efforts. During the 1990s HIV prevalence reduced in a number of populations in Uganda including pregnant women and attendees of sexual health clinics. As the greatest changes in HIV prevalence were seen in youngest adults, HIV incidence was also assumed to be declining. The analysis of behavioural data allowed the decline in prevalence to potentially be attributed to a concurrent decline in the number of casual and non-regular sexual partners (49). The data indicated the government campaigns had been successful at changing sexual behaviours and encouraging faithfulness.

The adoption of pre-exposure prophylaxis (PrEP) as a HIV prevention option will have important implications for monitoring sexual risk behaviours. The evaluation of a PrEP delivery programme will likely include a component on behaviours; the

use of PrEP may result in an increase in sexual risk behaviours such as CAI, which may offset the benefit of PrEP on reducing HIV incidence. The current evidence regarding risk compensation is mixed with some finding a reduction in condom use and an increase in STIs (50) and others no change (51-53) although longer periods of follow-up may be required to conclusively identify any changes.

2.4.1.5 Risk prediction

While behavioural data are essential for interpretation of epidemiological trends, from a clinical perspective, the data could also inform patient care. Clinical decision making uses a combination of experience, knowledge and assessment tools to make effective and good clinical decisions. Risk prediction models are used in clinical decision making and to help patients make informed decisions about their care. They typically use a number of predictors which are based on patient characteristics to predict health outcomes. For example, triaging is already part of routine clinical practice to determine who is at risk of developing cardiovascular disease and whether prescription of preventive medicine might be useful. The Framingham risk score is a long established risk prediction model used to quantify an individual's 10 year risk for cardiovascular disease. The risk score uses a number of patient characteristics (e.g. smoking, blood pressure and cholesterol) important to cardiovascular disease to mathematically determine an individual's risk (54).

The development of risk prediction models could be of similar benefit in sexual health. Sexual health services, as other public health infrastructures, are increasingly expected to deliver services with diminishing resources. With limited resources to offer all services, risk prediction could be used to assess an individual's risk of acquiring HIV and guide the offer of services. Risk triaging is

an option to help prioritise service delivery and ensure patients are receiving appropriate clinical and prevention services. Ideally, patient choice is paramount to determining what services are offered but often what patients want and expect may not be aligned with their need. In health care four types of need have been delineated and the presence of all four is required to equate to real need (55). These needs are those expressed by the individual (felt and expressed need) and also defined by the provider (normative and comparative need). Felt need by the individual is shaped by the individual's perceptions and knowledge (e.g. engaging in high risk behaviour) while expressed need is need that is translated into action (e.g. going to a GUM clinic). Normative need is defined by experts and can depend on the expert (e.g. need for PrEP) and comparative need is identified by comparing service provision between services (e.g. PrEP provision between clinics). However, a lack of expression of need does not necessarily mean there isn't real need as the inverse care law suggests that those who most need health care are least likely to receive it whereas those in least need use services more (56). Risk triaging may address some of these inequalities and may be a more viable option in the current climate. There is however the risk that patients may modify their need and hence their responses based on what they want, which could be relevant for the PrEP IMPACT trial where individuals may change their sexual behavioural history in order to meet the eligibility criteria for PrEP.

A recent review highlights that risk prediction is already used in sexual health particularly to identify screening thresholds above which individuals might benefit from STI tests (57). The risk prediction tools include sexual behavioural data specific to the population for which the tool was developed. An objective of the systematic review undertaken in this thesis will be to identify the key sexual

behaviours associated with HIV acquisition among MSM to inform the development of a HIV risk assessment tool.

These examples demonstrate the utility and scope of sexual behavioural data, though how the data are used will be partially determined by how they are collected. In the UK, the majority of behavioural data come from two types of behavioural surveys: population and targeted surveys.

2.4.2 Population-based cross-sectional surveys

Nationally representative HIV behavioural surveys are population-based and usually survey individuals in a random sample of households in a geographic area. They are more frequently used in countries with generalised HIV epidemics.

To date, there are three surveys in the UK that are repeated, cross-sectional and use multi-stage stratified random probabilistic sampling, where the sampling frame is the small user Postcode Address File, to recruit participants: Natsal (58), the annual Health Survey for England (HSE) (59) and the Opinions and Lifestyle Survey (OLS) (60). Random sampling ensures data are collected from a nationally representative sample of adults. All three surveys covered adults aged 16 years and over (Natsal 2010: 16-74 year olds). Natsal is the only survey specifically designed to measure sexual behaviours and is therefore more detailed and comprehensive than the general health surveys that only included a small component on sexual health in some years.

The studies are cross-sectional and measure prevalence of risk behaviours among MSM at specific time points. In repeated surveys, measures can be

compared over time if the same behaviours are collected. Natsal collects data through a combination of face-to-face interviews by trained field researchers and a computer-assisted self-interview (CASI) completed on a laptop. The more sensitive questions including those on sexual behaviours are collected through a CASI. OLS and HSE both use face-to-face interviews and pen and paper questionnaires.

Data from the most recent Natsal survey (Natsal-3) indicate that 73% of MSM reported anal sex in the prior year and 13% reported engaging in CAI with two or more partners in the past year (61). Twenty-two per cent of MSM had tested for HIV and 39% had attended a GUM in the last year. In comparison to Natsal, the proportion reporting same sex in the past 5 years was slightly lower (1.6%, 95%CI 1.0-2.6%) in HSE (62). MSM-specific results are not currently available from HSE or OLS.

2.4.3 Targeted cross-sectional surveys

In comparison to population-based surveys, surveys targeted at specific risk-groups can achieve larger sample sizes and have better capacity to collect population specific information. These surveys tend to be more affordable and can be more routinely conducted in populations with characteristics of interest. Whereas population surveys aim to be nationally representative, targeted surveys cannot often recruit a random sample as a reliable sampling frame is not available. In these situations it is more feasible to use non-random techniques such as recruiting MSM in venues, communities, through the internet and from clinical services.

In the UK, the vast majority of knowledge on behaviours associated with HIV among MSM comes from cross-sectional surveys that recruit MSM using convenience sampling techniques. The GMSHS recruits MSM attending gay social venues in London, Glasgow and Edinburgh (63, 64) to primarily document HIV (diagnosed and undiagnosed) prevalence and its association with sexual behaviours. MSM are asked to self-complete an anonymous questionnaire on sexual behavioural characteristics and provide an oral fluid specimen for HIV testing. As the study is anonymous, individuals are not given their HIV results. Another London based survey recruiting MSM from gyms similarly asks men to complete a questionnaire on sexual behaviour, drug use and HIV status (65). The additional benefit of these surveys is that they are repeated over time and can therefore monitor trends over time. The Gay Men's Sex Survey is another repeated cross-sectional survey targeting MSM; however recruitment methods have changed over time from Gay Pride events (66), to the internet (67, 68). The European Men-who-have-sex-with-men Internet Survey (EMIS) recruits using online websites including dating websites and the data are self-completed anonymously to cover a range of topics including sexual behaviours and HIV prevention needs. The internet has often been used to recruit MSM because it offers the opportunity to understand behaviours among men who may not be easily recruited in community venues and who are potentially at high risk of HIV (69, 70). The MESH project was a cross-sectional survey that used the internet to recruit a national sample of MSM living in Britain to understand in greater depth the sexual health of Black, Asian and minority ethnic MSM (71).

Respondent-driven (RDS) (72), and time location sampling (TLS) strategies are alternative methods to convenience sampling and are particularly useful for recruiting hard-to-reach MSM. These methods attempt to improve

representativeness of MSM samples by using systematic sampling procedures. TLS strategies rely on a sampling frame that comprises the venues, days and time periods where and when the MSM population congregates and then potential participants are recruited from randomly selected venue-day-time periods. RDS is a long-chain peer referral recruitment method where initial seeds are given coupons to pass onto members of their networks. Although there is no sampling frame and the likelihood of recruitment is based on the size of the seed's network, analyses are weighted to take this into account and allow results to be applied to the population. When used in conjunction with the service multiplier method, RDS can be used to provide additional information to estimate the population size and has been shown to give results comparable estimates (73). RDS has not been widely employed in the UK; one survey attempted to recruit Central and Eastern European MSM using RDS but without success (74). However due to logistical issues faced when conducting these surveys, it is still debatable whether these methods can ensure a representative sample of MSM (75).

Data from targeted surveys have been widely published in the literature. Between 1996 and 2005, CAI among all MSM (regardless of HIV status) was between 24%-48% in the UK (42, 65, 76). The overall trend suggests an increase in the proportion of MSM reporting any CAI with some stabilisation in the mid-2000s. CAI with ≥1 partner increased during the 1990s and early 2000s and has remained constant since then (63, 76-78). Latest sexual behavioural trends show an increasing trend in reported CAI during the previous year among HIV negative MSM from 42% in 2000 to 51% in 2013 ($p<0.001$) and in CAI with HIV negative partners ("serosorting") (20% to 30%,$p<0.001$) (20). CAI with a HIV positive

partner increased between 1998 and 2003 (13% to 20%), although afterwards a decline to 11% in 2008 was noted (65).

2.4.4 Key issues when measuring sexual behaviours

An examination of these surveys highlights some key considerations when collecting behavioural data among (HIV negative) MSM; those that are study type specific and those that are general considerations.

When I began my thesis, none of the identified sexual behavioural studies among MSM in the UK used cohorts to collect data. Cross-sectional studies can only measure behaviours at specific time points and though the repeated nature of the surveys facilitates population trends over time, these studies are subject to changes in the populations using community or social venues. For example, it is likely that the characteristics of MSM recruited in social venues have changed over time. With the increasing availability of web-based dating sites or phone apps to meet partners, MSM who use these technologies are likely to differ to individuals visiting social venues. As already highlighted, MSM recruited online are different to MSM from other recruitment methods (67). It is important to note that if the sampling bias remains constant between cross-sectional surveys then it is possible to monitor changes in risk behaviour over time. Finally, as cross-sectional surveys occur at the population level, interpretation of changes in behaviours can be difficult as any changes cannot be attributed to the individual, only the population. Therefore while they provide excellent knowledge of population trends, knowledge of sexual "career" is poorer. Cohort studies have been set up in Sydney, Australia (HIM cohort, (79)), British Columbia, Canada (80) and Amsterdam, Netherlands (81) to monitor trends in behaviours and infections over time. Generally, in these studies, men completed a self-

administered questionnaire and provided samples at regular intervals. Men were followed-up over time and incident infections measured. Cohort studies are inherently better for measuring risk factors for HIV transmission.

Probability sampling as used in population surveys recruits a representative sample and findings from these surveys are generalisable beyond the sample. In contrast, in convenience sampling men are not selected at random and selection bias prevents generalisability to the overall MSM population. For example, men who do not identify as gay and therefore do not visit gay venues would be excluded from these studies; in particular hard-to-reach MSM would be excluded. Convenience sampling compared with probabilistic sampling consistently recruits higher risk MSM (67, 70, 82). Therefore risk behaviours measured in these populations are likely to overestimate the prevalence of behaviours in the wider MSM population. However, probability sample surveys generally achieve small sample sizes, which limit the scope of analyses that can be conducted. For example, analyses cannot be stratified by HIV status or by previous GUM attendance, even if these variables are collected. These sub-analyses are important to determine whether behaviours differ in these sub-groups. The lack of generalisability of targeted surveys may be acceptable in light of a significant gain in in-depth information and analyses.

The majority of the surveys collect sexual behaviours from the “past year” or “ever”. Collecting information for a one year period can be subject to recall bias where there are differences in the accuracy of information recalled by participants and which differs between two groups for exposure or outcome information. Recall bias will distort the measure of association. Shorter recall periods of three months could potentially be less subject to recall bias.

Additionally, with a shorter recall period within-person changes over time could be better captured and would be more meaningful. A further aspect of the data collected is the questionnaire or interview length, which will be study setting dependent. Surveys collecting behaviours from MSM in social venues will likely need to be shorter than those completed online in order to be acceptable to participants. Data collection that is clinician-led would also need to be shorter than if for self-completed questions to ensure there is no major impact on clinic work burden.

Another consideration is how best the data should be collected. Examples include self-completion (paper questionnaire or online) or a face-to-face interview. Natsal included a self-completed component for more sensitive questions. If asked through an interview, there is the potential that social desirability may play a role in the responses. Social desirability bias may occur when participants respond in a manner that is viewed as favourable by others; for example, men may under-report behaviours perceived as risky. Self-administered anonymous questionnaires may reduce bias. Although in some settings, such as sexual health sites, collection of sexual behavioural data may not be considered sensitive and interviews may be deemed appropriate.

Some surveys collected biological samples in addition to self-reported behaviours, which allowed analyses of behavioural data by confirmed HIV status. Actual estimates of HIV prevalence can be calculated and the associated between behaviours and these outcomes investigated.

The study design employed including recruitment and data collection methods will depend on the aim and objectives of the study. These data have mostly been

collected to inform the HIV epidemic among MSM in the UK and advocate for HIV prevention initiatives, which can be broadly categorised as biomedical, behavioural and structural approaches with HIV testing underpinning all approaches.

2.5 Combination HIV Prevention approaches for MSM

In the early years of the epidemic, it was patients with AIDS and their care givers who organised preventative responses to the disease. This took the form of leaflets with information on the disease and how to avoid it (83). This then led to the formation of community groups who continued prevention efforts and it was only later organisations such as WHO and national governments became involved (84). In more recent years, greater political will, global awareness and significant increases in financial resources have strengthened HIV prevention though there is still a long way to go with data suggesting prevention services reach less than 10% of those at risk globally.

For HIV prevention to be successful, knowledge of the epidemic is required as well as an understanding of the broader determinants of the infection, namely the socioeconomic, cultural and environmental factors that affect the spread of the infection. To account for all these factors strengthened services utilising a combination approach to HIV prevention is advocated. Combination prevention is a combination of behavioural, structural, and biomedical prevention strategies and approaches, which should be tailored to the context and based on scientific evidence (85). Countries with successes in reducing HIV infection have used a combination approach (86, 87) no single intervention will provide complete protection against HIV infection; rather a portfolio of approaches is necessary to successfully tackle HIV.

2.5.1 Biomedical interventions

Biomedical interventions aim to reduce the risk of HIV transmission by reducing the risk of exposure occurring or by reducing the risk associated with an exposure. There are some proven biomedical interventions with evidence-base for MSM as well as others that require further research to prove their efficacy in preventing HIV infection (88).

2.5.1.1 Condoms

Since the beginning of the HIV epidemic when male condoms were first recommended for the prevention of HIV transmission the evidence base for the effectiveness of condoms as a physical barrier to HIV has grown. Condom use remains the mainstay of HIV prevention among MSM and is highly effective at reducing the risk of HIV transmission. One study reported a 78% reduction in the per-contact risk of HIV receptive AI (RAI) when compared with CRAI (89). However, the occurrence of breakages and slippages (90) and, importantly, the inconsistent use of condoms can have significant implications for condom effectiveness as a prevention strategy. Inconsistent condom use is known to increase the risk of HIV acquisition (91, 92). Among a cohort of HIV negative MSM, only 34% reported consistent condom use (93), even though it was the most commonly reported HIV prevention strategy.

2.5.1.2 Circumcision

The evidence for circumcision among MSM is inconsistent and it is not currently recommended for HIV prevention (94). The pooled effect estimates for HIV or STI acquisition were not significant and the only protection afforded from circumcision was to men reporting insertive AI (IAI) (being the top partner) (OR:

0.27, 95%CI 0.17-0.44). Circumcision is not effective partly because the greatest transmission risk for MSM is through CRAI where the individual's circumcision status is irrelevant and the partner's is relevant (95).

2.5.1.3 Antiretroviral prevention

The availability of ART to reduce the risk of HIV infection has increased HIV prevention options among MSM in recent years. There are three main streams of research for using ART for prevention: i) post-exposure prophylaxis (PEP) ii) pre-exposure prophylaxis (PrEP) and iii) treatment as prevention (TasP). Each is dealt with separately below.

PEP

The clinical effectiveness of PEP to reduce HIV acquisition has not been well-established in any population (96); however the availability of data from animal studies and a retrospective case control study have provided some evidence of protection which led to national guidance in the UK (97) that supports the clinical prescription of ART after a sexual exposure. Guidance recommends a risk versus benefit analysis for every patient and, for those who are considered at high risk, combination therapy should be offered for 28 days.

PrEP

A recent review concluded that taking HIV drugs prior to exposure does reduce the risk of HIV acquisition when trialled in high risk populations including MSM (RR: 0.33, 95%CI 0.2-0.55) (98). In the iPrEX trial which was conducted in the US, South American countries and Thailand, the antiretroviral drug emtricitabine (FTC)/tenofovir disoproxil (TDF) reduced the risk of HIV acquisition by 44% and

by 73% when adherence increased to 90% (10). Despite these encouraging results, a number of challenges remain before PrEP could be widely employed. A key question is whether risk compensation is likely among men using PrEP as increased sexual risk taking could counteract the benefits of HIV prevention. Other challenges include addressing the low adherence observed in the trial, the implications of long-term use for toxicity, the development of viral resistance and the most feasible regimen (daily vs. intermittent dosing). Further implementation challenges including the costs and the appropriate messaging also require consideration (99).

In 2012, an effectiveness trial in real life settings began as an immediate versus deferred open label trial in England. An interim analysis in 2014 indicated that PrEP was highly protective against HIV (86% relative reduction in HIV acquisition), which resulted in the trial offering all MSM in the deferred arm PrEP early (52). In December 2016, NHS England announced they will be making £10 million available to PHE to enrol 10,000 participants into a clinical trial of service delivery over three years (100). The PrEP-Impact trial will aim to address the outstanding questions about need, uptake, adherence and duration of use of PrEP and it is anticipated the majority of those recruited will be MSM. During this time, PrEP has been available for online purchasing (e.g. https://www.iwantprepnow.co.uk/).

TasP

The final application of ART is as treatment as prevention where HIV drugs can prevent onward transmission between serodiscordant couples. The HPTN 052 trial was a landmark study showing that early initiation of antiretroviral treatment (at CD4 counts of between 350 and 500 cells/μL) among serodiscordant couples,

primarily heterosexuals, reduced transmission between partners by 96% (101). The trial results led WHO in 2013 to recommend ART be offered to everyone living with diagnosed HIV and in serodiscordant relationships. More recently, the PARTNER study demonstrated the effectiveness of TasP to prevent any within-couple transmissions of HIV among MSM (102). However, at the population level, its impact on transmission will be limited due to high ART coverage among MSM unless it is coupled with increased HIV testing (103) given that a sizable proportion of infections are from MSM recently infected and unaware of their serostatus (104). Increased testing and TasP are considered to be the main contributors to the recent decline in new diagnoses among MSM (22).

2.5.1.4 Microbicides and vaccines

Rectal microbicides are topically applied to the rectal mucosa and could reduce the risk of HIV acquisition but they are still in early stages of clinical investigation for MSM (105). HIV vaccines are still in developmental stage and the development of a safe and effective vaccine continues to remain a challenge.

2.5.2 HIV testing

HIV testing and counselling underpins the effective implementation of other prevention approaches as without knowing one's serostatus, steps cannot be taken to reduce the risk of acquisition or onward HIV transmission. Knowledge of serostatus is particularly relevant to community level strategies such as serosorting and seropositioning as these risk reduction strategies can increase the risk of HIV (106). Practising CAI with partners incorrectly assumed to be HIV negative (i.e. same serostatus) will increase the risk of acquisition especially as the receptive partner. To have any impact on HIV incidence, the levels of testing coverage achieved would need to be high. The impact of increased first time and

repeat testing has already been observed in a number of GUM clinics and to replicate this nationwide would require scaling up of repeat testing.

New strategies are being explored to reduce barriers to testing, increase HIV testing uptake and reduce the burden of undiagnosed HIV. Self-testing, where men take a sample, perform the test and interpret the results in private, became legal in the UK in April 2014 and available in 2015 and is at an early stage of service implementation. It is, however, an acceptable method to encourage repeat testing (107-109) but concerns such as linkage of people with positive results into counselling services, treatment and care requires further exploration and evaluation (108, 110). Self-sampling, where an individual sends the sample to a laboratory for testing, is, in contrast, widely available. Studies in the UK have shown its acceptability and potential to increase HIV testing (111, 112). Other strategies with some evidence of increasing HIV testing include intensive peer counselling and testing in community settings (113).

2.5.3 Behavioural interventions

Behavioural strategies for HIV are those that modify risk behaviours including decreasing number of partners, increasing condom use, encourage counselling and testing for HIV, decreasing substance use and sharing of needles and syringes. These interventions motivate behaviour change at the individual and social group level using a number of motivational, community and peer-group approaches.

2.5.3.1 Individual-level

Individual-level interventions include one-to-one or face-to-face counselling, information provision, or skills-building by a trained individual. Less than a

quarter of MSM (21%) attending GUM clinics in England are offered behavioural interventions and if they are, basic counselling was the most common intervention offered (11). Counselling is the provision of information and discussion of strategies to reduce and mediate HIV risk with a trained counsellor (peer or non-peer). The evidence for the effectiveness of individual-level interventions to reduce CAI is inconsistent. Counselling (114), especially one-off, in isolation is unlikely to influence behaviour change over time and should be combined with other more potent interventions. However a recent review indicated that individual-level behaviour change could be effective at reducing risk-related behaviours especially if the intervention is delivered face-face and straight after a HIV negative result (115). A review of motivational interviewing (MIn) evaluated 10 randomised control trials (RCTs) among MSM (mostly from the US) and reported no significant associations between MIn and reductions in HIV/STI acquisition, unsafe sexual behaviours and only a short-term impact on alcohol and other drug use (116). The authors concluded that while MIn is acceptable to MSM it had no impact and its role as a prevention strategy is uncertain. In the UK, the National Institute for Health and Clinical Excellence (NICE) advocates 15-20 minute one-to-one structured discussions with high risk individuals including all MSM to address risk-taking reduction (117), which is reinforced in the national safer sex guidelines (118).

2.5.3.2 Group-level

Group-level interventions are those that are delivered to a small group of people and focus on individual-level components as well as group activities e.g. group discussions with peers, peer group education and workshops. Peers are popular opinion leaders who might promote positive behaviours in a community and as

they are seen as credible role models they are more likely to influence behaviour change.

The evidence for group-level interventions is consistent when the impact on changing risky sexual behaviours are evaluated; these interventions changed risk behaviours with one study reporting a 30% reduction in CAI compared to the group receiving no or minimal interventions (114). Group-level skills building (e.g. condom use, safer sex negotiation) through practice and role plays could be even more effective at changing behaviour. Biological outcomes were not always measured and when measured, the evidence of their effectiveness on STI/HIV endpoints was not convincing (114).

2.5.3.3 Community-level

These interventions are delivered by or within a defined 'community' and include peer outreach work and involvement of influential leaders in a community. Peer outreach can be an effective means to reach certain groups of MSM as these activities can be conducted online and via apps on mobile phones. Strategies often include use of mass media, social marketing, and community mobilisation. These interventions are effective and could lead to a 30% reduction in CAI compared to minimal HIV prevention (114). Encouragingly, effectiveness was also observed in studies with longer follow-up times suggesting sustained changes in behaviour can be achieved (119).

Behavioural strategies embracing a multilevel approach may have more success at affecting behaviour than those working at a single level.

2.5.4 Structural interventions

Structural factors are those that are outside an individual's control but influence the vulnerability of the individual to HIV infection. They include social (e.g. stigma), cultural (e.g. religious beliefs), political (e.g. laws) and economic factors (e.g. income). Structural interventions for HIV prevention alter the structures that affect outcomes and help to reduce stigma associated with HIV and barriers preventing uptake of services including HIV testing, care and treatment. Interventions that enable uptake and are culturally sensitive are vital for effective prevention (120). Examples of structural interventions are evident from the early years of the epidemic when needle and syringe programmes were established to expand access to clean needles among injecting drug users and reduce the risk of HIV infection from sharing needles. In some settings, particularly Africa and the Middle East, decriminalisation of same sex behaviour is a key structural intervention and a first step in tackling HIV prevention among MSM. Since 2012, HIV treatment has become freely available to all patients living in England regardless of how long they have been in the UK (121). The change in the law will enable some groups such as undocumented migrants, including MSM migrants to now freely access treatment and care.

2.6 Summary

Since the thesis began there have been two developments that affect HIV prevention among MSM. PrEP has come to the foreground of HIV prevention and is a real option for MSM to consider either as part of the trial or through online purchasing. Secondly, repeat HIV testing has significantly increased in some GUM clinics and contributed to a decline in new HIV diagnoses among MSM. With condom use, these biomedical interventions are important for HIV

prevention but their success will also depend on structural interventions that promote access to prevention, testing and care and behavioural interventions that significantly and sustainably reduce risk behaviours. A combination of prevention approaches will be necessary to have a measurable effect on HIV incidence.

Though an extensive array of effective strategies are available for HIV prevention, their success is also closely linked with ensuring men at risk who require support are offered and accept the preventions services. For example, it will be important to better understand how many MSM may need PrEP and how best to identify men at risk who should be offered PrEP. Behavioural insights into MSM attending GUM clinics that could lead to standardised risk assessments could improve HIV prevention for MSM. It is therefore important that collected data are accurate and reliable and a number of methodological issues have been highlighted in this review that should be considered when conducting behavioural studies.

3 Methodology

3.1 Introduction

In this chapter I describe the methods used to meet the objectives outlined in Chapter 1. Each section describes a component of the research including my role in the study and the results chapters (chapters 5-8) correspond accordingly. The methods for the systematic review are included with the review results in Chapter 4 as is custom when conducting a systematic review.

I chose a mixed methods approach to the research to ensure the utility of behavioural data in clinical settings and the potential of these data to enhance HIV prevention services offered and delivered to HIV negative MSM could be investigated holistically. The quantitative research facilitated measurement of HIV incidence among MSM attending GUM in England, collection of behavioural data and the derivation of a HIV risk assessment tool in this population. The qualitative aspects ensured service provider and user views on behavioural data utility were incorporated into the findings of the research.

3.2 HIV incidence and predictors of HIV acquisition among MSM attending GUM clinics

In this section I describe how I used national surveillance data to undertake a secondary data analysis on HIV incidence and risk factors for HIV acquisition. A retrospective open cohort study design was employed to follow individuals over time and determine incidence. A cohort study was possible because a population of men who were disease free at the beginning of the study and who could have developed the outcome over time was identifiable. This design also resulted in the calculation of incidence rates and comparisons between different groups.

3.2.1 Data source

I used the genitourinary medicine clinical activity dataset (GUMCAD) to calculate HIV incidence among MSM. GUMCAD is a mandatory national reporting system of attendance-based patient-level data, which was set up in all GUM clinics in England in 2008 (122). The database contains socio-demographic (age group, ethnicity, sexual orientation, region of residence, country of birth), HIV testing and STI screening and diagnosis information for all patients at all attendances. Data are anonymised and patients can be longitudinally followed within clinics using a unique identification number specific to the clinic. However, attendances between clinics cannot be captured within GUMCAD.

As the database is attendance-based, all services and treatment offered will be recorded for each attendance. Consequently, a single attendance could have multiple clinical records (e.g. chlamydia test, gonorrhoea test, chlamydia diagnosis).

3.2.2 Definitions

3.2.2.1 HIV negative MSM among GUM clinic attendees

I defined MSM as men who have ever self-reported having had sex with another man. GUMCAD captures information on sexual orientation at every attendance to a GUM clinic and allows the response to change, which it may do over time due to disclosure or change of sexual identity. If a male had at any attendance disclosed their sexual orientation to be homosexual or bisexual, they and all their records, including those pertaining to periods of heterosexual activity (or where sexual orientation was unknown), were included in this analysis. In terms of hierarchy of risk, having male-male sexual contact was considered to be the highest risk for HIV acquisition and since the reason for change in sexual

orientation is not documented, this approach was considered to be the most appropriate.

I determined the HIV status of the individual at their first attendance to the GUM clinic in 2012 using the retrospective and subsequent clinical records (if an individual had any). MSM were defined as HIV negative or not known to be HIV positive i) if they had no prior record of a HIV diagnosis or of a HIV-related care attendance or if ii) they had a negative HIV test result at the first attendance, which was inferred if there was no record of a HIV diagnosis on the day of the test. If there was no HIV negative test at this attendance but evidence at a later attendance of a negative HIV test they were included in the study population.

3.2.2.2 Repeat testing MSM

GUMCAD only collects information on whether an individual tested for HIV and a HIV diagnosis. No further information is collected on the recency of the infection for those diagnosed with HIV. It is not possible to determine from the records whether the HIV diagnosis pertains to a long standing infection or a recent infection. To establish whether a diagnosis was also a new infection my study population was further restricted to MSM who tested for HIV at least twice in a one year period (i.e. men who were repeat testers). To be a repeat tester and included in the incidence analyses, the individual had to have at least two HIV test codes recorded in GUMCAD that were more than 42 days apart but within a year at the same clinic.

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Any HIV test within 42 days of the first one was considered to belong to the same episode as the first test. All clinical episodes are defined as lasting 42 days in GUMCAD; therefore any re-attendance for the same condition within 42 days of

the first attendance is considered to be the same episode. A 42 day rule is used as a pragmatic approach for surveillance and is applied to all counts of HIV/STI tests and diagnoses in GUMCAD. It limits double-counting that occurs due to disparate dates reported for tests, diagnoses and treatments.

3.2.2.3 HIV seroconversion

A HIV diagnosis occurring within a year of the last HIV negative test was defined as a HIV seroconversion or an incident HIV diagnosis. Repeat testing annually is in line with HIV testing guidelines which recommends, at a minimum, annual HIV testing for MSM (47).

3.2.2.4 STI diagnoses by type and time period

In order to examine the relationship between previous or current STIs and HIV acquisition, three different STI diagnosis groups were created from the GUMCAD records.

- An acute STI diagnosis was a record of any of the following: Chlamydia, gonorrhoea, syphilis (primary, secondary and early latent), lymphogranuloma venerum (LGV), non-specific genital infection (NSGI), chancroid, first episode of genital warts and genital herpes and donovanosis.
- A bacterial STI was a record of any of the above except genital warts and herpes.
- A rectal bacterial STI included a diagnosis of gonorrhoea, chlamydia, NSGI and LGV made at the rectal site. Site-specific reporting codes were introduced in 2011 and rely on clinics performing site-specific testing. The coding is used in a hierarchy so that someone diagnosed with an infection

at all three sites (rectal, genital, pharyngeal) would only be reported as rectal.

Two different time periods were used to refer to the STI diagnoses:

- Clinical history pertained to STI diagnoses in the year prior to the first attendance in 2012
- STI diagnoses made at the first attendance in 2012

Specific information on the type of diagnostic test is not collected in GUMCAD and will be different from clinic to clinic. However, everyone who is tested for STIs is recommended to have the most accurate diagnostic test in its class and according to national guidelines (123). All laboratories performing testing should also be properly accredited (Clinical Pathology Association/United Kingdom Accreditation Services accredited).

3.2.3 Survival analysis

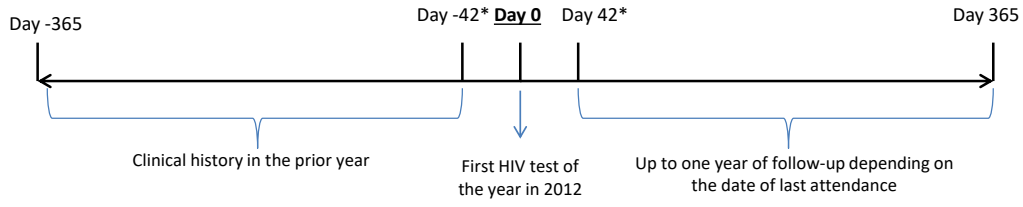
As the outcome of interest in this analysis was time until acquisition of HIV, I employed survival analysis methods to measure annual HIV incidence. Survival analysis is relatively easy to repeat once the data management has been conducted. Annual HIV incidence was defined as the *total number of HIV seroconversions divided by total follow-up time at risk in a one year period* for the cohort.

HIV seroconversions were calculated as above (3.2.2.3). The total follow-up time at risk was calculated separately for each individual in the cohort and then summed. Individuals were at risk until they either seroconverted or could no longer be followed up, in which case, men did not experience the outcome of

interest (HIV seroconversion). For these latter individuals, the incomplete observation of failure time (time to seroconversion) is known as right censoring. It occurred for two reasons: i) an open cohort approach where individuals could enter and leave the cohort at any time over a one year period and ii) follow-up was only possible until the end of available data. I have assumed for this analysis that censoring was unrelated to the outcome which is conceivable as men probably move between clinics due to clinic choice and convenience rather than leave the cohort but this movement cannot be captured in GUMCAD.

To determine an individual's follow-up time, I followed MSM from the date of their earliest negative HIV test in 2012 for up to one year until they either seroconverted or for those MSM who remained HIV negative until their last attendance in the 12 months after their first test (Figure 3.1). As a result of the different start and end times, each individual had variable follow-up lengths. The date of last attendance was chosen because we could ascertain HIV status from GUMCAD; an absence of a test or diagnosis would highly suggest the individual is negative.

Figure 3.1 Schematic of HIV incidence calculations



*All HIV tests 42 days before or after the first attendance (i.e. Day 0) are part of the same clinical episode and attributed to Day 0. Where relevant, subsequent HIV tests also 42 days apart.

HIV incidence was expressed per 100 person-years (py) with 95% confidence intervals (CI). Once data management was complete, incidence was calculated

in STATA (STATA commands: ‘stset’ and ‘strate’), overall and for sub-groups including by demographic characteristics and available clinical history (section 5.5). Clinical history included STI diagnoses as defined above and having prior HIV tests and/or sexual health screens.

The Kaplan-Meier method was used to graphically investigate the cumulative incidence, which is given by: (1-*S*(t) , where *S*(t) is the survivor function and is a measure of the probability of surviving until at least time *t*). The cumulative incidence (STATA command: ‘sts graph’) is the probability of becoming infected during follow-up and was expressed as a percentage with 95%CI.

3.2.4 Clinical and demographic risk factors for HIV acquisition

To identify risk factors for HIV acquisition, I used a two-step approach where in the first step (univariate analyses) associations between individual characteristics and the outcome (HIV incidence) were investigated and the p value used to determine if there was a statistical association. In the second step, I included variables that were associated in a multivariable regression analysis, which is a technique that examines the effect on the outcome variable when any one of the independent variables is varied while the other independent variables are fixed. The results will determine statistical significance and provide an estimate of the size of the effect.

In univariate analyses, associations between HIV incidence and clinical and demographic characteristics were evaluated using the log-rank test. Demographic variables included age group (15-24, 25-34, 35-49 and 50+ years) and ethnicity (white, black, other and unknown). The log-rank test compares the hazard functions (where the hazard function is defined as the instantaneous

event rate at time *t*, i.e. it is the failure rate at time *t* among individuals who are still at risk at time *t*) of the two groups at each observed event time and is considered an appropriate test for survival data that have been right censored. If the null hypothesis, which states that the survival curves of the two groups are the same, is true the p value of the association between the characteristic and outcome would be greater than 0.05 and not considered statistically significant.

Variables with marginal associations ($p<0.1$) in univariate analyses were included in multivariable Cox proportional hazards models (STATA command: 'stcox'). The Cox model is the simplest model as it does not make any assumptions about the shape of the underlying hazards; only that the hazards for individuals with different values of the independent variables are proportional over follow-up time. It is preferable to Poisson regression, which assumes a constant hazard over time that is unlikely to be the case for HIV risk. In multivariable regression, a manual stepwise backward approach was used to sequentially remove variables not significant ($p>0.05$) in order of the p value magnitude. The statistical significance of explanatory variables was assessed using the likelihood ratio test before removal (STATA command: 'lrtest') to arrive at the final model. Adjusted hazard ratios (aHR) and 95%CI were reported for risk factors significantly associated with HIV acquisition ($p<0.05$ using the likelihood ratio test) (section 5.6).

Not all MSM had attended the same clinic in the prior year and these men had no clinical history. Regression models would treat these men as having missing data for these variables. However, they did not have missing information and rather than exclude these MSM from risk factor analyses, I combined the MSM without an attendance in the prior year with those who did attend but were not diagnosed

with a STI or did not have a HIV test. This assumes that if they did not attend it was because they did not require a STI screen or HIV test. To lend support to this assumption, HIV incidence did not differ between the two groups (those not attending and those attending but without being tested or diagnosed with a STI), suggesting similar HIV risk.

The relative contribution of each predictive factor was determined by calculating population attributable risk (PAR) for HIV infection, which combines the adjusted HR and the proportion of repeat testers with the variable using the formula: proportion(HR-1)/proportion(HR-1)+1 (124).

3.2.5 Sensitivity analyses

A sensitivity analysis is a repeat of the primary analysis substituting alternative decisions for assumptions or decisions that could seem arbitrary. The analyses were conducted to better understand the degree of uncertainty in the outputs and the inputs that contributed to that uncertainty. I performed four sensitivity analyses on the original HIV incidence methodology to test the robustness of the method and the incidence estimates obtained. The first three analyses impacted the follow-up time and the fourth looked at a sub-sample of MSM with attendance history.

3.2.5.1 Mid-point for seroconversion

Although the date of HIV diagnosis can be captured in datasets, the date of HIV acquisition cannot be directly observed and the event is known only to have occurred at some time point between the last negative and first positive test. The primary analysis, which follows seroconverters from the date of the last HIV negative test to the date of the first HIV positive test, assumes that an individual

seroconverts the day of his HIV diagnosis. Since this is highly unlikely I examined the uncertainty around this measure by using the mid-point between the negative and positive test as the date of seroconversion and the end date for those diagnosed.

I identified the start date (the first negative HIV test) and the end date (date of HIV diagnosis) and then calculated the mid-point of the follow-up time and used that as the new end date. For example, if an individual entered the analysis on 01 July 2012 and was diagnosed on 31 December 2012, the follow-up time is 184 days and the midpoint is 92 days which equates to a date of 30 September 2012.This method has previously been discussed and used in other cohorts (125, 126) (results in section 5.7.1).

3.2.5.2 Right censoring at thirteen months after HIV negative test

Although testing guidelines recommend annual HIV testing, it is highly unlikely men repeat test exactly every year. To account for this, I allowed an extra month of follow-up so that more MSM had the opportunity to return for a HIV test. I employed the same methodology as the primary analysis except men were followed from the date of their earliest HIV test for up to one year and one month until they either seroconverted or until their last attendance in the 13 month period after their first test (results in section 5.7.2).

3.2.5.3 Right censoring at 365 days after first HIV negative test

If we presume that men would have attended the clinic for another HIV test if there had been any further risk after the last attendance date (i.e. censoring was related to outcome), we can also assume that men remained HIV negative between their last attendance and the end of the year of follow-up. I, therefore,

right censored men who did not seroconvert at exactly 365 days after their first HIV negative test and not at their last attendance date (i.e. all HIV negative MSM received 365 days of follow-up). This change did not impact follow-up for those who seroconverted (results in section 5.7.3).

3.2.5.4 HIV incidence and risk factors among MSM with clinical history

The population of MSM was restricted to those that had at least one attendance record in the 365 days prior to the first attendance in 2012 (i.e. had clinical history). The HIV incidence and risk factor analyses were repeated in this sub-population to understand if there were any differences with all repeat testers (results in section 5.7.4).

3.2.6 Comparison of repeat and non-repeat testers

The population of HIV negative repeat testers (i.e. MSM included in HIV incidence analyses) were compared to MSM who did not have two HIV tests in one year but were not known to be HIV positive ('non-repeat testers'). I compared the demographic profile, clinical history and clinical outcomes at the first attendance in 2012 of the two populations and used the chi-squared test to determine significant differences ($p<0.05$) (results in section 5.8).

3.2.7 Role of candidate

At the time of this piece of work, I was already using GUMCAD to better understand the MSM population attending GUM clinics and it was my idea to use the data source to measure incidence. The final method was developed with input from my PHE supervisors. I conducted the analysis and the do file I used in

STATA was independently checked by a GUMCAD scientist for additional rigour. I led on the interpretation of the data, however all my supervisors fed into this process especially when I published the work in a peer-reviewed journal.

3.3 Behavioural study among HIV negative MSM attending GUM clinics

Having described what can be learnt on HIV incidence and risk factors from existing data sources, here I describe a study that collected standardised behavioural data from clinics to determine the sexual behavioural profile of MSM attending GUM and identify behavioural predictors of HIV acquisition.

3.3.1 Development of behavioural questionnaire

PHE in collaboration with a group of behavioural experts met in 2011 to develop a key set of questions that could be routinely asked in clinical settings. The questions were drawn from existing questionnaires and studies and were questions that were likely to already be collected in clinics. They, therefore, had the advantage of already being validated. These studies included: EMIS (European MSM Internet Survey), NATSAL, GMSHS and the Gym Survey. The behavioural questionnaire was tested on a panel of MSM in a Terrance Higgins Trust focus group.

Once the questions were finalised, a paper questionnaire was developed with the publications team at PHE. The finalised questionnaire is included in Appendix 3 and included questions on total sexual partners, partners with whom CRAI and condomless insertive anal intercourse (CIAI) was practiced. The rationale for the inclusion of each question is described in Box 3-1.

Box 3-1 Rationale for each question included in sexual behavioural questionnaire

Question 1 and 1a: Total numbers of sexual partners and numbers in the last three months that are new are documented markers of high risk behaviour among MSM. The questions give an overview of risky behaviour in the population.

Question 2 and 3 (including sub-questions): Questions 2 and 3 focus on seroconcordant (same HIV status) and serodiscordant (different HIV status) CRAI and CIAI in the last three months. A question on the number of HIV negative partners was not included as this number can be deduced from the other answers. Questions 2 and 3 will estimate the prevalence of the seroadaptive behaviours (e.g. serosorting) to determine the extent to which men adopt these HIV risk reduction strategies. This information has not previously been systematically collected from clinic attending MSM.

Question 4, 4a and b: Behaviours in the last 3 months may miss the last act of CRAI and for this reason these questions were included. The reasons for not using a condom at the last CRAI act were considered useful for clinicians as it could lead to a discussion on condom use and facilitate condom promotion. The new sexual history taking guidelines recommend assessing condom use at the last sexual contact including its correct use among all clinic attendees being assessed for STIs (127). The question on reasons for not using a condom was omitted from the questionnaire of one of the study sites (Manchester), because they do not routinely collect this when taking sexual history in their clinic.

Questions 5-9: These questions on previous clinic attendance, HIV testing and STI history were to be completed by patients who had **never** attended the clinic before. The purpose of these questions was to gather baseline data on men for whom there was no previous clinical history in GUMCAD. GUMCAD cannot link individuals between clinics so

unless an individual has previously attended the same clinic, no clinical history information will be available for that individual.

In addition to the behavioural questions, the date of completion (i.e. the attendance date) and the individual's local clinic identification number was also included to facilitate identification of the individual's clinical records in GUMCAD. It was essential to link the behaviours to biological surveillance as it was part of this research's objectives to provide a more comprehensive description of the HIV epidemic in GUM attending MSM.

Cognitive semi-structured interviews were conducted at Mortimer Market Clinic (MMC) and Archway Clinic, London, with MSM not known to be HIV positive. The purpose of these interviews was to assess men's understanding of the questions, ensure the language was appropriate and assess how well men recalled information related to the previous three months. Men who did not have sufficient English speaking and reading skills were excluded from the study. A purposive sampling strategy was used to recruit up to 10 men to ensure essential characteristics that are anticipated to affect the responses were covered. These included broad age bands, ethnicity, sexual behaviours and first time attendance at the clinic. A sampling matrix was developed to guide recruitment of men for each quota (Table 3.1).

Table 3.1 Sampling matrix to guide recruitment of HIV negative MSM

	CRAI last 3 months	CIAI last 3 months	Ever CRAI
Age			
15-24	1	1	2
25-34	1	1	2
35-49	1	1	2
50+	1	1	2

Ethnicity:			
White	2	2	4
Black	1-2	1-2	2
Other	1-2	1-2	2
Attendance:			
First time	4	4	5
Attended before	1-2	1-2	3
	Total: 5-7	**Total: 5-7**	**Total: 8**

Ethical approval for the cognitive interviews was obtained from the NRES Committee London - City Road & Hampstead (REC reference No:13/LO/0475). I also obtained a research passport form that gave me clearance to conduct research with patients attending NHS Camden sites including MMC and Archway.

I spent up to one day a week between July and August 2013 at the men's sexual health clinic at MMC. I also spent 1 day a week at Archway during September. At the beginning of the day and in the afternoon when the clinic shifts changed, I individually met the health advisors, nurses and clinicians and briefed them on the study. They were also given the patient information sheet, which contained information on the study, its purpose and the risks and benefits of participating, (Appendix 4) to hand out to MSM interested in participating. Participants were identified as MSM and HIV negative by one of the clinical care team during the routine clinical consultation and asked if they were willing to participate in qualitative interviews about their recent sexual history. Interested men were given more information about the study by me before verbal consent was taken. I screened the individual and if they met the quota requirements, we arranged a mutually convenient date and time for the interview at the clinic (either straightaway or at another time). This initial process did not lengthen the men's clinic visit beyond 10 minutes and was often conducted while the patient was waiting for tests.

The interview was conducted in a private room available in the building. At the interview, prior to starting, the participant was given time to ask questions and complete the written consent form (Appendix 4). A copy of the form was given to the individual. A topic guide, which had been developed to aid the discussion and cover the themes of interpretability and recall, was used during the interview (Appendix 4). Men were given the sexual behavioural questionnaire and asked to complete it while thinking out loud the thought processes that brought them to their answer. Prompt questions were used where clarification was required or to address key issues that were not covered during the think-a-loud process. Participants were encouraged to complete all the questions; however they could also avoid those that they found uncomfortable or did not want to answer. At the end of the interview the participant was asked a few structured questions that covered the general aspects of the questionnaire such as its length, language and overall acceptability. The interview was audio-recorded unless the participant requested that it was not.

The interview lasted approximately 30 minutes to 1 hour, at the end of which the participant was compensated for their time with a £20 gift voucher. After each interview, I made brief notes on a blank master questionnaire. The same master questionnaire was used for notes across all the respondents. The respondents were differentiated using unique ID numbers that was also linked to the file number of their audio-interview. No identifying information beyond that collected for the screening questionnaire was gathered from men.

In total, 10 HIV negative/not known to be positive MSM were recruited to participate and of these seven were interviewed. The remainder did not attend

their interview date. The demographic and sexual behavioural breakdown of interviewed men is presented in Table 3.2.

Table 3.2 Demographic and sexual behavioural characteristics of MSM interviewed at MMC and Archway

Characteristic		Sample
Age:	15-24	1
	25-34	3
	35-49	3
	50+	0
Ethnicity:	White	5
	Black	0
	Other	2
Attendance:	First time	6
	Attended before	1
Sexual behaviour:	CRAI last 3 months	4
	CIAI last 3 months	6
	Ever CRAI	7
Total		**7**

*African, Caribbean, other ** Asian, Chinese, mixed and other

There was variation in recall of total partner numbers in the last three months. Men with few partners remembered the exact number, whereas those with more than 10 guessed. Therefore asking for an exact number of partners could be misleading when interpreting the findings. There was some confusion in relation to the question on how many of the total partners were “new”. Men were unsure how to interpret “new” and what time period it related to, that is, whether the question asked about new partners in the last three months or “ever”. The question would have been better rephrased as “how many of all your partners in the last 3 months have you never had sex with before?”

When asked the HIV status of their recent partners, a common theme to emerge was the trust placed on regular partners. Regular partners were assumed to be HIV negative either because the partner was not asked or because they were

told by their partner they were negative. Even with regular partners, men felt HIV testing was too private and personal a matter to be done with the partner. Men felt that HIV status was too personal to always broach, especially with casual encounters. Therefore, in general, men did not know or were assuming the HIV status of their partner.

When men were asked to consider how they determine the numbers of receptive and insertive partners, some men reported guessing the numbers in each category based on their current preferences. These preferences changed over time and depended on other factors such as how they were feeling and who the partner was. For the rest, they were clear on the numbers in each group especially for those with low partner numbers.

A number of options were given in the questionnaire to understand why a condom was not used at the last condomless sex act. The options were found to be appropriate and comprehensive. However, men did report not understanding the word “dipping” (penetration followed by rapid withdrawal). Men found it embarrassing and not a word that they had come across. They would have preferred a clearer definition e.g. non-penetrative sex.

All men reported the questionnaire was appropriate and acceptable. Since MSM are already asked questions related to their sexual behaviour when they attend a GUM clinic, the questionnaire was not intrusive, was not too long and the language was generally simple to understand. One man suggested the questions could be better ordered where the more personal questions that might suggest you or your partner could be HIV positive should come towards the end. This

would allow the individual time to become more comfortable about being questioned on recent sexual behaviour.

All men but one reported their responses would not differ between the self-completed questionnaire and face to face questioning by healthcare staff because they are used to answering sexual behavioural questions in GUM clinics. One man reported that he was more likely to under-report unsafe sexual behaviours in a questionnaire as it is easier to convince yourself that any unsafe sexual events did not occur whereas a conversation would help highlight the problem.

Due to logistical issues, I was unable to conduct the cognitive interviews prior to the questionnaire being implemented and unable to make any changes to the questionnaire in light of the interviews. I still conducted the interviews because should the questionnaire become more widely implemented in the future the results of the interviews could still be beneficial at that stage and the necessary changes could be made then. The results of the interviews could also help interpret the findings of the study.

3.3.2 Definitions

3.3.2.1 Baseline attendance

The baseline attendance was the clinic attendance where the behavioural questionnaire was completed during the study period.

3.3.2.2 STI definitions

STI diagnoses at the baseline attendance are referred to as STIs at baseline and those in the previous year were those diagnosed in the year prior to the baseline attendance. The type of STI diagnosis groups are described in 2.2.2.4. Incident HIV infections were those that were diagnosed after the baseline attendance.

3.3.2.3 Six hierarchical seroadaptive behaviours

The reported behaviours in the previous three months to the attendance were categorised sequentially into six mutually exclusive hierarchical seroadaptive behaviour categories (i.e. behavioural categories that use HIV status to inform sexual decisions), with no CAI being the least risky and no risk reduction strategy the most risky:

1. No CAI – men reported having no condomless receptive or insertive anal intercourse partners
2. Monogamy – men reported only one partner, who was HIV negative and with whom they reported CAI (receptive or insertive)
3. Top only – men only reported CAI as the insertive partner with one or more partners (if only one partner, that partner was HIV positive/or unknown status)
4. Serosorting - men reported CAI (receptive or insertive) only with partners believed to be HIV negative
5. Seropositioning – men only reported CIAI with HIV positive and/or unknown status partners, while CRAI was always with HIV negative partners
6. No risk reduction strategy - men reported CRAI with HIV positive and/or unknown status partners

These categories have been modified from previous work in the US (128). The six categories were collapsed into three for the purposes of univariate and multivariable analyses due to small cell sizes in some groups: i) Safer sex (no CAI and monogamy) ii) Seroadaptation (top only, serosorting, seropositioning) iii) No risk reduction strategy.

3.3.3 Data collection

3.3.3.1 Study design and implementation

A cross-sectional study design was employed to survey HIV negative MSM; therefore sexual behaviour data were collected from men at one time point. These data were subsequently linked to GUMCAD to prospectively follow-up individuals using a cohort study design and determine clinical outcomes including HIV incidence.

MSM who were i) not known to be HIV positive and ii) attending one of the participating GUM clinics were asked to participate in the behavioural study.

PHE had a working relationship with a number of GUM clinics in England in 2011, which conducted enhanced surveillance and participated in research studies. These sentinel GUM clinics were invited to participate in the behavioural monitoring study. The final sites were selected based on i) number of HIV negative MSM attending the clinic per year, ii) geographical representation of inside and outside London iii) feasibility of and interest in participating. Five sites participated (Table 3.3). MSM recruited from these five GUM clinics are unlikely to be reflective of all MSM attending GUM. In particular MSM attending Dean Street and MMC are unlikely to be representative. Dean Street clinic accounted

for 18% of new HIV diagnoses among MSM in London and MMC another 15% in 2009 (personal communication, Rajani Raghu).

Table 3.3 Numbers of HIV negative MSM attending between 2009-2011

Clinic name	Number of attendances	Number MSM/quarter
Manchester Royal Infirmary (O)	7,000	590
Royal Sussex* (O)	13,200	1,100
Mortimer Market Centre (MMC) (I)	17,800	1,500
Dean Street (I)	37,700	3,140
John Hunter (I)	6,500	540
Total	**82,200**	**6,870**

I=inside London, O=outside
*Claude Nicol centre at Royal Sussex was recruited

I visited each of the sites prior to initiation of the study and presented the study aims and rationale to the clinical team and began discussions on the logistics of implementing the study. To ensure the study was fully integrated into routine care and successfully run, a main contact person was established for each clinic and each clinic decided for themselves i) the length of the study, ii) the starting date, iii) whether MSM would self-complete the paper forms or complete them with the clinician and iv) for men self-completing, the most appropriate point at which to complete the form. Although clinics could opt for self-completion of the questionnaire, they were encouraged to run the study as staff-led because in routine practice, clinical staff take a sexual history during the consultation and the study aimed to mirror clinical practice where possible.

All clinics opted to run the study for three months in the first instance. It was later extended to six months due to poor recruitment rates. Implementation of the study was staggered with Manchester starting in September 2012, the three London clinics in October and Royal Sussex in November 2012. The staggered

approach allowed London clinics to complete other on-going studies. All clinics except Manchester opted for self-completion of the questionnaire because of the potential impact on consultation times. This was a particular concern for larger clinics such as Dean St, which see large numbers of HIV negative MSM. The wording of Manchester's questionnaire was modified so the clinician could read the questions to the patient. In the other clinics, different approaches were initially taken to implement the questionnaire e.g. receptionists asked men to complete the questionnaire while waiting for the appointment or leaving questionnaires in consultation rooms so staff could give them to men once it was established they met the study criteria. Both approaches yielded low response rates as reception staff were reluctant to hand out a sexual behavioural questionnaire and clinical staff forgot to hand out the forms or the questionnaires were moved/removed from the rooms. As a result, clinics modified the delivery so that receptionists placed the questionnaire in all men's folder and clinical staff invited eligible men to complete the questionnaire during the consultation. In Manchester, the clinician simultaneously completed the questionnaire and the clinic's own sexual history proforma.

In addition to providing sites with a behavioural questionnaire, all clinics opting for self-completion were also given patient information sheets should the patient request extra information on the study (Appendix 5). The sheet detailed the background, purpose of the study and the benefits and risks to the individual. Regardless of the completion method, the staff member filled in the patient ID number and attendance date. The patient ID is a unique identification number specific to the patient in that clinic and allows an individual to be tracked over time in the clinic.

Completion of the questionnaire required no more than 5 minutes. A collection box was set up for the questionnaires. Men who declined to participate were asked to leave the empty behavioural questionnaire in the collection box so uptake and acceptability could be estimated. Clinics were provided pre-paid labels so questionnaires could regularly be batch returned to PHE.

After three months, each of the clinics was re-visited to present preliminary site-specific results and to encourage an improvement in recruitment. After extension, the study continued till end of March 2013 for all clinics except Royal Sussex, which chose to continue till end of April 2013 as they wanted more time to improve the number of questionnaires returned.

3.3.3.2 Sample size

The primary outcome of interest in this study was HIV incidence and the research examined whether incidence differed among those who engaged in CRAI with partners and those that did not. Engagement in CRAI has the highest estimated per-act probability of acquiring HIV (138/10,000 exposures to an infected source) associated with any sexual exposure (129). The null hypothesis states there is no difference in HIV incidence among those that do and do not engage in CRAI. A sample size calculation was undertaken to calculate the size of the population required to test this hypothesis.

There are four important components of sample size calculations: type 1 error (α), power, the probability of the outcome in the unexposed group and the relative risk of the outcome. The type 1 error is the probability of detecting a statistically significant difference when there is no difference (false positive). The

power is the probability of detecting a statistically significant difference when a difference does exist.

HIV incidence in the unexposed group (the group that did not engage in CRAI) was estimated to be population incidence, which was calculated as 2% from the secondary data analysis of GUMCAD (130). The results of the systematic literature review (section 4.4.5) indicated that the relative risk of HIV among those engaging in CRAI is approximately four. As convention, I set α at 0.05 (that is, a less than 5% chance of making a false positive conclusion) and power at 80% (an 80% chance of detecting a difference between the two populations when there is a real difference).

Based on these parameters, a total sample size of 480 (with 240 in each group) would be required to detect a difference in HIV incidence of 6% between the two groups (2% in unexposed vs 8% in exposed). This calculation was undertaken in STATA using the 'sampsi' command.

Approximately 2,300 MSM not known to be HIV positive were anticipated to attend the study clinics each month based on the quarterly GUMCAD returns for 2009-2011 (Table 3.3). Assuming the clinics participate, on average, for 6 months, approximately 13,600 men will be eligible. Assuming a response rate of 15%-30%, we expect between 2,040-4,080 behavioural questionnaires to be completed during the study. A recent notes audit of MSM attending a subset of GUM clinics in England identified that 10% of HIV negative MSM reported CRAI in the last 6 months (11). Therefore, there would be sufficient numbers of MSM who engage in CRAI in the last three months as along as the recruitment rate is closer to 30%.

3.3.4 Data management

The returned questionnaires were scanned and validated using scanning software (Cardiff Teleform v10 Information Capture System). The software removed the need for double data entry and reduced the time required at this stage of data management. A data dictionary and coding scheme was developed to ensure consistent coding during scanning.

Once data were scanned, automated validation checks highlighted any uncertainties in the data that had to be resolved before information could be saved. These uncertainties included checking open text fields and numbers that were not clearly written and/or scanned. These checks covered most the data quality issues; however additional manual checks were performed to further validate the data. For example, for every questionnaire, the patient ID number and date were checked to ensure correct scanning. This was principally important for dates which were not valid or correctly read by the scanning software. Attendance dates were not always completed. I replaced empty date fields with the date the forms were received at PHE as a proxy date. Once the validation process was completed, data were saved in a Microsoft Excel database in a secure drive only available to me. The scanning and validation was conducted every month to allow regular surveillance outputs.

Although substantial validation was conducted in Teleform, the software is not designed to facilitate in depth validation of responses and further cleaning was conducted in STATA. The Excel database was imported into STATA and a do file was written to conduct this part of the validation. An example of internal validation is a scenario where a man stated having two CRAI partners and then

reported that of these, two were HIV positive and one was of unknown status, these two subsequent responses on partner status were replaced with a missing value (“.”). In all instances where the responses to the sub-questions did not match the overall response or were not valid responses, the response to the overall question was assumed to be correct and the responses to the sub-questions were replaced with a missing value (“.”).

Some data cleaning was also done to improve data completeness. There were a large number of questionnaires where the question on numbers of partners with whom CRAI (question 2) and CIAI (question 3) was practiced was missing. I used information provided for other questions to complete this field where possible. If the numbers of CRAI/CIAI partners that were HIV positive (questions 2a and 3a) and of unknown status (questions 2b and 3b) were completed and were ‘0’, I assumed that the number of CRAI/CIAI partners was also ‘0’ as long as total numbers of partners was not greater than four. This was the chosen cut-off, which may have underestimated the proportion who engaged in CAI as some may have been miscategorised. Further, if either the numbers of partners that were HIV positive or of unknown HIV status was the same as total number of partners, I replaced value of the total number of CRAI/CIAI partners to equal the total number of partners.

At the end of the study, once all the questionnaires were received, scanned, cleaned and validated, the behavioural data were linked to the clinical records held in GUMCAD. This was conducted as a three-step process. In STATA, the clinic name, patient ID and date of attendance from the questionnaires were linked to the equivalent fields in GUMCAD for each individual, using a do file containing the merge and append commands. The GUMCAD data extract from

29th May 2014, which included records from 2008 until the end of the first quarter of 2014, was used for linkage. Through this process, men were linked to their clinical records at the behavioural visit and to all prior and subsequent visits (if there were any).

MSM not matched in the first step, were then matched in the second step. An algorithm was developed in Microsoft Access that used more "fuzzy" criteria (e.g. partial patient id, clinic name and date of attendance) to match these men to GUMCAD. "Fuzzy" matching refers to matching that is not perfect and where allowances are made to take into account errors in reporting patient id numbers. The same GUMCAD extract with the three matching fields was imported into Access with the three matching fields for men who could not be matched. Two queries were created that matched men who had similar but not identical patient IDs, where the only difference was the addition of characters or numbers at the beginning or end of the ID. For example, an individual recorded as "MMC223344" in the behavioural data and as "223344" in the GUMCAD data attending the same clinic would be matched through these queries. Fuzzy matches were sense-checked before being accepted. Once this was completed, men who now had new patient IDs were matched again to GUMCAD as in the first step to extract all their records. No further fuzzy or manual matching was attempted for men who still remained unmatched.

In the final step, the behavioural records were combined with the matched clinical records to produce an overall STATA database that included all attendances at the study site between 2008 and the first quarter of 2014 and all the behavioural information for the visit where a questionnaire was also completed (baseline attendance). In order to conduct this, the new patient ids identified from fuzzy

matching were updated in the behavioural database and the database was merged with the clinical matched records in STATA. Each individual's clinical records contained the variables age, ethnicity, country of birth, residence and diagnosis and clinic service codes (as in Table 3.4). This table was then ready for data analysis. For a minority of men who could be linked on patient id but not attendance date, I used the next nearest attendance data within 42 days of the behavioural attendance as the alternative behavioural attendance date. I considered this a sensible approach as I knew the attendance dates were not always accurately reported.

Table 3.4 Example of a combined GUMCAD and sexual behavioural information table (final dataset)

Visit number	Clinic name	Patient ID	Region of residence	Age	STI_ code*	Attendance date	Numbers sex	New partners
1	MMC	RRR3546	TMX	35	S2	23/09/2012	.	.
2	MMC	RRR3546	TMX	35	P2	29/01/2013	10	30
3	MMC	RRR3546	TMX	36	D3	15/03/2013	5	10
4	MMC	RRR3546	TMX	36	C11A	15/03/2013	5	10
	Visit number 2 is the first visit at which a behavioural questionnaire was completed, which is why visit 1 has no behavioural information. Visit 1 is included because **all** records matching the patient ID and clinic name of Visit 2 are extracted from GUMCAD. At the two subsequent attendances, a behavioural questionnaires was also completed							

*STI code refers to the SHAPPT codes used in clinics to assign diagnoses and clinical services provided to patients

The behavioural dataset and final dataset were securely held in the same drive. The database was additionally password protected. Paper questionnaires were securely locked with access limited to the team. Data collection, storage and use were Caldicott compliant.

3.3.5 Statistical analyses

2.1.1.1 Acceptability of the study

I measured the acceptability of the study by calculating recruitment rates where the denominator was the number of HIV negative MSM attending the participating clinics during the study period as identified from GUMCAD. I also looked at the quality of completed questionnaires by measuring completion rates of each question. These results were conducted by clinic of attendance (results in section 6.4).

3.3.5.1 Prevalence of sexual and seroadaptive behaviours

I present proportions of MSM reporting each behaviour, e.g. the proportion of HIV negative MSM reporting CRAI in the past 3 months and present these

proportions by clinic of attendance, age group and country of birth and ethnicity (results in section 6.9 and 6.10). I present the proportions of MSM categorised into seroadaptive groups. I conducted descriptive analysis of seroadaptive behaviours by available demographic and clinical history data. Age group and a composite variable made up of country of birth and ethnicity were the two demographic variables used. These two variables are correlated and so as to reflect both in multivariable analyses (and subsequent risk prediction models) without including a large number of categories, I combined the two to create five new categories: white UK born, white European, white non-European, non-white UK born and non-white born abroad. Using the three collapsed seroadaptive categories I examined univariate associations between available factors and seroadaptive behaviours using the Chi-squared test (results in section 6.11).

3.3.5.2 New HIV diagnoses at the behavioural attendance

I calculated the proportion of new HIV diagnoses at the baseline attendance. Univariable analyses were conducted to explore associations between demographics, previous clinical history and being diagnosed with HIV (results in section 6.12). Multivariable analyses were not possible due to the small number of endpoints.

3.3.5.3 Incidence of HIV

For men who returned to the same clinic after the behavioural attendance, I conducted prospectively analyses to measure HIV incidence. MSM were followed from the behavioural attendance until the last attendance occurring before the end of March 2014 or until the date of their HIV diagnosis. The methodology used to measure incidence and identify risk factors has been described in 3.2.

Univariable analysis of the associations between clinical and behavioural variables and HIV incidence are presented (results in section 6.13). Multivariable analyses were not possible due to the small number of HIV infection endpoints.

3.3.5.4 Non-response analysis

Men who completed the questionnaire ('recruited men') were compared with those who attended the study clinic during the study period (according to their GUMCAD records) but who did not complete a questionnaire ('not recruited') to determine whether there were any systematic differences between the two groups (results in section 6.14). For example, I explored whether more high risk men participated by comparing prior STI rates and subsequent HIV incidence in recruited and non-recruited men. To achieve this analysis, I created a second STATA database of all HIV negative MSM that attended the five clinics during the study period and created a field to differentiate recruited men from those not recruited.

Due to the low recruitment rate and differences observed between the two groups for the outcome, weighting that involved post-stratification was employed to align the sample to all HIV negative MSM attending the five clinics and account for recruitment bias. I used inverse probability weighting where persons under-represented were given a weight larger than one while those in the over-represented groups were given a weight smaller than one. I weighted the age, ethnic and geographic distribution of my sample to all HIV negative MSM attending the five clinics. For example, if 6% of all HIV negative MSM were aged 15-24, white UK-born and attending a London clinic compared to 4% of the sample, an individual in this category would be assigned a weight of 1.5 (6/4). I conducted weighted analyses for new diagnoses at baseline and HIV incidence.

Both point estimates and the univariable analyses were repeated to account for the weighting. The weighted outputs for are presented separately in the results (results in section 6.14.1). I did not weight all the analyses presented in the chapter because I had not recruited MSM based on any sampling strategy and therefore I did not need to weight in order to account for any potential over-sampling.

I also examined item non-response for the questions on CAI partners. Both these questions had the lowest completion rates so I examined the nature of the missing data (results in section 6.14.2 and appendix 8). I compared the missing values by sub-groups e.g. clinic of attendance, demographics, previous clinical attendance and history and total partner numbers. P values are reported using the Chi-squared test. I also examined whether missing values were related to the outcome because if they are they may be selectively missing, where, for example, individuals not completing information on sexual behaviours could also be more likely to be infected with a STI. In this case data are not missing at random (MNAR) and their values cannot be recovered by other covariates. If there is no association with the outcome and there are systematic differences in the unobserved values of missing data, these data are considered missing at random (MAR) and multiple imputation (MI) would recover the correct distribution of the missing values using the relationship with the observed covariates.

Secondly, I investigated the association of CRAI and CIAI partners, where completed, with the other covariates. Any association between these variables would suggest there was some value in predicting missing values based on other measured covariates. In order to examine these associations I used multinomial logistic regression; number of CRAI/CIAI partners was the dependent categorical

variable and age, ethnicity, clinic of attendance, and other behavioural responses were the independent variables.

3.3.6 Ethics and consent

Ethical approval was not sought for this study. The PHE team argued that this behavioural study aimed to standardise the collection of sexual behavioural data from MSM attending GUM clinics. A clinic audit emphasised these data are collected as normal part of clinical practice (11) and the behavioural questions were developed to be consistent with current practice and were therefore viewed as an extension to public health surveillance of attendees at GUM clinics. In particular, this study was established in response to an urgent public health problem (ongoing HIV transmission among MSM) to better understand risk and improve HIV prevention. Under the guidance published by NRES (http://www.hra.nhs.uk/research-community/before-you-apply/determine-whether-your-study-is-research/), the project was considered to be in the area of 'usual public health practice/surveillance' and not research. Individual clinics also sought guidance from their own Research and Development departments. The view of the Medical Director of the PHE (at the time HPA) had been sought and he concurred that this study constituted public health surveillance, not research. Further, clinics were advised to make the 'Information and the Health Protection Agency' leaflet available to patients who wanted to know how their data would be used. The questionnaire contained some brief information on what the data would be used for and completion of any part of the questionnaire was taken as consent to allow the behavioural information to be used and clinical outcomes followed over time.

3.3.7 Role of candidate

I wrote the study protocol including data management components and I drafted the first version of the questionnaire that would be used to collect the minimum amount of sexual behaviour information. To achieve this I used existing literature and survey questions to identify the questions. Once drafted, I set up a meeting with academic researchers from UCL, LSHTM, City University and MRC Clinical Trials Unit who had a specific interest in sexual behaviour for their input on the questionnaire and to explore whether they believed it could be used to inform an intensified prevention programme including a risk assessment tool. All comments from the group and supervisors were considered, though I decided which comments/changes were to be incorporated into the final version. The Word version of the questionnaire was piloted with colleagues from within the PHE HIV team, which did not lead to any changes. It was also piloted by THT on a panel of HIV negative gay men who suggested inclusion of the terms “bottom, passive” and “top, active” to better describe receptive and insertive anal sex, respectively.

My PHE supervisors invited clinics, on my behalf, to participate in the behavioural study. These clinics were part of PHE’s GUM clinic research group. Of the 13 clinics approached, five were interested in participating. I visited these clinics to discuss and initiate the survey. I undertook day to day management of the study and all the analyses described in this section. Statistical support was sought from a PHE statistician to ensure that the weighting and weighted analyses I performed was correct. My supervisors were involved in providing support in the interpretation of the data and giving feedback on analyses.

I had planned to test the questionnaire formally before implementation and to achieve this I designed, conducted and analysed the cognitive interviews. I obtained NHS ethical approval for the cognitive interviews. However, due to timings, I had to conduct these interviews after the study.

3.4 Risk perception, risk scores and tiered HIV prevention services

This section describes two sets of semi-structured interviews undertaken to better understand what use service providers would have for systematically collected behavioural data and the acceptability of risk assessments and tailored HIV prevention services among MSM. Semi-structured interviews were chosen as they allowed in-depth information to be collected, where participants could influence the topics and unanticipated issues could emerge while also allowing pre-defined themes to be discussed. The approach also allowed the conversation to flow more naturally.

3.4.1 Semi-structured interviews with clinical staff

Four of the five clinics participating in the behavioural study were also asked to participate in the semi-structured interviews. These clinics were: Manchester, Royal Sussex, Dean Street and John Hunter. From each clinic, three GUM staff involved in the study was asked to participate in the interviews. Staff were invited to participate by the clinic lead and participation was voluntary.

Once staff members were identified, a mutually convenient time was agreed for the interview, which was conducted face-to-face in all cases. Prior to initiation of the interview, the purpose and outline of the study was explained to the

interviewee. A topic guide with themes and specific questions was developed to be used as reminders and probes during the interview (see Box 3-2 for key topics and Appendix 6 for full guide). The themes included the challenges and successes of the study and the utility and long term feasibility of behavioural surveillance. The interviews lasted between 30-45 minutes and were audio-recorded.

Box 3-2 Key areas of exploration within the interview topic guide

Key areas to explore:

1. Feasibility of long-term behavioural surveillance: paper questionnaire, self-completion, longitudinal surveys
2. Utility of behavioural surveillance: usage of behavioural data, linkage to clinical outcomes, risk profiling of MSM
3. Risk assessment tool: utility, important features of a tool

3.4.2 Semi-structured interviews with HIV negative MSM

The interviews with service users were conducted in collaboration with a joint UCL and PHE project, called SANTE (http://www.isrctn.com/ISRCTN16738765). SANTE is a mixed methods study to develop and pilot a package of targeted and evidence-based sexual risk reduction interventions for MSM and young people attending GUM clinics. A work package of the project included interviews among MSM to understand current attitudes and approaches to risk assessment and experience of behavioural interventions. The objectives of this work stream and my research overlapped sufficiently to justify a collaborative approach.

I wrote a study protocol to describe how the semi-structured interviews would be conducted among HIV negative MSM and developed a topic guide, the questions

of which were later combined with SANTE questions for MSM. My questions relating to HIV risk-perception, risk scores and tailored HIV prevention services were retained with additional questions on STI risk perception and behavioural interventions included to meet SANTE's objectives (see Box 3-3 for key areas and Appendix 6 for full guide).

Box 3-3 Key areas to explore HIV risk perception and risk assessment for the interview topic guide

Key areas to explore:

1. Reasons for attending the GUM clinic
2. Perception of HIV risk: chances of getting HIV and reasons for beliefs, HIV risk changing over time
3. HIV risk score: attitudes to being given a risk score, effect on service utilisation, negatives, positive
4. Triaged prevention: attitudes to risk triaging, negatives, positives

The other study documents (sampling matrix, patient information sheet and informed consent form) were developed by SANTE researchers Carina King and Maryam Shahmanesh and used for the MSM interviews. The topic guide was piloted with a member of the patient and public involvement group that was set up by SANTE. I had the opportunity to interview him to test the length of the interview, determine the appropriateness of questions and to practice interview technique. At the end the volunteer provided feedback to help improve the questionnaire and the interviewing technique.

A purposive sampling matrix was developed to recruit 20 MSM based on location and age group (Table 3.5). As these interviews were exploratory in nature, up to 20 informants were considered sufficient to explore perceptions in HIV risk and

attitudes to a score and achieve saturation of information. Ten MSM were recruited from Claude Nicol, Brighton and 10 from Mortimer Market Centre and Archway clinics in London. These sites were chosen because they were part of the SANTE project. The inclusion criteria were: i) men who have sex with men and other gay men ii) aged 16 and over, iii) agreed to participate. Men were excluded if they i) did not speak English and ii) declined audio-recording of the interview. The HIV status was not part of the inclusion criteria as it was not relevant for the SANTE project. However, it was anticipated that the majority of men attending these GUM clinics would be HIV negative at the time of their visit.

Table 3.5 Purposive sampling strategy to recruit MSM

Location	Age group (years)	Number
Claude Nicol	16-25	3
	26-50	3
	>50	4
Mortimer Market Centre	16-25	4
	26-50	3
	>50	3

The interviews were split with the SANTE researchers; I recruited MSM from MMC and a SANTE researcher recruited at the Claude Nicol. The interviews were conducted between July and December 2015. When individuals attend the MMC GUM clinic they complete a form on entry which documents their age, gender, sexual orientation and reason for attendance. The reception staff use the information in the form to triage to the most appropriate staff type (e.g. clinician, nurse). I was given permission to view and use the completed forms to identify eligible participants. I approached the eligible individual in the waiting room, explained the broad purpose of the study and provided the information sheet (Appendix 6) to read. As the interview was expected to last between 30-45 minutes, men who were interested were given the choice to be interviewed

immediately (especially if they were waiting for tests or results) or to come back at a mutually convenient time.

At the allocated time, any available private room in the clinic was used. Men were given the opportunity to ask questions, and then finally decide if they wanted to continue. Prior to starting, the participant was asked to complete the written consent form (Appendix 6) and a basic demographic profile sheet that collected information on age, ethnic group and self-identified sexual orientation (Appendix 6). Participants were informed the interviews would be audio-recorded and direct quotations may be used in the reports and publications but that their identity would remain anonymous at all times. At the end of the interview the participant was offered a £20 voucher as a thank you.

3.4.3 Data Management

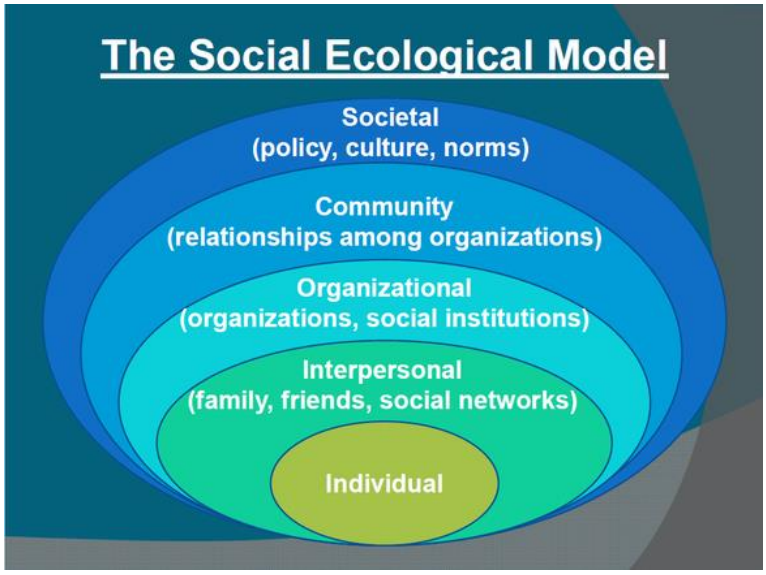
No patient identifiable information was collected during any of the service user or provider interviews. The information collected was securely held at the HIV & STI department and the audio files were securely stored on departmental drives. The audio-recorded files were transcribed verbatim by an external agency. The notes and recorded files were kept securely locked with access limited to team members. Paper records and the electronic files were only kept until the end of the study. After completion of transcription, analysis and write-up, the files were destroyed.

3.4.4 Data Analysis

There are several ways that behaviours could be defined and conceptualised. A number of theories focus on the individual as the centre of behaviour with external factors having an impact to a certain extent. However, it was likely that

risk perception would be based on behaviours that would not exist in isolation to wider determinants such as social networks so the adoption of theories based on the individual could underestimate the impact of social contexts on behaviours. Therefore, I chose a conceptual framework that moved away from the individual and allowed greater focus on the individual and the environment. Specifically, I adopted the social ecological model (SEM) (131) (Figure 3.2) as a theoretical framework for the data analysis of risk perception. The SEM operates at multiple levels and recognises the complex and inter-related interactions an individual has with different levels of a population. The SEM as a framework facilitated an understanding of the multifaceted effects of factors that might affect behaviours and subsequent risk perception of HIV.

Figure 3.2 Social Ecological Model*



*Source of image: http://bullypreventiontoolkit.weebly.com/what-is-prevention.html

The transcripts were analysed using a thematic analysis based on the Framework approach (132). This approach allows analysis to be based on predefined themes and allows new themes to emerge from the accounts of the

research participants. The process synthesises the interviews into a thematic matrix. The steps I followed using this approach were as follows: 1) familiarisation with the data through reading the transcripts and listening to the audio files 2) developing a thematic framework, which includes developing codes 3) coding the transcripts according to the framework; this was an iterative process as more data were analysed the framework was modified 4) and finally once the data were fully coded into themes and sub-themes, a descriptive analysis was conducted (results in section 7.3 and 7.4). The approach also allows detailed between and within case analysis. Data management and analysis was conducted using Microsoft Excel (version 10). The same process was followed for both sets of interviews.

The transcripts from the service user interviews were independently analysed by a second researcher from the SANTE project. The themes from these interviews were corroborated with the researcher and any differences were discussed before final themes were agreed on.

3.4.5 Ethics

I did not obtain ethical approval for the semi-structured interviews with clinical staff as participation was considered part of their professional role. Ethical and R&D approval for the interviews with service users was obtained by the SANTE team from the London-Westminster NRES Committee (REC reference No:15/LO/0690) and UCL (Ref: 14/0835). I also obtained a research passport form that gave me clearance to conduct research with patients attending the two participating sites.

3.4.6 Role of candidate

There were two sets of qualitative interviews that I performed. For the first, my academic supervisors suggested I conduct semi-structured interviews with key clinical staff to explore the utility of collecting behavioural data. I designed the topic guide, which was reviewed by supervisors and adapted accordingly. I recruited interviewees based on who was willing to be interviewed, conducted the interviews and analysed and interpreted the results.

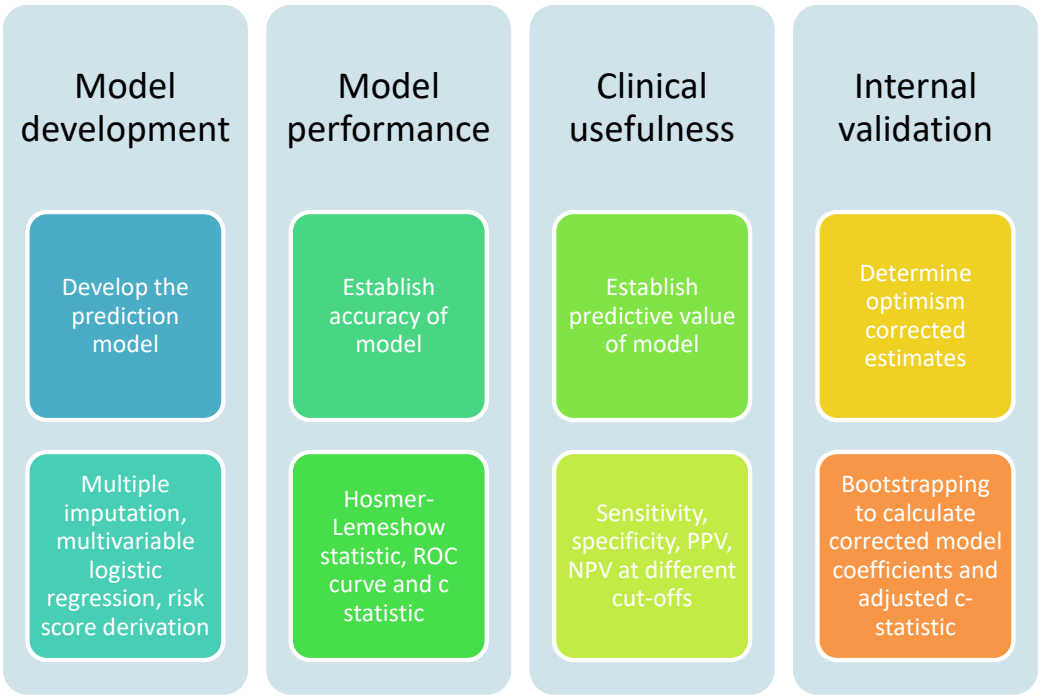
The second set of interviews was conducted to gain the service user perspective on providing sexual behavioural data and being risk assessed. I conceived the idea and content of the semi-structured interviews with MSM. I was particularly interested in understanding risk perception among MSM. I developed the protocol and topic guide, with review from my supervisors. However, my UCL supervisors realised another similar project was ongoing (SANTE) within the same department and so we, as a group, met and decided to work jointly. The SANTE team, as already mentioned, gained ethical approval for the interviews, developed the sampling matrix and the demographic and consent forms. I adapted my topic guide to include the questions that SANTE wanted asked (I reworded the questions on risk perception to also ask about STI risk perception and included a new section on behavioural interventions that was developed by SANTE). I split the interviews with the SANTE researcher based at Brighton and conducted those at MMC. I independently analysed all the interviews and corroborated the results with another SANTE researcher who had also independently analysed the results. We agreed the key themes arising from the interviews. The supervisors and wider SANTE team provided support to interpret the findings and with the writing of the manuscript for publication.

3.5 Risk assessment tool

In this final section I describe the steps I undertook to develop and validate a clinical decision making tool predictive of HIV infection among MSM attending GUM clinics in England. The methods used here were informed by published literature on risk prediction, particularly tools developed for HIV and STIs and the TRIPOD checklist (https://www.tripod-statement.org/). The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) checklist helped ensure a standardised approach to reporting of the methodology and results.

An overview of the steps and statistics are presented in Figure 3.3 and the details are included in Appendix 7.

Figure 3.3 Methodological framework for developing and validating a HIV risk assessment tool*



*modified from Falasinnu *et al* (133)

3.5.1 Overview

I developed four risk prediction models using:

i) GUMCAD variables only

ii) GUMCAD variables with behavioural study variables

iii) Reduced behavioural, clinical and demographic variables

iv) Multiple imputation of reduced model to examine impact on model derivation and validation (sensitivity analysis)

3.5.2 Model development and risk score derivation

Two conceptually different risk prediction models can be developed for MSM. The first would identify individuals likely to be infected with HIV at the current attendance at a GUM clinic ("diagnostic tool"), and the second would identify the subsequent risk of acquiring HIV among those HIV negative ("prognostic tool"). Although the methodological framework for both is the same, the procedures to develop a prognostic tool are statistically more complex with fewer established methodologies for all aspects of model development. I undertook the development of a diagnostic tool that would determine an individual's likelihood of being infected at a given GUM attendance and the HIV prevention services offered to those who test HIV negative.

3.5.2.1 Data source

I used two data sources for model development: GUMCAD for the demographic and clinical data and the behavioural study for the sexual behavioural variables. Model development was restricted to MSM participating in the behavioural study, whose records could be linked to GUMCAD.

3.5.2.2 Outcome

The outcome of interest for the diagnostic tool was a new diagnosis of HIV (as recorded in GUMCAD records) at the baseline attendance at a GUM clinic. As the number of HIV endpoints identified in the behavioural study was limited I also included other high risk STIs (rectal chlamydia and gonorrhoea, syphilis and LGV) in the outcome to allow more stable risk models to be developed. These STIs were chosen as proxy endpoints of HIV. Rectal gonorrhoea and chlamydia prevalence is high among MSM who engage in RAI (134). Rectal gonorrhoea (125, 135, 136), syphilis (130, 137), and rectal chlamydia (135, 136) have been shown to be independently associated with HIV acquisition so that men with these infections are more likely to acquire HIV than men who do not. Co-infection of HIV and rectal infections has been reported to be 25% overall (138) and 10-23% for chlamydia and 9% for gonorrhoea (139, 140). As well as syphilis being associated with HIV acquisition, the prevalence and incidence of syphilis among HIV positive MSM is high (141, 142). LGV is strongly associated with HIV infection among MSM (143) with 67-100% of LGV cases co-infected with HIV. LGV is caused by chlamydia serovars and as the transmission mechanisms are the same as chlamydia, LGV is likely to also be associated with HIV acquisition. These data show that as well as being associated with HIV acquisition, co-infection with these high risk bacterial STIs is high among HIV diagnosed MSM, though to a lesser extent for rectal infections.

The inclusion of these bacterial STIs resulted in the creation of a composite endpoint, which, while not the desired outcome is a pragmatic approach that will allow me to demonstrate the development of a risk tool as a proof-of-concept. The outcome is a binary variable (0= no outcome, 1= outcome).

3.5.2.3 Candidate predictors

Candidate predictors include variables from GUMCAD and the behavioural study. I included clinical variables relating to the prior year (e.g. syphilis and gonorrhoea diagnoses) associated with HIV infection identified from HIV incidence analyses as well as prior rectal STI and HIV tests or STI screens as these variables may be associated with high risk STI outcomes. I also included socio-demographic variables (reported sexual orientation at baseline attendance (heterosexual, bisexual, homosexual), age group, quintile of deprivation, residence (London/outside London), ethnicity and country of birth). Deprivation was not directly available from GUMCAD but was assigned using the residence data available. The behavioural variables included were total numbers of partners and numbers of CRAI and CIAI partners.

Thirty four per cent of MSM had not attended the clinic in the previous year. Rather than counting these data as missing and excluding men with no clinical information on the previous year or grouping them with other MSM, I created an additional binary variable called “did not attend in prior year” to account for them where ‘0’ referred to men who attended in the prior year (reference group) and ‘1’ to men who did not attend. I chose this approach in preference to the one adopted in the HIV incidence analyses (section 3.2.4) because I did not have to make any assumptions of the risk of men who did not attend in the prior year.

3.5.2.4 Continuous variables

Age and the behavioural variables were continuous variables that were categorised in the models. Though information is lost through this approach, it is a simple way to deal with non-linear variables. In this analysis, the relationship between these independent variables and outcome was not linear. I categorised

the variables using available literature and past behavioural surveys to determine the optimal cut-off points. The behavioural variables were categorised to: 0, 1, 2-4 and >4 partners and age was categorised as previously described (see section 3.2.4).

3.5.2.5 Missing values

The completeness of the socio-demographic data available from GUMCAD was between 97%-100%. Clinical history was 100% complete. As discussed in Chapter 6, completeness of the behavioural variables varied from 70-98%. The numbers of sexual partners was completed for 98% of returned questionnaires compared to 70% for questions relating to numbers of CRAI and CIAI.

In the primary analysis, I chose complete case analysis, where only individuals with complete information for all variables were included (models 1-3). This analysis relies only on the observed data and excludes individuals with missing data. I also conducted a sensitivity analysis using MI where missing data were imputed to create a complete dataset (model 4). This approach was considered appropriate because the results from behavioural study suggested missing data were not related to the outcome (of a high risk STI) and could potentially be imputed using the other measured variables (section 6.14.2). Similar results between the complete case and MI models could suggest missing data are randomly distributed and the complete case is an unbiased analysis. Greater details are provided in the multiple imputation section (3.5.6).

3.5.2.6 Developing the risk prediction score

I ran multivariable logistic regression on the candidate predictors and used the regression coefficients in prediction scoring. For each variable in each of the four

models, I reported the odds ratio (OR), β regression coefficient and 95%CI for both parameters and p value.

In the first two models (sections 8.4 and 8.5) I used a full model whereby all a priori selected candidate predictors were included, without any further variable selection. This method avoids selection bias of predictors. However, the large number of variables (especially once the behavioural variables were included) and the small number of outcome events led to two issues with the models.

Firstly, some variables perfectly predicted the outcome, that is, some variables were highly predictive of the outcome and for some combination of the covariates all the observations had the same event status. The statistical outcome was a minus infinity coefficient and STATA dropped the observations that led to the problem. A better alternative was to use Firth's bias reduction method as this method always produces finite parameter estimates by reducing the bias on the problematic regression coefficient (144). I employed this logistic regression method in STATA for this model and the subsequent reduced model (model 3).

Secondly, as well as large numbers of predictors, the use of categorical variables that are modelled using dummy variables increased the number of coefficients. I used the "events per variable (EPV) 1 to 10 rule of thumb" (145) to calculate the EPV of each model as the number of events divided by the number of regression coefficients. An EPV of less than 10 would suggest the model is 'over-fitted'. In an over-fitted model the predictions do no generalise to new subjects outside the sample so that risk is over-predicted for high risk patients and under-predicted in low risk patients.

As the value was below 10 for both models, I reduced the number of candidate predictors included in model 3 as a potential solution (section 8.6). In multivariable modelling for risk prediction, selecting variables based on their p values from univariate analyses is not a recommended strategy (145) though it was often the strategy used in the literature. I used published literature and the findings from this thesis to determine which candidate predictors should be included in the third model. The same variables were included in model 4 though regression analyses were based on an imputed dataset and the STATA command 'mi estimate' was used to obtain the model parameters.

For each of the models, I calculated the probability of being infected at the baseline attendance for a hypothetical man to illustrate the analytical process: a white European MSM aged 34 years, living in London in the 3rd quintile of deprivation, whose sexual orientation was homosexual, and who had not attended in the prior year being diagnosed with HIV/high risk STI. The analytical steps involve calculating the odds of the outcome and using it to determine the probability (Box 3-4).

Box 3-4 Probability of being infected with HIV

Log odds of outcome = *regression equation [intercept + (variable value x coefficient) + all additional (variable values x coefficients)]*

-4.32 + -0.11 + 0.41 + -1.41 + -0.34 + -0.09 + 3.03 = -2.83

Odds of outcome = $e^{(-2.83)}$
Odds of outcome = 0.059
Probability of outcome = [0.059 / (1 + 0.059)] x 100
Probability of outcome = 5.6%

Unless an automated program is available to calculate an individual's probability of being infected in clinical settings, this method would be impractical and

unfeasible as it is time consuming. In model 3 I also used the points score method (146) to calculate a risk prediction score as it can be easily calculated on a score sheet. This method has been commonly used when developing prediction models including for HIV and STI but it is less accurate at predicting the outcome than probability scoring.

In the points score method, the β coefficients were multiplied by 10 and rounded to the nearest whole integer. This created weights for each regression coefficient that ranked the predictors in relative importance. The whole integer corresponded to the points given to an individual for that risk predictor. The points from all predictors were then summed to calculate the total number of points for each individual (the 'risk score'). I plotted the number of outcomes by quartiles of risk score to visualise the relationship and mapped the points to the estimated probability of being infected at baseline.

3.5.3 Model performance

Accuracy and generalisability are important issues related to the use of risk prediction scores. Calibration and discrimination were documented in the literature as the most common measures to assess model performance and its accuracy.

Ideally, performance should be measured in an external dataset as an assessment of the predictive performance of the model. However, this was beyond the scope of the thesis. The two model performance statistics were instead documented for the development dataset to measure apparent performance by the following means.

3.5.3.1 Calibration

Calibration is necessary to assess the extent to which the risk predicted by the model reflects the risk observed in the population. For example, when the model predicts 10% probability of having the outcome for a patient, the observed frequency of the outcome should be approximately 10 out of 100 patients with such a prediction. I graphically assessed calibration by plotting the expected (predicted) number of infections against the number of observed infections. As my outcome was binary (i.e. 0 or 1), I collapsed the predictions into groups of similar probabilities and then for each group I plotted the mean observed outcomes for each group on the x axis against the mean predicted probability on the y axis. Perfect concordance between observed and predicted risk would produce a line on the 45° line. Deviations away from the line would suggest the model does not predict what is observed in the population.

The second measure of calibration, which is a modification of the plot, is a statistical test known as the Hosmer-Lemeshow goodness-of-fit test, which compares the observed values to the predicted by decile of predicted probability. In the first of the ten groups are the observations with the lowest 10% predicted probabilities and the second group contains the 10% of the sample with the next smallest predicted probabilities until the tenth group which has the observations with the highest 10% of predicted probabilities. The Hosmer-Lemeshow p value was calculated in STATA using the ‘estat gof’ command. If the p value is less than 0.05 this is indicative of a poor fit. The test was used for Models 1-3. In Model 4 (MI model), it was not statistically correct to average p values across the imputations so I used the first imputation to calculate the p value.

A well-calibrated model does not necessarily discriminate well between those at high risk and those at low risk and therefore an additional measure of performance is important.

3.5.3.2 Discrimination

Accurate predictions discriminate between men who acquired HIV/high risk STI and those who did not. The concordance (c) statistic was used to determine how well the model classified patients. In logistic models where the outcome is binary, the c statistic is the equivalent to the area under the receiver operating characteristic (ROC) curve, which plots the sensitivity against 1-specificity at consecutive cutoffs for probability of outcome. In the results I present the ROC curve and the c-statistic with 95%CI for each model. The c-statistic for model 4 (MI model) was based on the first imputation. These parameters were calculated using 'lroc' in STATA. The model should have high discrimination ability and a value of above 0.7 is generally considered acceptable for clinical practice. At 0.7 or above, the corresponding sensitivity and specificity values will also be high.

3.5.4 Clinical usefulness

To be clinically useful, an optimal cut-off threshold (or probability of infection) should be determined so that clinical staff know when MSM should be referred for HIV prevention services. To define this threshold, I calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the false positive rate at different risk probabilities. Based on these values and the trade-off between them, the most appropriate threshold was suggested for each model. The optimal threshold traditionally maximises the sensitivity and specificity and this method was also adopted here. These values were obtained

using the command ‘estat classification, cutoff(*x.x*)’ in STATA. These values were only calculated for the first imputation in model 4 (MI model).

The sensitivity, also known as the true positive rate, measures the proportion of MSM infected with HIV that are correctly identified while the specificity, also known as the true negative rate, measures the proportion of uninfected men that are correctly identified. The PPV measures the proportion of true infections among MSM assessed to be infected and is dependent on the prevalence in the population (i.e. those truly infected and those falsely considered to be infected) while the NPV measures the proportion of truly uninfected MSM among all MSM assessed as being not infected. The false positive rate measures the number of positive results among truly uninfected MSM. This rate was considered important for clinical usefulness because individuals who test negative for HIV (i.e. those who are truly negative) at the visit but who were assigned a high probability of being infected are the ones who are likely to be targeted for HIV prevention services.

3.5.5 Internal validation

Validation is essential prior to clinical use to test whether the associations identified between exposures and outcome may be due to chance. The purpose of internal validation is to determine whether the predictions generated from the model are valid and reproducible when applied to a new population, a population that was not used to develop the model. However, as internal validation is conducted on the same population that was used to derive the model, the corrected statistics will still be over optimistic of the true performance characteristics. True performance characteristics can only be obtained from external validation.

I chose bootstrapping to validate my results; it is considered the most efficient method as it uses the entire sample. In bootstrapping, the statistical software is programmed to repeatedly sample from the observed dataset, with replacement, to form a large number of bootstrap datasets, each the same size as the original dataset. The bootstrap samples represent samples from the population while the observed dataset represents the population of interest. The model that has been fit to the original data is also fitted to each of the bootstrap datasets.

At random, 1,000 samples were drawn from the original data and the model was fitted to each bootstrap dataset and the c statistic estimated using each fitted model and bootstrap dataset. The c statistic was estimated by applying the fitted model from the bootstrap dataset to the original dataset. The difference in the c statistic for each bootstrap sample was calculated and the average across all bootstraps was taken. The estimate of optimism was then subtracted from the original estimate to give an optimism corrected estimate. I was unable to identify established theoretical models and techniques to calculate the 95%CI for the corrected c-statistic.

I also internally validated calibration using the same bootstrapping approach. The calibration slope, unlike the Hosmer-Lemeshow test, could be internally validated. It, too, measures the agreement between the observed and predicted risk of outcome. As it typically has a value of one in the development model, I only calculated the value after internal validation when it is either below or above one. A value of below one indicates some predictions are too extreme. One of the direct bootstrapping outputs was the slope value.

I did not validate the entire MI dataset as I was unable to find established statistical methods or software that could help with this process. Instead, I internally validated the first imputed dataset as has been previously reported (147).

Bootstrapping was conducted in R Studio using the 'rms' package after data management in STATA.

3.5.6 Multiple imputation

In the sensitivity analysis, I used an imputed dataset rather than a complete case dataset. The non-response analyses conducted within the behavioural study indicated the data were MAR and probably also MNAR (at least for being diagnosed with HIV at baseline). Based on these results, I considered MI an appropriate method to deal with the missing data. Although there is no set cut off at which MI is appropriate, MI can handle datasets with a large amount of missing data and since none of the variables in this study had more than 30% missing information, I used MI for all variables with missing information. I imputed the following variables: origin of birth and ethnicity, sexual orientation, deprivation, residence in London, and numbers of CRAI and CIAI partners using the STATA command 'mi impute'. I choose Multiple Imputation by Chained Equations (MICE) (148) where each missing variable is imputed using its own imputation model in a single imputation. One of the variables with missing values is regressed as the dependent variable on the other variables and the missing values are replaced with predictions (imputations) from the regression model. This process is repeated for every variable with missing data. The cycling through for each variable is known as one iteration and at the end of one iteration all the missing values are replaced. The process is again repeated for a number

of cycles with the imputations updated at each iteration. This method was chosen as it allows multiple variables to be imputed at the same time and is a flexible approach that can use different variable types.

During imputation convergence was not achieved (a state that should be achieved when the distribution of the parameters governing the imputations has become stable). Further investigation highlighted the problem arose due to collinearity between numbers of partners and numbers of CRAI or CIAI partners where values for all categories of numbers of CRAI (or CIAI) partners could only be “0” when total partners was “0”. To overcome this problem I dropped MSM who had no information on numbers of total partners and treated this variable as complete (so that it did not need to be imputed). Over half of these excluded men (59%) also had no information on numbers of CRAI and CIAI men and therefore any values generated from MI would not be accurate as the remaining variables, which were socio-demographic, may not be as predictive when determining the behavioural outputs.

I created ten imputations to the multiple imputation data. Five is considered the minimum number of iterations that should be used to produce valid results and ten would provide additional efficiency. I included data augmentation options when running MI to address potential problems caused when using variables with missing data to predict for other variables with missing data. In the situation of perfect prediction, infinite odds ratios are produced. Data augmentation overcomes this problem by adding extra data. This data is given a small weight so that analyses remained unaffected. The variation between the imputations reflects the uncertainty with which the missing values can be predicted from the observed data.

After convergence, I checked whether data were successfully imputed by comparing summary statistics (e.g. mean, standard deviation) of the original data with the imputed datasets. I also examined the distribution of other covariates and the outcome for those with CRAI partners between imputation models.

3.5.7 Subsequent infections

I used survival analysis to prospectively follow MSM included in the final model from baseline (the attendance where a questionnaire was completed) until their last attendance occurring before 31st December 2016 or until they were diagnosed with HIV or a high risk bacterial STI, whichever came first. I calculated HIV incidence as described in 3.2 and compared incidence by the estimated probability risk groups generated at baseline in model 3 to determine whether MSM diagnosed with a low probability of being infected at baseline also belonged to the group among whom subsequent incidence was low (section 8.8).

3.5.8 Role of candidate

The development of a HIV risk assessment tool underpinned the thesis and it was part of the outline of the PhD that I was given. It was an idea formed by my PHE supervisors. I however undertook the design of the tool using a literature review that summarised existing methods in sexual health. I sought statistical support with certain aspects of the development. A UCL statistician provided overall guidance on how to determine performance statistics and internal validation though I wrote the code and conducted the analyses. He also provided assistance in interpreting the findings. Another statistician at PHE advised on whether it was appropriate to conduct multiple imputation, he checked my

STATA code and provided support in interpreting the findings including providing quality assurance.

3.6 Statistical software

I used two statistical software packages to conduct the analyses in the thesis. The majority of analyses were conducted in STATA 13.1 (StataCorp, College Station, TX) although R Studio was also used.

3.6.1 STATA 13.1

All the data cleaning, management and analyses conducted to report HIV incidence and predictors of HIV infection was done in STATA. Similarly, for the behavioural study, all statistical management including data linkage to GUMCAD was conducted using STATA 13.1. The majority of model derivation including multiple imputation and performance testing was undertaken in STATA.

I created do files to save all the commands that were run for each step of the data management and analysis. This ensured everything was recorded and was transparent. It also allowed analyses to be repeated and updated when necessary with relative ease. These do files are also important for future reproducibility.

3.6.2 R Studio

I chose R Studio to internally validate the models using the 'rms' package which can be downloaded within the software. The data management was conducted in STATA as it is more user-friendly but as the rms package was simple to

understand and implement in R Studio compared to STATA, I used R Studio for this part of risk model development.

As with STATA, all the R code used for these analyses were saved in R studio to allow replication and reproducibility.

3.7 Conclusions

This chapter has described the methods employed in the thesis and demonstrated the range of quantitative (HIV incidence, risk prediction, risk models) and qualitative (cognitive and semi-structured interviews) methods applied to answer the research question. The methods for the systematic review are included with the review results in the following chapter, which examines HIV incidence among MSM.

4 Literature review of HIV incidence, risk factors for HIV acquisition and population attributable risk

4.1 Introduction

Trends in new HIV diagnoses are not necessarily reflective of current trends in HIV incidence as the infection could have been acquired at any time prior to diagnosis and is dependent on HIV testing behaviours. Estimation of HIV incidence is an essential public health tool that characterises those at current risk of HIV infection, allows monitoring of trends over time and contributes to the development and evaluation of prevention interventions. There are a number of methods that could be used to measure HIV incidence from prospective cohort studies to cross-sectional studies that rely on serological testing to identify recently infected individuals.

Often risk factor analyses are conducted in conjunction with incidence studies. Risk factors are those characteristics or exposures of an individual that increase the likelihood of acquiring the infection or developing the disease. Identifying risk factors associated with HIV infection will identify groups at higher risk of infection, among whom resources should be focussed and prevention services targeted. Although MSM are considered to be a higher risk population for HIV than other groups (e.g. heterosexuals), risk is not homogenous in this population and some sub-groups are at greater risk of acquiring HIV than other MSM sub-groups. A compilation of relevant risk factors for HIV among MSM would identify these sub-groups.

While understanding individual risk is important to understand causality, individual level interventions may not impact HIV incidence at the population

level. The population attributable risk (PAR) can provide this information as it measures the reduction in infections that could occur if the exposure were to be removed from the population. The PAR is a more relevant public health measure than measures of association as it examines the strength of association between the risk factor and outcome while also accounting for the prevalence of the factor in the population. Those risk factors strongly associated with HIV infection and with a large PAR will help inform policy and prevention activities because targeting them will likely have the greatest impacts on HIV transmission.

4.2 Rationale for review

I conducted a literature review of HIV incidence among MSM populations, firstly, to document HIV incidence estimates from the UK and establish whether estimates from MSM populations from countries with similar epidemics (e.g. Australia, Canada and US) are comparable. I recorded methods used to calculate HIV incidence and in particular critically examine the methods that are relevant for informing calculations of HIV incidence using secondary data and cohort studies.

Secondly, I searched the literature to document risk factors for HIV acquisition and the population attributable risk of these predictors. Clinical and demographic risk factors for HIV infection will inform risk factors analyses that will be carried out during the secondary data analysis. Further, the behavioural variables associated with infection will be used to inform the development of behavioural studies among MSM in England. The PAR could allow identification of risk factors that are key for reducing HIV transmission.

In the next sections I describe the steps I took to systematically search the literature (excluding grey literature) to document HIV incidence among MSM populations and known risk factors for HIV acquisition and their PAR.

4.3 Methods

4.3.1 Search strategy

I searched Medline using the OVID platform because it is the most widely used search engine for biomedical literature. Key Mesh terms and text words were searched (shown in italic) for HIV incidence (Box 4-1): [Incidence OR *Incidence* OR *seroconversion* OR HIV Seropositivity OR Disease Transmission, Infectious/ OR *transmission* OR acquisition] AND [HIV Infections/ or HIV/ or HIV-1/ OR *HIV-1*] AND [Homosexuality, Male/ OR men who have sex with men OR male homosexuality]. For risk factors of HIV acquisition, the same search terms were used in addition to: [Risk Factors/ or exp Risk/ OR *risk factor**]. The search strategy for population attributable risks included those for risk factors in addition to: [*attributable risk* OR *population risk*].

Box 4-1 Search terms and strategy for HIV incidence review using Medline via OVID

1. exp Incidence/
2. incidence.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. 1 or 2
4. seroconversion.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. exp HIV Seropositivity/

6. exp Disease Transmission, Infectious/
7. transmission.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. acquisition.mp.
9. 3 or 4 or 5 or 6 or 7 or 8
10. HIV Infections/ or HIV/ or HIV-1/
11. HIV-1.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. 10 or 11
13. 9 and 12
14. Homosexuality, Male/
15. men who have sex with men.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
16. male homosexuality.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
17. 14 or 15 or 16
18. 13 and 17
19. limit 18 to (english language and humans and yr="2000 -Current")
20. 3 or 4 or 5
21. 20 and 12
22. 17 and 21

4.3.2 Inclusion criteria

Any study design that measured i) HIV incidence and/or ii) risk factors for the acquisition of HIV and/or iii) population attributable risk among MSM were eligible for inclusion. For studies on HIV incidence, only those that reported HIV incidence rates, incidence density or incident number of infections were included.

All studies published between 2000 and July 2012 were included in the review and the date of the last search was 17th July 2012. Studies published before 2000 were less relevant because incidence would potentially pertain to an era before the availability of ART treatment. Review articles were excluded unless overall meta-analyses were performed or weighted estimates were calculated and presented. Unpublished studies, studies published in non-English language journals and conference abstracts were not considered for inclusion.

4.3.3 Study selection

Articles were screened in three stages to identify relevant papers for inclusion. Titles were reviewed on-screen and those that made met the criteria were saved. The abstracts of these articles were reviewed and screened for retrieval. Abstracts that met the inclusion criteria were accepted for full review. For titles without abstracts, the full paper was included in the review process. References of review articles were hand searched and any relevant studies not previously identified were screened and full-texts reviewed.

4.3.4 Data extraction and quality assessment

Data were extracted from the final list of included studies. A standardised data collection form was developed in Microsoft Excel and key data capturing study design, study population, study setting, outcomes and quality score were entered for each paper. Outcome measures for incidence were incidence rates or incident numbers and for the risk factor review, measures of effect include odds ratios, hazard ratios and risk ratios. For multiple papers reporting incidence in the same cohort, only the most recent was included.

Quality assessment of the included peer-reviewed articles was carried out using a modified form of the established criteria known as AXIS (149). A number of the questions were study design specific; therefore, I only used quality assessment questions that were applicable to any study type and ensured the questions assessed all aspects of the study (methods, results and discussion) (Box 4-2). On the basis of the seven questions completed for each published article, each study was assigned a quality rating (quality score): low (+), medium (++) and high (+++). Papers satisfying four or less of the questions were assigned a low score, five to six were assigned a medium score and satisfying all seven questions achieved a high score.

Box 4-2 Quality assessment of articles

Were the aims/ objectives of the study clear?
Was the study design appropriate for the stated aim?
Was the study population clearly defined?
Were the methods sufficiently described?
Were the basic data adequately described?
Were the discussion/conclusions justified by the results?
Could the study be replicable in other populations?

Though a systematic review has not been conducted, I have included the PRISMA checklist in appendix 1 to highlight the steps in this review. A meta-analysis was not performed as the objective of the review was to compare estimates across settings rather than pool them into a combined estimate. No specific assessment was undertaken for risk of bias across studies as I considered the risk of assessment bias of individual studies sufficient to highlight the issues with the studies. The risk of bias for individual studies was conducted as a general discussion in section 4.6.1.3 using examples from the included studies rather than a formal assessment. This approach was undertaken to allow

the methodologies employed to estimate incidence and calculate risk factors to be critically appraised for biases.

4.3.5 Role of candidate

I decided that HIV incidence needed to be reviewed as it was important for the methodology and subsequent chapters (behavioural study). I undertook systematic review training from UCL library including how to build search terms and which database to use. I then conducted the review, synthesised the results and interpreted the findings. My supervisors provided input in the interpretation of the findings.

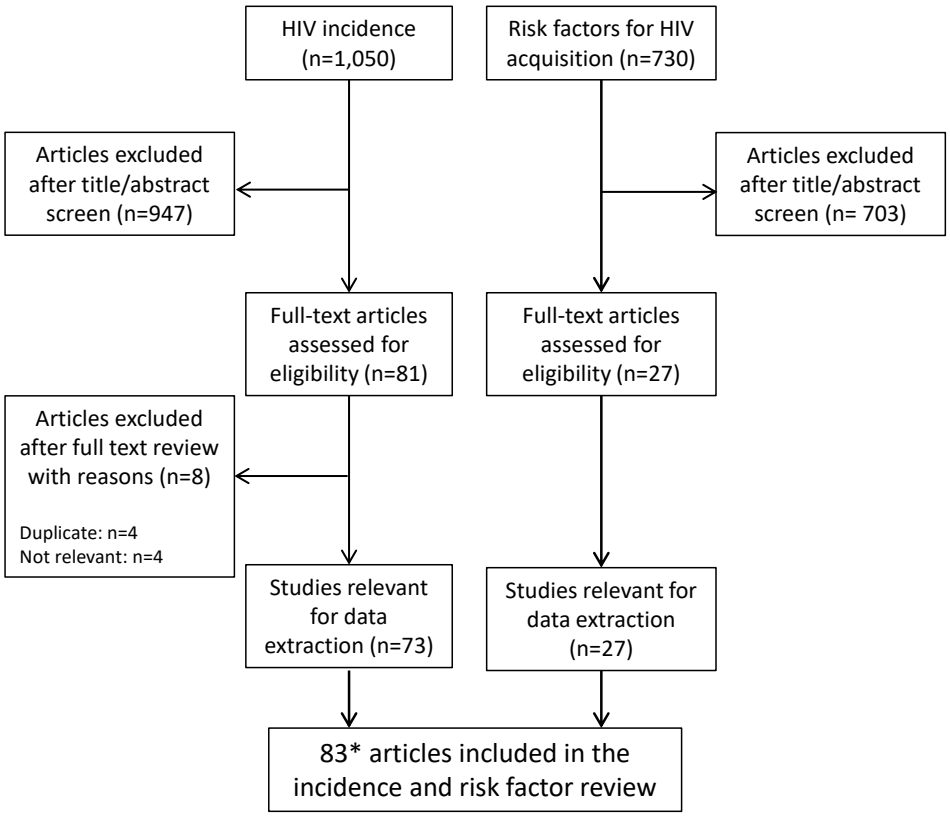
4.4 Results

4.4.1 HIV incidence and risk factors

In total, 1,050 titles were reviewed and of these 103 abstracts were identified for reviewing. Eighty-one papers were read in full and 73 published articles were relevant and met the inclusion criteria for HIV incidence among MSM (Figure 4.1). An overview summary of each paper is provided in Appendix 1.

For the risk factor review, 47 abstracts were reviewed and 27 read in full and all were accepted. Of these papers, 17 were also included in the incidence review. An overview summary of each paper is provided in Appendix 2. The three titles and papers included for the population attributable risk review were also included in the risk factor review. Therefore, in total, 83 published articles reported HIV incidence and/or risk factors for HIV acquisition and population attributable risks (Figure 4.1). Data were extracted for the 83 articles.

Figure 4.1 Flow chart of search strategy and final papers included in review



4.4.2 Study setting

Thirty-nine per cent (n=32) of the 83 studies were reported from North America, the remainder were from Europe (n=22), Asia (n=11), Australia (n=8), South America (n=7) and three in a number of countries. Of the 73 papers reporting HIV incidence, the most frequent study setting was STI and HIV testing sites (n=30, 41%), followed by MSM recruited in community venues (n=17), and the majority of the remainder were a combination of clinical and community based settings.

4.4.3 Study design and methodology

Half of all studies included in the review of HIV incidence estimates were longitudinal cohort studies conducted retrospectively (n=10) or prospectively (n=26). Another 22 were cross-sectional surveys, five used modelling, four used RITA on surveillance data, five a combination of these methods and one RCT. Surveillance data and modelling techniques were used to derive national HIV incidence estimates while those from longitudinal cohorts and cross-sectional surveys estimated incidence in sub-groups of the MSM population.

Longitudinal studies and the RCT directly measure HIV incidence as persons who start the study are HIV negative and are then followed-up over a period of time during which new HIV infections are identified. In these studies incidence was either calculated as the midpoint between the last HIV negative date and first positive date or simply as the interval of the two dates. HIV incidence was calculated as the number of seroconversions (N) during person years (py) of follow-up (N/py) and was expressed as per 100 py.

HIV incidence can be measured using serological testing where a diagnostic serum sample is taken at a single point in time. HIV testing will determine whether the individual is HIV positive and a further laboratory test (RITA testing) as described in section 2.2 can determine the recency of infection. This methodology can be applied in cross-sectional studies to calculate incidence (e.g. (26, 150-152)) and to surveillance data to calculate number of incident infections (e.g. (153, 154). Both approaches include sero-negative and positive individuals and in the cross-sectional studies the formula (or a variation of the formula) in Box 4-3 can be used to calculate incidence and express it as a percentage per year.

Box 4-3 Formula to calculate HIV incidence using RITA to determine recent infections

$$(n/N) \times (365/T) \times 100$$

where n is recent infections, N is new diagnoses and T is mean window period

The mean window period is the mean time an individual's immune response remains below the threshold at which the infection is considered as recent. The period differs between individuals and depends on the serological tests used. Serological testing was also used to determine the number of incident cases nationally.

Other study designs, where no information on sero-negative persons is available, indirectly measure incidence based on HIV diagnoses. New HIV diagnoses reported through national surveillance are tested for recent infection and results are extrapolated to give population estimates of incidence that, in the included studies, were expressed as incident cases or a rate. Alternative modelling techniques included modified back-calculation methods that account for changes in the incubation period between infection and onset of symptoms due to availability of treatment. In the UK, a Bayesian evidence synthesis approach was used to estimate HIV incidence (6). A number of different data sources were used in this approach including data from national surveillance, unlinked anonymous surveys and behavioural surveys were included. A multistate model simultaneously estimated HIV prevalence and incidence using all the available data.

The study design for risk factors were catalogued into the following groups: case-control studies (n=5), cohort studies (n=16), RITA testing on cross-sectional surveys (n=1), RCT (n=2) and combination of the above (n=3). In general, multivariable logistic regression models were run to report adjusted ORs with 95%CI for significant ($p<0.05$) risk factors in the case-control studies and cox proportional hazards regression models were used to report adjusted HRs for cohort studies and the RCT. One study, however, only reported unadjusted ORs from univariable analyses.

4.4.4 HIV incidence estimates

The HIV incidence estimates presented in this section are categorised by world region and summarised in Table 4.1 to facilitate better comparisons between regions and recruitment type.

UK

There are no HIV incidence estimates for MSM in the UK as a whole. The majority of data apply to England, Wales and Northern Ireland for MSM attending GUM clinics. In the late 1990s to the early 2000s incidence remained relatively stable from 1.5% to 3.5% (26, 27, 155, 156). During this time, incidence among MSM attending London GUM clinics was 1.8/100 py (157) and 3% (26). More recently in 2008/09, an incidence of 8.3/100 py was reported among MSM with previous history of STIs (158), however the estimate is based on a small sample size from one clinic. Incidence in the general MSM population was estimated to be two- to three-fold lower at 0.9% in 2007 (6). In Scotland, incidence was 1.5/100 py between 1980 and 2009 with no change over time (159). Incidence ranged from 15-17/100 py for MSM aged less than 44 years, while in older men it declined to 7.7/100 py.

Rest of Europe

Incidence estimates were reported in the Netherlands, France, Spain, Italy and one study in Scandinavian countries, which reported incident numbers from the 1990s (160). Estimates ranged from 1% to 6% depending on the country, time period and specific MSM sub-population. Six studies from the Netherlands reported incidence rates of 1.3-8.6/100 py in the mid to late 1980s after which it dropped to 1.3-2.0/100 py (81, 151, 161-164). MSM recruited in GUM clinics reported higher incidence rates that increased over time. Incidence estimates were also higher among users of PEP (6.4/100 py) (162). In the late 1980s in Spain, incidence was between 4.7-8.3/100 py after which it declined in the 1990s, with some evidence for an increase in the early 2000s (2.2-3.3/100 py) (165-167). A community survey in 2009 in France reported an incidence of 3.8% (168), that was lower among MSM aged 35 and older (2.5%), while the rate in the general MSM population was 1% (153). Italy reported estimates similar to other European countries in the early 2000s for MSM attending GUM clinics (5/100 py) (169).

North America

The majority of the studies in North America are from the United States (67%). The number of incident cases ranged from 27,000 in 2006 to 29,300 in 2009 (154, 170, 171). As a rate it was approximated as 0.7% for MSM residing in Florida (172). Among MSM recruited from GUM clinics incidence widely ranged between 1.4% and 7.1% with no suggestion of an increase since the mid-1990s (146, 150, 152, 173-183). Among certain sub-groups incidence was higher: 12% among MSM with syphilis (150), 6.3% among amphetamine users (173) and 9.2-11.0% among men of black ethnicity (182, 183). Incidence rates were

comparable among MSM recruited from the community (1.8-7.0%) (184-186). Eight studies were conducted in San Francisco alone from 1993 to 2007, where incidence was 1.1-6.6% and 1.4-3.8/100 py, respectively, with no observed change over time.

All estimates for Canada relate to the late 1990s and early 2000s. Incidence was estimated to be approximately 1% to 1.5% among MSM from all settings (187-193). Studies found incidence to be higher among MSM who also inject drugs (3.9/100 py) (188) and younger MSM (20-39 years: 1.2/100 py) (187).

Australia

Two of the five studies gave national incidence estimates and the remainder pertained to MSM populations in Sydney, Melbourne and Victoria. In the mid-1990s, incidence was estimated to be 2.1% (194) with more recent estimates from 2000 to 2006 at approximately 4,731 incident cases (195). Incidence in Sydney was 0.8/100 py between 2001 and 2007, which was 5.3/100 py among MSM having CAI with HIV positive partners (196) and 1.2/100 py in 2006-2009 (92). No trends over time were observed. Incidence was 1.3/100 py among PEP users (197).

South America

All estimates were among MSM from Rio de Janeiro, Lima and Buenos Aires. In these community recruited studies, incidence from RITA testing varied between 6-12% in the 2000s (198-200) and from cohort studies 2.9-3.9/100 py in the mid-1990s and 2000s (201-204).

Asia

Incidence estimates among MSM have been reported in China, Taiwan and Thailand. Since 2005, HIV incidence in MSM in China was between 2.6-5.6/100 py (205-211). A meta-analysis reported incidence in China to be between 2.6-9.4% (212). Between 2003 and 2007, incidence among community recruited MSM in Bangkok increased from 4.1% to 7.7% and was comparable to a study among clinic attendees (8.2/100 py) (213, 214). A cross-sectional study in Taiwanese bathhouses reported increasing incidence from 7.8% in 2004 to 15% in 2007 (215).

Other

In a meta-analysis of HIV incidence among MSM from different industrialised regions and recruitment settings, HIV incidence was 2.5% (2.3-2.6%) between 1995 and 2005. Incidence did differ between countries but not by year. In the US among MSM from community venues incidence was 2.4% (2.2-2.6), from HIV test sites: 2.5% (2.1-2.8) and from GUM clinics: 3.8% (3.2-4.5). Incidence was comparable in Europe (2.5%, 2.1-2.9) but lower in Australia (0.98%, 0.8-1.2) (216).

Table 4.1 Overall HIV incidence (95%CI) in MSM populations by recruitment venues and year

Region	Country	VCT/GUM clinics	Community	Combination of venues	General MSM population
UK	England, London	1.8/100 (0.9-3.2), 1997-98	-	-	-
	England and Wales	-	-	-	0.9% (0.5-1.3), 2002-07
	England, Wales and Northern Ireland	1.5-3.5%, 1999-2004	-	-	-
Rest of Europe	Netherlands	0.9-4.4%, 1991-2009	1.1-6.7/100,1984-2002	1.3-8.6/100, 1984-2009	-
	Spain	0.5-8.3/100, 1988-2003	-	-	-
	France	-	3.8% (1.5-6.2),2009	-	1.0/100 (0.9-1.2), 2008
	Italy	2.7/100 (2.5-3.5), 1984-2003	-	-	-
North America	United States	1.6-7.1, 1989-2008	1.8-7%, 1994-2001	1.6-2.5, 1995-2003	27,000-29,300, 0.7/100, 2006-09
	Canada	0.6-2.4/100, 1992-2003	-	0.6-1.9/100, 1995-2003	1,452, 2008
Australia		2.1%, 1993-1999	0.8-1.7/100, 2001-07	-	19,689, 1981-2006
South America	Brazil	12%, (6.1-18), 2004-05	3.3/100 (1.9-4.7), 1994-98	2.9/100 (1.4-5.1), 1998-2001	-
	Peru	-	3.5/100 (2.3-4.7), 1998-2000	-	-
	Argentina	-	3.9-6.7, 2001-2003	6.3% (4.4-8.3), 2006-08	-
Asia	China	-	2.6-9.4, 2005-2010	-	-
	Thailand	8.2/100 (3.7-18.3), 2008-09	4.1-7.7%,2003-2007	-	-
	Taiwan	-	7.8-15/100, 2004-08	-	-

*Units for HIV incidence are only expressed where figures are reported from a single study or where the group of studies used the same units. 95% CI are only reported for single studies

4.4.5 Risk factors and population attributable risk

In total, 43 significant risk factors for HIV acquisition were reported in the 27 articles. The risk factors covered sexual behaviours, alcohol and drug use, clinical history (e.g. previous STIs) and demographics. Significant risk ratios (RR), HR or OR with 95%CI and the reporting study are summarised in Table 4.2 and Table 4.3. To better facilitate comparisons between studies, I have combined risk ratios and hazard ratios for risk factors obtained from cohort studies in one table because hazard ratios can be considered the relative risk of the event occurring at time *t* (Table 4.2). As logistic regression considers proportions rather than rates and measures odds ratios rather than hazard/risk ratios, I have separately presented them (Table 4.3). However, in discussing these effect measures I have assumed that the odds ratio approximates the relative risk as HIV incidence was less than 5% in most studies (where it was measured), and was therefore a rare outcome.

The most frequently reported risk factors for HIV acquisition related to sexual behaviours including CAI by partner type (i.e. casual vs. regular), partner HIV status (i.e. HIV positive, negative or partner of unknown HIV status) and sexual position (i.e. receptive or insertive role). The RR/HR estimates for CRAI were between 3.9 and 12 (81, 190, 212, 217) and the ORs were between 2.4-2.7 (152, 218). The HR of 12 was based on a small sample and the large confidence intervals reflect the uncertainty of the estimate. After adjusting for other measured risk factors including potential confounders, CRAI with assumed HIV negative partners was less risky (HR: 1.9, 95%CI 1.4-2.7) than with HIV positive (3.4, 95%CI 2.3-5.1 and 6.5,95%CI 2.1-20) (177, 192) or unknown status partners (RR/HR: 2.9, 95%CI 2.1-3.8) (177). However the overlapping 95%CI suggest these differences may not be significant. Jin *et al* came to a similar

conclusion. MSM reporting CAI with HIV negative regular partners were at increased risk of infection (3.2, 95%CI 1.0-10.0) (217). OR for CRAI with HIV positive or unknown status partners were similar to the RR at between 2.7- 4.1 (174, 219). CIAI was less frequently included in studies and values were of lower magnitude than for CRAI. Koblin *et al* reported CIAI with HIV negative partners decreased the risk of HIV infection (HR: 0.5) and CIAI with HIV positive partners slightly increased it (HR: 1.6) (177). The RR/HR for CAI with HIV positive/unknown status partners was between 4.4-16.1 (217) and for HIV negative partners it was 2.2 (217). ORs between 3 and 6.8 were reported for CAI with HIV positive/unknown status partners (220, 221). As well as considering the position of anal intercourse and the status of partners, a number of studies also examined the risk associated with partner type and HIV infection. MSM reporting CAI with casual partners were three times at higher risk of HIV (163) and five to six times at greater risk when practicing CRAI (81, 192). The OR of CAI with a casual negative partner was reported to be 4.3 (95%CI 1.3-13.9) (221) and CRAI was as high as 57 (95%CI 6.7-489) (222) although this final study was a small case control study. One study only reporting unadjusted risk factors found MSM were twice as likely to acquire HIV when having casual sex (210).

In addition to CAI, high numbers of sexual partners was predictive of subsequent HIV infection. Although the studies defined the cut off for high numbers of partners and the time period differently, in general, more than five partners in the last year was considered to be associated with infection. The RR/HR ranged from 1.8-5.1 (81, 92, 177, 190, 203) (Table 4.2) and the OR ranged from 1.1-6.5 (174, 208, 223) (Table 4.3). Increasing numbers of partner numbers also increased the risk of infection. MSM reporting 4-9 partners were 1.6 times at

higher risk (95%CI 1.1-2.4), whereas MSM reporting 10+ partners were 1.8 times at higher risk (95%CI 1.2-2.7) (177).

A previous gonorrhoea, syphilis or prevalent HSV-2 infection were significantly associated with HIV acquisition. Gonorrhoea increased the risk of HIV by 2.5 and 5.8 (81, 177), syphilis by 2.5-3.6 (92, 206, 210, 212) and prevalent HSV-2 by 1.7 (224) and 2.2 (225). ORs were also reported for syphilis infection (OR: 11.4) (208) and prevalent HSV-2 infection (1.8) (223). Amphetamine use doubled the risk of HIV (152, 173, 177). Additionally, inhaling nitrates doubled the risk of HIV infection in two studies (146, 219).

One study conducted among a prospective cohort reported an association between erectile dysfunction medication (OEM) (1.9, 1.5-2.5) and amyl nitrate (1.3, 1.1-1.7) with HIV acquisition. The presence of methamphetamine or amyl nitrate with OEM had a synergistic effect and was associated with an eight fold increase than among those just taking OEM (226). The role of alcohol use and HIV acquisition was less frequently examined and only two studies reported alcohol use as an independent risk factor for HIV acquisition. More than 60g of alcohol at one weekly sitting increased the risk (OR: 3.6, 1.1-11.4) (222) and moderate alcohol use (HR: 1.97, 1.3-3.0) was associated with HIV compared to no alcohol use (177).

Age and ethnicity were the only demographic variables associated with infection. In studies conducted in the US, MSM of black (2.2 (152), 1.99(177)) or Latino (1.9 (152)) ethnicity were at elevated risk of acquiring HIV compared to white MSM. Results from two studies provide some evidence that younger age is associated with HIV acquisition; this is however not conclusive. Being aged less

than 30 years (2.7, 95%CI 0.5-2.0 (225)) and 40 years (1.9 (146)) were reported as risk factors although in the first study the confidence intervals include one suggesting this is not a significant relationship.

Table 4.2 Risk factors for HIV acquisition, adjusted risk ratios and hazard ratios

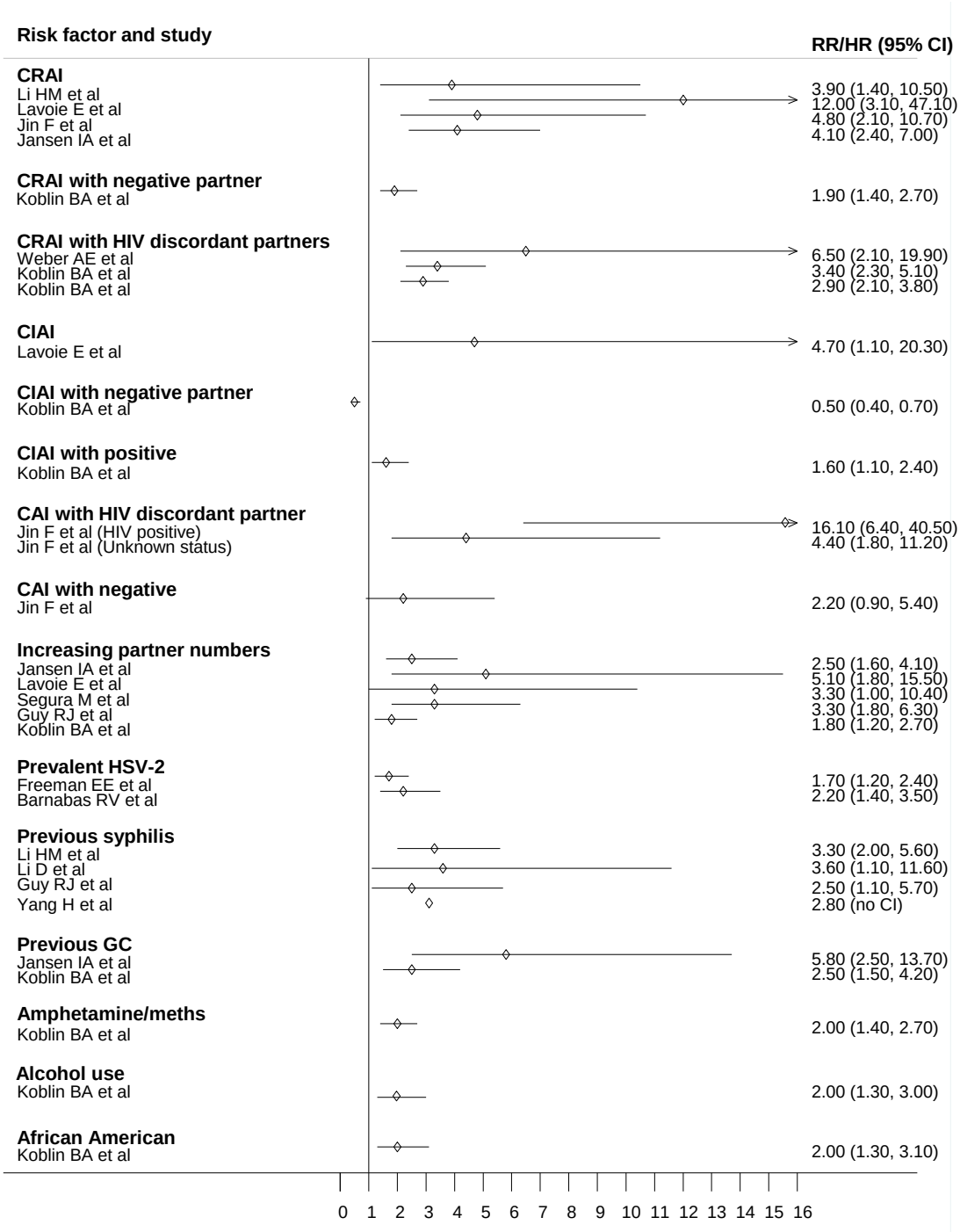
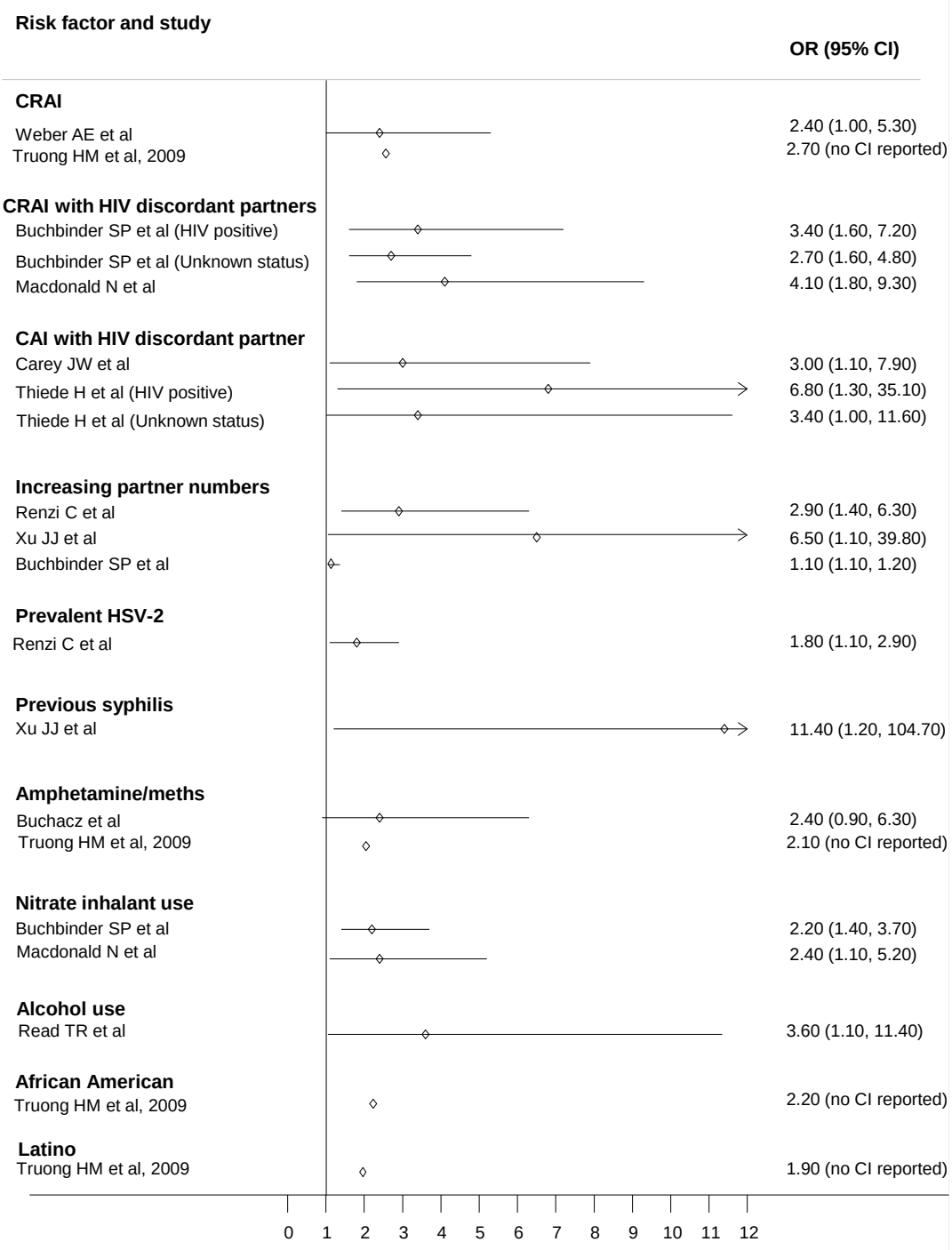


Table 4.3 Risk factors for HIV acquisition, adjusted odds ratios*



*all adjusted odds ratio except Truong HM et al

The relative importance of predictors of HIV acquisition was examined by calculating the PAR. Koblin *et al* and Buchbinder *et al* used logistic regression models to obtain estimates for PAR. Koblin *et al* reported the largest proportion

of HIV incidence was accounted by having four or more sexual partners (32%), followed by alcohol or drug use before sex (29%), CRAI with unknown status partners (28%) and CRAI with HIV negative partners (22%) (177). Black ethnicity and a previous gonorrhoea infection accounted for less than 10% of all infections (5% and 4.3%, respectively). Buchbinder *et al* found increasing numbers of partners and nitrate use had the greatest PAR (28% each), while 15% was accounted for by CRAI with a partner of unknown status and 12% by CRAI with a HIV positive partner (174). Guy *et al* combined the HR of the risk factor with the prevalence of the risk factor (92). Eighty-six per cent of HIV infections were accounted for by CAI with a known HIV positive partner (34%), CAI with a partner of unknown status (33%) and more than 10 casual partners (19%).

4.4.6 Quality assessment

Overall, the articles scored well in the quality assessment. Of the 74 papers examining HIV incidence, 8% (n=6) were rated low, 55% (n=41) scored medium and 36% scored the highest. There was a small difference by study design type: 38% of the cohort studies were rated high compared to 32% of cross-sectional studies. In the risk factor analysis, 15% of papers (n=4) were rated low, 41% as medium and a further 44% were scored high.

4.5 Summary of findings

Overall, HIV incidence estimates from all industrialised countries except Australia and Canada were comparable. Incidence was high during the late 1980s after which it declined and there is no strong evidence to suggest that incidence has significantly changed since the 1990s. Estimates from low or middle-income countries were higher with some countries such as Taiwan reporting an increase

in incidence over time. These countries also have high HIV prevalence among MSM, which in countries such as Thailand has been increasing in recent years (227-230), and evidence of on-going high risk behaviour even among MSM who know they are HIV positive, which contribute to onward transmission of HIV (231-233). It has been proposed the epidemic among MSM in South America is driven by MSM while in South and South East Asia the situation is more complex with a number of groups including sex workers and MSM contributing to overall population level HIV prevalence (234).

HIV incidence differed between different sampled populations of MSM. Incidence was approximated at 1% in the general MSM population, while among populations attending STI or VCT sites incidence was 1-8% in high-income countries and up to 12% in low/middle-income countries. Among community-recruited MSM it was 1-7% in high-income countries and 3-15% in low/middle-income countries. MSM recruited in and/or attending clinical settings are a higher risk population and have higher levels of reported risk behaviours (9), which is reflected in the higher incidence estimates compared to the wider MSM population. MSM from community venues were of comparable risk to MSM from GUM clinics. There may be a number of reasons for these findings. Recruitment from community venues and GUM clinics leads to conveniences samples that are only representative of those populations and not of the wider MSM population. Representation of the wider population can only be achieved using probabilistic sampling. A comparison of behaviours in these different recruitment populations showed that more high risk behaviours are reported in the first two groups compared to probabilistic samples (61, 235). The two populations may not be mutually exclusive; MSM recruited from community venues may also attend GUM clinics, which will increase similarities in HIV risk between the two

populations. Half of men from community surveys in London are known to attend GUM clinics (9). Third, community organisations and NGOs may have a greater role in providing HIV testing and sexual health care in low/middle income counties compared to industrialised countries where the role of GUM clinics is firmly established. This could lead to the recruitment of a higher risk population in community venues in these countries. Finally, community incidence estimated from serological testing may be overestimated as there is the potential for some long standing infections to be misclassified and the sample size may not be large enough to produce reliable and robust estimates.

The review identified significant heterogeneity in HIV risk among MSM, with certain sub-groups reporting high incidence and risk. Men injecting drugs, using methamphetamine, and practising CAI with HIV positive partners had higher levels of HIV incidence. HIV negative MSM reporting CRAI were at greater risk of acquiring HIV infection than those that did not report CRAI and the risk was greatest when CRAI was practiced with serodiscordant partners (i.e. HIV positive partners). Additionally, partner numbers, previous history of STIs such as syphilis and alcohol use were found to be significantly associated with HIV risk. Few demographic factors were considered important; black ethnicity was associated with increased risk in the US. African-American MSM carry a disproportionate burden of HIV, which is not explained by risky sexual practices (236) but is probably reflective of the barriers in testing and care they experience. Compared to white MSM in the US, they are less likely to be aware of their HIV status, less likely to be on treatment once diagnosed and have higher levels of untreated STIs (237, 238).

Although this review did not aim to document seroadaptive behaviours, some of the identified risk factors could be categorised as seroadaptation. Seroadaptive behaviours are employed to reduce the risk of HIV acquisition and could be protective when compared with CAI and no seroadaptive practices (128). The success of these strategies is, however, based on reliable ascertainment of the individual's HIV status and that of their partner. Men employ serosorting, a strategy where a HIV-concordant partner is chosen, but there is an on-going debate on the effectiveness of serosorting as an HIV prevention approach (239, 240) as it is unclear the extent to which serosorting is based on the assumption of seroconcordance rather than a discussion with the partner. In this review, CRAI with HIV negative partners was associated with a lower risk of HIV acquisition but the overlapping 95%CI with CRAI with HIV positive partners suggests no difference in HIV risk between serosorting based on presumed negative status and engaging in CRAI with HIV positive partners. The benefits and protective role of serosorting may in fact be limited to mutually monogamous relationships where couples test HIV negative and for all other MSM, if serosorting is practiced, it is likely to only be effective when practiced with other prevention methods e.g. condom use. MSM reporting CIAI with HIV positive partners were found to be at increased risk of HIV than with HIV negative partners (177). This may be an indication of seropositioning where the HIV negative man only takes the insertive sex position during CAI based on the lower probability of acquiring HIV in the insertive rather than receptive position (241) and highlights there is still risk associated with this seroadaptive behaviour.

From the available data on the PAR of HIV risk factors, it is evident that although the HR of different risk factors may be similar, for example, for CRAI and STIs, the relative low prevalence of STIs in the population compared to CRAI results in

a smaller PAR for STIs. Therefore, reductions in partner numbers and CRAI with serodiscordant partners will have a greater impact on the occurrence of new HIV infections among MSM than reductions in the prevalence of STIs. Few studies considered PAR and therefore missed the opportunity to use this measure to identify specific behaviours for targeted interventions.

4.6 Reflections

On reflection, I should have conducted the literature search in a second database to gain a better understanding of whether I had potentially missed any publications for the review. This approach would have strengthened the literature review and been in line with the PRISMA checklist. Further, I should have performed a formal assessment of bias, which would have been according to standard practice, rather than having a general discussion of the biases that were relevant and important for interpreting incidence estimates. Nevertheless, I have included the PRISMA checklist in Appendix 1 to show that though this literature review does not meet all the requirements of a systematic review, it has been conducted using a systematic approach.

4.7 Discussion

4.7.1 Methodological considerations

4.7.1.1 Longitudinal studies

The advantage of prospective longitudinal studies is that follow-up of MSM at regular time intervals for testing is possible. However, the studies are subject to a number of limitations. They could require several years in duration to robustly estimate incidence as the number of seroconversions that occur is dependent on

the level of incidence in the population. Loss-to-follow up may introduce an important bias as men who are lost to the study could be different to those that remain and if these differences are related to HIV risk, it is likely that incidence in these two populations will be different. This bias and its impact on HIV incidence was rarely discussed by the prospective cohort studies included in this review. Yang H *et al* did not find loss to follow-up was associated with risk factors (210) while Yan H *et al* concluded true incidence was probably higher than their estimates due to higher loss to follow-up among MSM who reported higher risk behaviours at baseline (209).

While the limitation of waiting years for sufficient numbers of seroconversions can be overcome through retrospective cohorts; these studies have their own considerations. Frequency of HIV testing and motivations for testing will impact incidence estimates derived from the testing history of a retrospective cohort or from open cohorts where MSM can leave or join at any time point. In these studies incidence is determined in a population that repeat tests for different reasons and if the reason for repeat testing is not independent from the risk of HIV, for example if repeat testing is more frequent among MSM engaging in high risk behaviours, incidence will be overestimated (157, 185). The interval between HIV tests is of significant importance when incidence is estimated over shorter time periods. For the reasons discussed above, MSM participating in these types of studies could repeat test years apart or repeat test frequently (165, 175, 176, 187); and those who test more frequently have a greater chance of being included in the study, which would bias estimates towards frequent testers and would result in overestimated incidence estimates (242). By increasing the follow-up time, this bias is reduced. One study addressed this limitation by weighting estimates based on an individual's probability of being included in the

study (183). It is possible repeat testers may actually have lower risk behaviours and incidence and represent the worried well who regularly test irrespective of their sexual behaviours (243).

Longitudinal studies do, however, provide direct estimates of HIV incidence, are more easily comparable over time and allow HIV incidence to be measured in specific sub-populations of MSM. However few cohort studies have been conducted and reported in the literature since 2000, which in addition to the limitations discussed above, could also reflect stable HIV incidence, as any changes in incidence are more likely to be published.

4.7.1.2 Serological testing for incidence estimates

One of the advantages of serological testing over longitudinal studies is the ability to determine incidence among first-time or once-only testers. Serological testing removes the need for repeat testing as a single serological sample is tested using RITA. There are however challenges in serological testing that can bias HIV incidence estimates.

In contrast to community surveys, population estimates based on RITA testing of new HIV diagnoses only uses information on those testing and is dependent on the population coming forward for testing (153, 171). Currently, challenges in providing robust estimates include low coverage of recent testing of new diagnoses and limited information on population HIV testing. Population HIV testing, will similarly impact estimates obtained from serological testing in longitudinal studies (176). In both types of studies, motivations for and changes in frequency of HIV testing will impact incidence estimates. The number of recent infections detected will be a function of the probability that an individual will get

tested and be classified as recent. Estimates based on RITA may be inflated if repeat testing increases in the population for any reason, if individuals test because of symptoms of primary infection (244), or STI symptoms and if men test for HIV soon after a recent exposure rather than later on in the window period (245). In all of these scenarios MSM are more likely to be identified as recently infected and if the proportion identified as recent may be higher than what would have been observed in the general MSM population diagnosed with HIV, incidence will be overestimated. In order to calculate population estimates from serological testing and control for the biases introduced by assumptions made when extrapolating estimates from a sample to the population, multiple imputation and stratified analyses by testing frequency are conducted in the US (154, 170). However, to more accurately reduce the uncertainty in estimates, improved HIV surveillance and coverage of RITA testing is essential for population estimates from serological testing of new diagnoses.

4.7.1.3 Biases in risk factor analyses

Some of the important biases identified in this review are discussed below. The biases have been catalogued into three main groups: selection bias, information bias and confounding.

Selection bias can arise when the population recruited into the study does not represent the target population either as a result of biased sampling, selective losses to follow-up, or non-response. Studies with inclusion criteria that resulted in a higher risk population of MSM being recruited (e.g. sex with another man in the last three months to one year) will produce results that are not representative of lower risk MSM (177, 201, 203). Conversely, recruiting men who had sex with another man in the past five years (217, 226) may only produce results

generalisable to a lower risk population. Non-response bias can occur during recruitment and is problematic in studies where the response rate is low. The results will be biased if there is a difference between MSM that participated compared to those that did not and the direction of the bias will be dependent on the population recruited. If more high risk MSM are likely to participate, higher estimates than the true ones will be reported. Response rates were often not reported by the studies nor were any potential impacts on the results discussed, which make it difficult to compare the studies and evaluate the impact of this bias. Finally, the choice of controls in case-control studies can also contribute to selection bias. The recruitment of controls that are too similar to cases as reported by Macdonald *et al* will bias towards the null and the resulting odds ratios will be conservative with the possibility that associations between the exposure and outcome are missed (219).

Information bias occurs during data collection. Recall bias is likely to have impacted a number of the studies, particularly case-control studies (219, 220, 222) where the participant knows their HIV status. Knowledge of HIV status could influence responses to recent sexual and other behaviours. Further, questions relating to situations where the participant's judgement will have been impaired e.g. when under the influence of alcohol or drugs (217), can also impact recall. Recall bias may be likely when the recall period is longer. Questions that relate to the previous three months are likely to produce more accurate responses than those that ask about the last year and if recall differs by HIV status, estimates will be biased. In studies examining sexual behaviours or drug and alcohol use, social desirability bias is an important consideration. HIV risk behaviours are sensitive and can be stigmatised and when self-reported are commonly underreported. Lavoie *et al* found a risk association between HIV and condom

use during anal sex with a serodiscordant or casual partner, which may be due to condom failure but could also be due to bias in reporting this preventative behaviour (190). The use of computer assisted interviews may mitigate this bias as questions can be privately completed (219, 221, 246). In cohort studies, behaviours may change over time due to cohort participation where as a result of participating responses change over time, or due to prevention counselling provided by study staff. This could impact long running cohorts such as the Amsterdam Cohort Studies (81), Omega Study (191) and the HIM cohort (217) and lead to underestimation of risk associated with sexual behaviours.

Confounding occurs when a variable is a risk factor for an outcome and is also associated with the exposure of interest in the target population. The main effect of the variable on HIV acquisition can be measured by including confounders as variables in multivariable models. All the studies, except one, reported adjusted risk estimates where the potential for confounding for measured variables was controlled for. However, in practice it is possible that there are potential confounders that were not measured.

While not relevant to systematic errors, small sample sizes have consequences for random errors. Both the robustness of estimates, which will be reflected in the wide confidence estimates, and lack of generalisability to the broader MSM community will be impacted (219, 221, 222). Inherent to a small sample size and also an issue for populations with low HIV incidence will be the small number of seroconversions that are detected. It limits the precision of estimates obtained and the power to detect other predictors e.g. those related to oral transmission as reported by Weber *et al* (218).

4.7.2 Implications for thesis

HIV incidence is higher among GUM attending MSM populations than the general population. This is almost certainly the case in the UK and highlights the importance of focussing HIV prevention initiatives in this population. Available global data suggest that among most MSM populations incidence has remained stable during the 2000s although recent estimates are lacking. In England, the last estimate from the general GUM attending population is a decade old (26). The work in this thesis will determine whether HIV incidence has changed since the last estimates and it will also determine the risk factors for HIV among GUM attending MSM. Although clinical and sexual behavioural risk factors were identified from this review, only one of the risk factor studies was relevant to the UK context. Tailoring prevention initiatives requires a full understanding of those characteristics that increase the risk of infection in the target population and which are the most important from a public health perspective.

5 HIV incidence and predictors of HIV acquisition among MSM attending GUM clinics

5.1 Introduction

Through the literature review I identified the different methodologies that have been used to measure HIV incidence among MSM populations. Within the UK, two main methods have been employed: modelling among the general MSM population and ad hoc studies using residual blood specimens among MSM attending GUM clinics. All the evidence suggests MSM attending GUM clinics are a higher risk population, a population that reports higher frequency of sexual risk behaviours than MSM that do not attend GUM and among whom incidence is higher.

There are, however, no recent estimates of HIV incidence in this high risk population of MSM and to date no methodologies to allow routine measurement of incidence and change over time. HIV incidence estimates are essential parameters to describe the current HIV epidemic and identifying sub-groups at greatest risk of infection. Incidence estimates can also inform local clinical practice and HIV prevention activities and policies. The recent implementation of GUMCAD, the national surveillance of tests and diagnoses from GUM clinics in England has allowed a unique opportunity to estimate HIV incidence among MSM. Here, I employ a simple approach using these data to present HIV incidence in a GUM attending population of MSM in 2012 and predictors of acquisition.

5.2 Aims and Objectives

The overall aim of this analysis was to calculate HIV incidence among MSM attending GUM clinics in England. The specific objectives included:

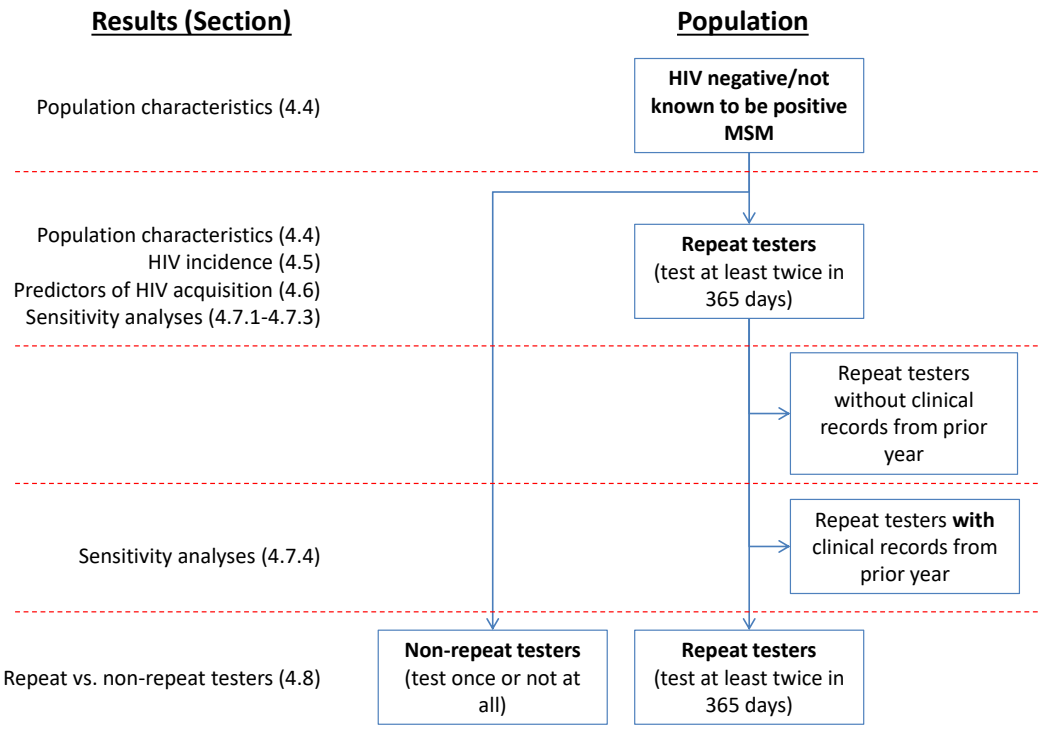
- Using a standardised approach to calculating HIV incidence using clinical diagnosis and service use data submitted by GUM clinics
- Identifying clinical and socio-demographic predictors for HIV acquisition
- Investigating the representativeness of repeat testing MSM

5.3 Overview of methods and analyses

To achieve these objectives, I undertook a secondary data analysis using GUMCAD, as outlined in section 3.2, in which an open cohort of HIV negative MSM were followed from their first HIV test at a GUM clinic in 2012 for up to one year until they either seroconverted or until their last attendance in the 12 month period after their first test.

In the following results sections, I describe the characteristics of the overall HIV negative MSM population attending GUM as well as the characteristics of repeat testers (MSM with two HIV tests in a one year period) (Figure 5.1). Repeat testers were a sub-set of the overall population. The incidence and predictors analyses and the majority of sensitivity analyses were conducted in this population. I end the results with a comparison of repeat and non-repeat testers to investigate the representativeness of repeat testers.

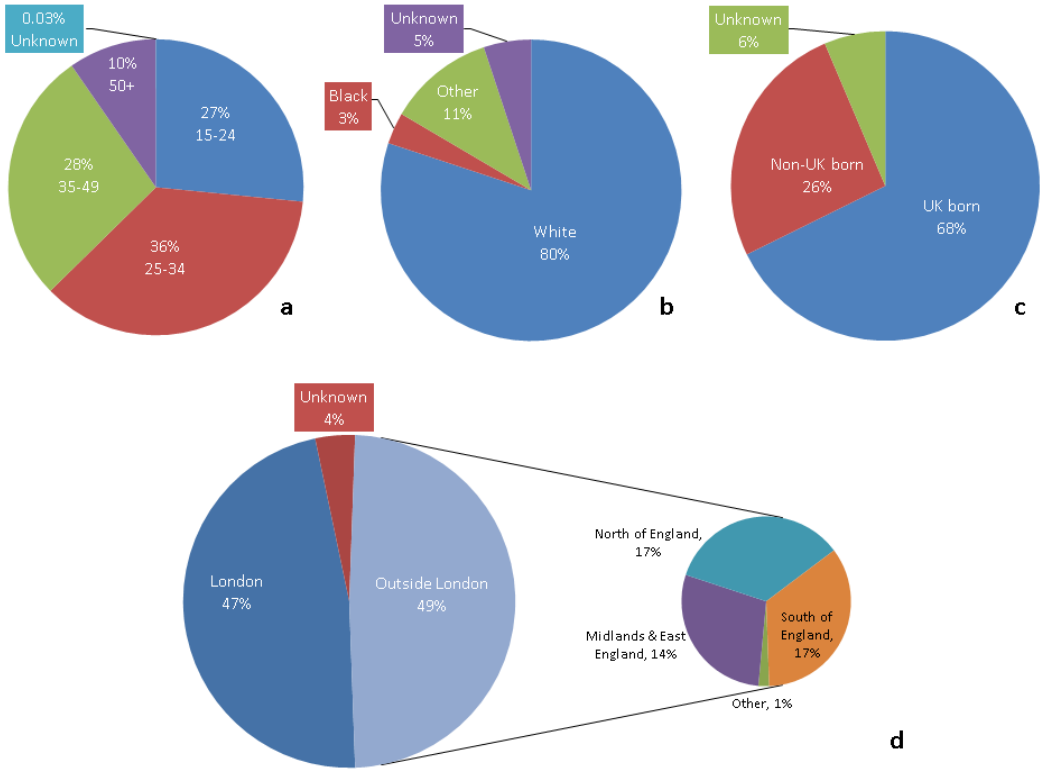
Figure 5.1 HIV negative MSM population and sub-populations with associated results



5.4 Study population characteristics

In 2012, 85,505 MSM not known to be HIV positive attended a GUM clinic in England. The mean age of attendees was 34 years (standard deviation (SD) 21.2). Eighty per cent were of white ethnicity, over two-thirds were born in the UK and almost half were resident in London (47%) (Figure 5.2). Of the other ethnic groups, 4% were Asian (n=3,644, belonging to 'Other') and 3% were of black ethnicity; with 45% of them black Caribbean, 35% black African and the remainder of other black ethnicity.

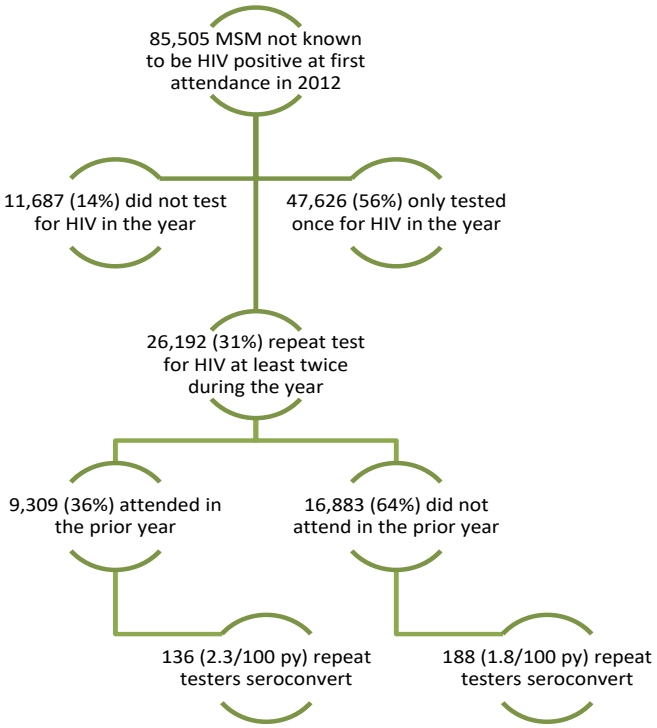
Figure 5.2 Characteristics of MSM not known to be HIV positive attending GUM clinics in England, 2012 by a) Age group b) Ethnicity* c) UK birth d) Residence



*'Other' ethnicity comprised: Asian, Chinese, mixed and other

The first attendance in 2012 was the first recorded attendance at the GUM clinic since 2008 (when GUMCAD records began) for 57% of men, while 25% had attended the same clinic in the year prior to their initial attendance in 2012. After the initial attendance in 2012, only 41% re-attended the same clinic within 12 months (but more than 42 days after the first attendance) (median attendances per annum: 3, interquartile range (IQR) 2-4). Of all MSM not known to be HIV positive, 14% did not test for HIV at the first attendance in 2012 or in the following 12 months, 56% tested for HIV once and the remainder (31%, 26,192) tested at least twice at the same clinic during 365 days ("repeat testers") (Figure 5.3).

Figure 5.3 Flow chart of MSM not known to be HIV positive attending GUM clinics in England, 2012



These repeat testers were included in HIV incidence analyses. Just over a quarter were young (15-24 years), the majority were of white ethnicity (80%) and two-thirds were born in the UK (Table 5.1). Demographically, repeat testers were similar to all MSM not known to be HIV positive. At the first attendance in 2012, 19% of repeat testers were diagnosed with an acute STI. Of all repeat testers, 9,309 (36%) had attended the same clinic in the year prior to their first attendance in 2012 (Figure 5.3). Of these, 95% had tested for HIV or had a STI screen in the previous year, 26% were diagnosed with a bacterial STI, of which 20% were rectal infections. Only 417 (4.5%) MSM had taken PEP in the previous year.

5.5 HIV incidence

The 26,192 MSM contributed 16425.1 person years (py) of follow-up time. Average follow-up time was 0.6 (SD: 0.2) person years. There were 324 seroconversions during follow-up, giving an HIV incidence of 2.0/100 py (95%CI 1.8-2.2) in 2012. Incidence differed by sub-groups of the population (Table 5.1).

Table 5.1 Demographic & clinical characteristics and HIV incidence among repeat testing MSM attending GUM clinics in England, 2012 (n=26,192)

Characteristic	Number (%)	Number of seroconversions	HIV incidence/100 person years (95%CI)	*p*[a]
Age group				0.07
15-24	7,281 (28)	89	2.0 (1.6-2.4)	
25-34	10,003 (38)	128	2.0 (1.7-2.4)	
35-49	6,779 (26)	92	2.1 (1.8-2.6)	
50+	2,123 (8)	14	1.0 (0.6-1.8)	
Unknown	6 (0.02)	1	29.3 (4.1-2.1e+02)	
Ethnicity				0.01
White	20,826 (80)	241	1.8 (1.6-2.1)	
Black	1,018 (4)	21	3.2 (2.1-5.0)	
Other	3,305 (13)	42	2.0 (1.5-2.7)	
Unknown	1,043 (4)	20	3.1 (2.0-4.8)	
UK born				
Yes	17,193 (66)	193	1.8 (1.6-2.1)	0.007
No	7,556 (29)	118	2.5 (2.1-3.0)	
Unknown	1,443 (6)	13	1.4 (0.8-2.5)	
Residence				0.006
London	12,620 (48)	178	2.2 (1.9-2.6)	
Outside London	11,614 (44)	116	1.6 (1.3-1.9)	
Unknown	1,958 (8)	30	2.4 (1.7-3.4)	
Clinic location				0.02
London	14,182 (54)	197	2.2 (1.9-2.5)	
Elsewhere, England	12,010 (46)	127	1.7 (1.4-2.0)	
At initial visit in 2012:				
Bacterial STI[b]	4,380 (17)	88	3.2 (2.6-4.0)	<0.001
Acute STI[c]	5,032 (19)	91	2.9 (2.4-3.6)	<0.001
Total	**26,192**	**324**	**2.0 (1.8-2.2)**	

[a] Univariable analyses excluded individuals with missing information

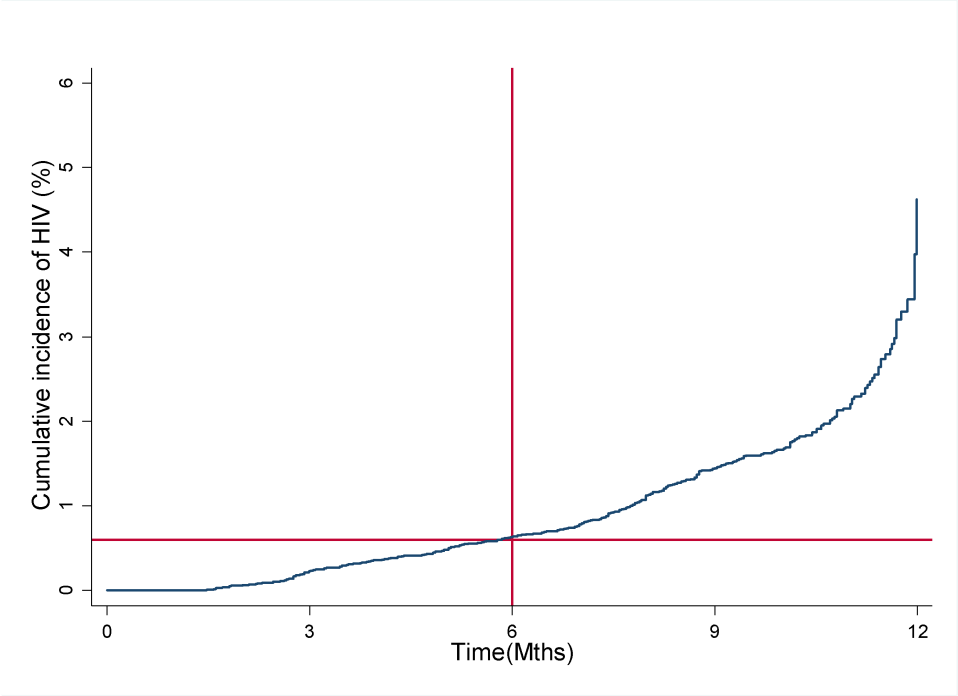
[b] Bacterial STI includes: Chlamydia, gonorrhoea, syphilis (primary, secondary and early latent), lymphogranuloma venerum (LGV), non-specific genital infection (NSGI), chancroid, and donovanosis

[c] Acute STI includes all the above and first episode of genital warts and herpes

MSM of black ethnicity reported higher incidence (3.2/100 py) than MSM of white ethnicity (1.8/100 py), while incidence was lower among those born in the UK (1.8/100 py). Incidence was also higher among MSM attending London clinics (2.2/100 py) and men with a bacterial STI diagnosis at the initial attendance in 2012 (3.2/100 py). Incidence was non-significantly higher among MSM attending in the prior year (2.3/100 py, 95%CI 1.9-2.7) compared to non-attenders (1.8/100 py, 95%CI 1.6-2.1). The unadjusted and adjusted hazard ratios are described in section 5.6.

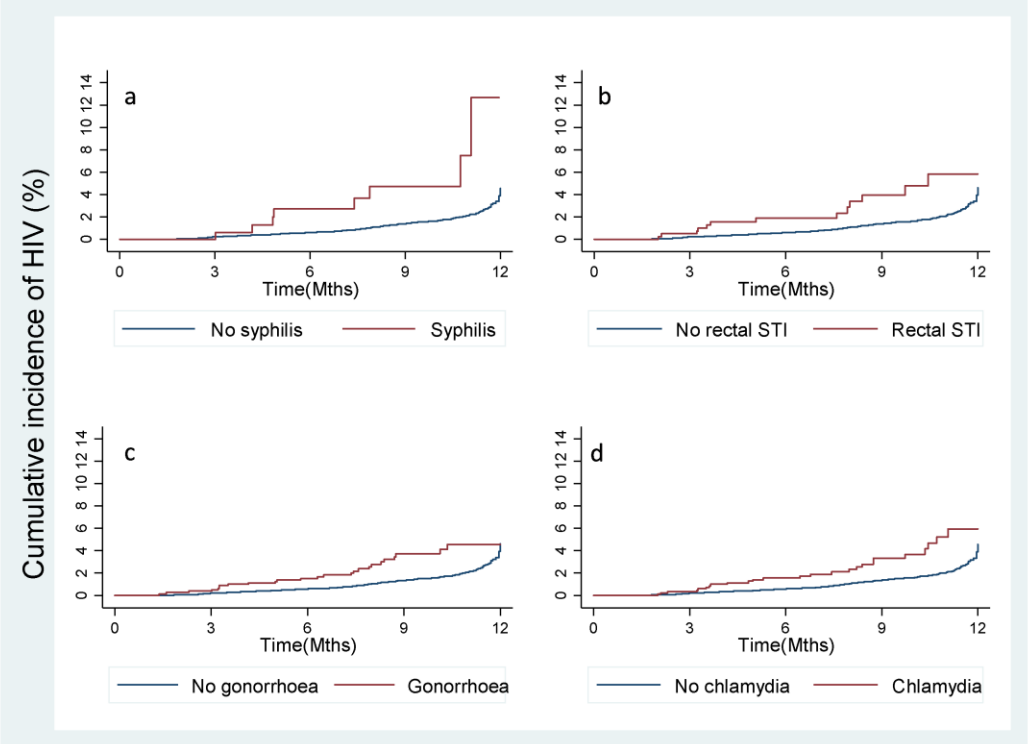
During the year of follow-up, cumulative HIV incidence was 4.6% (95%CI 3.3-6.5), meaning, almost 5% of MSM were newly infected and diagnosed with HIV within a year of the first negative test. The graph shows that at six months less than 1% of MSM were newly infected (0.6%, 95%CI 0.5-0.8) but cumulative incidence rose more steeply during the second six months of follow-up. A large increase was observed towards the end of follow-up due to the occurrence of three seroconversions among a small number of men still at risk.

Figure 5.4 Cumulative HIV incidence among repeat testing MSM attending GUM clinics in England, 2012



When cumulative incidence was examined by sub-groups of MSM who were diagnosed with a STI in the previous year, 13% (95%CI 5-30) of MSM with a previous syphilis infection came back within a year with HIV compared to 6% (95%CI 4-9) with a previous chlamydia and 5% (95%CI 3-7) with a gonorrhoea infection (Figure 5.5).

Figure 5.5 Cumulative HIV incidence among repeat testing MSM attending GUM clinics in England, 2012 by a) syphilis b) rectal STI c) gonorrhoea d) chlamydia in the prior year



5.6 Predictors of HIV acquisition

Fourteen variables had a p value <0.1 in univariate analyses and were included in multivariable analyses (Table 5.2). Five variables remained significantly associated with HIV acquisition in the final model. Of the demographic variables, only residency in London was associated with a 1.4 times higher risk of HIV acquisition (95%CI 1.1-1.8). Both a bacterial STI and a rectal bacterial STI at the initial attendance in 2012 were associated with increased risk of acquiring HIV in the subsequent year (aHR:1.4 and 2.1, respectively). Two clinical markers from the previous year were also predictive of HIV infection: a previous syphilis or gonorrhoea infection. MSM previously diagnosed with syphilis were more than four times at greater risk of going on to acquire HIV (aHR: 4.1, 95%CI 2.0-8.3).

Table 5.2 Predictors of HIV acquisition and population attributable risk among repeat testing MSM attending GUM clinics in England, 2012 (n=25,313)

Characteristic	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	*P*	PAR* (95%CI)
Demographics:				
Ethnicity				
White	1.0	n.s.	0.06	
Black	1.7 (1.1-2.7)	n.s.		-
Other	1.1 (0.8-1.5)	n.s.		
UK born	0.7 (0.6-0.9)	n.s.	0.144	-
Resident in London	1.4 (1.1-1.7)	1.4 (1.1-1.8)	0.002	19% (8.8-30)
Attending a London clinic	1.3 (1.0-1.6)	n.s.	0.090	-
Initial attendance in 2012:				
Bacterial STI[a]	1.9 (1.5-2.5)	1.4 (1.0-1.9)	0.045	9.3% (3.3-17)
Acute STI[b]	1.7 (1.3-2.2)	n.s.	0.261	-
Rectal infection[c]	2.8 (1.9-4.1)	2.1 (1.3-3.3)	0.003	3.0% (1.0-7.1)
In the prior year:				
Acute STI	1.9 (1.4-2.7)	n.s.	0.457	-
Syphilis	3.4 (1.7-6.9)	4.1 (2.0-8.3)	<0.001	2.1% (0.7-4.8)
Chlamydia	2.2 (1.4-3.4)	n.s.	0.12	-
Gonorrhoea	2.2 (1.4-3.3)	2.1 (1.4-3.2)	0.001	3.8% (1.4-7.4)
NSGI	1.4 (0.8-2.3)	n.s.	0.915	-
PEP	1.5 (0.7-2.9)	n.s.	0.891	-
HIV test/STI screen	0.9 (0.7-1.1)	n.s.	0.196	-

n.s.: not significant

*PAR only calculated for risk factors significant in multivariable analyses

[a] Bacterial STI includes: Chlamydia, gonorrhoea, syphilis (primary, secondary and early latent), lymphogranuloma venerum (LGV), non-specific genital infection (NSGI), chancroid, and donovanosis

[b] Acute STI includes all the above and first episode of genital warts and herpes

[c] Rectal sites for gonorrhoea, chlamydia, NSGI and LGV

The population attributable risk of living in London accounted for the greatest proportion of HIV infections (19%). The clinical markers at the initial attendance accounted for another 12% while the clinical markers from the previous year together accounted for 6% of all HIV infections. The PAR for a prior syphilis infection was 2.1% (95%CI 0.7-4.8%), which means that 2% of HIV infections that occurred in the study population could be accounted for by a previous syphilis infection. In total, the predictors identified in this analysis accounted for just over a third of all infections occurring in the population.

5.7 Sensitivity analyses

In the primary analysis, incidence was based on person years of risk where individuals were followed from the date of the last HIV negative test to the date of the first HIV positive test (for seroconverters) or to last attendance (for those remaining negative) and risk factor analyses were based on all repeat testers. I conducted four sensitivity analyses to investigate the robustness of these particular aspects of the methodology:

i) Person-years at risk for seroconverters was modified to the mid-point between last negative date and date of diagnosis
ii) Person-years at risk for non-seroconverters was modified to the last attendance in the 13 months following the first negative test
iii) Person-years at risk for non-seroconverters was modified to exactly 365 days following the first negative test
iv) The risk factor analysis was restricted to those with at least one clinical record from the 365 days prior to the first attendance in 2012

5.7.1 HIV incidence using mid-point of seroconversion

The number of MSM included and the number of seroconversions remained unchanged. However, the person time of follow-up reduced slightly from 16425.1 py to 16336.5 py. This had no impact on HIV incidence in 2012: using the mid-point method, incidence was 2.0/100 py (95%CI 1.8-2.2).

5.7.2 Right censoring at one year and one month after first HIV negative test

Eight-four per cent of MSM not included in the incidence analyses only attended the clinic once in the study period (i.e. the first attendance in 2012). Of these

men, 91% (n= 45,739) did have a HIV negative test at the attendance. When the follow-up period was increased from one year to one year and one month, 200 additional MSM had a second HIV test in this extra month. These men were included in the study cohort. The number of seroconversions increased from 324 to 343 such that 9.5% (19/200) of these men were diagnosed with HIV at this attendance. However, there was no impact on HIV incidence as it remained 2.0/100 py (1.8-2.2).

5.7.3 Right censoring at 365 days after first HIV negative test

The total follow-up time substantially increased from 16425.1 py to 26027.5 py when MSM who remained HIV negative were right censored at 365 days after their first HIV negative test and not at their last attendance date. As the follow-up time only increased for MSM who did not become HIV positive, the number of seroconversions remained the same. The large increase in follow-up resulted in a significantly lower HIV incidence: 1.2/100 py (95%CI 1.1-1.4).

5.7.4 HIV incidence and risk factor for acquisition among MSM with clinical history

HIV incidence among MSM who had clinical history from the previous year (n=9,309) was 2.3/100 py (95%CI 1.9-2.7) and was comparable to all repeat testers. Incidence was significantly higher among those with a diagnosis of an acute STI (3.4/100 py) or bacterial STI (3.7/100 py) (Table 5.3). These increases were due to higher incidence among MSM diagnosed with chlamydia (4.5/100 py), gonorrhoea (4.3/100 py) or syphilis infections (7.1/100 py). Incidence did not differ by genital infection of warts or herpes.

Table 5.3 HIV incidence among a subset of repeat testing MSM attending GUM clinics in England with clinical history from the prior year, 2012 (n=9,309)

Characteristic	Number (%)	Number of seroconversions	HIV incidence/100 person years (95%CI)	*p*
HIV test/sexual health screen	8,889 (95)	134	2.3 (2.0-2.8)	0.10
PEP taken	417 (4.5)	9	3.3 (1.7-6.3)	0.27
Bacterial STI[a]	2,396 (26)	56	3.7 (2.8-4.8)	<0.001
Acute STI[b]	2,672 (29)	58	3.4 (2.6-4.4)	<0.001
Rectal infection[c]	380 (4.0)	13	5.4 (3.2-9.5)	<0.001
NSGI	916 (9.8)	17	2.9 (1.8-4.7)	0.23
Chlamydia	855 (9.2)	25	4.5 (3.1-6.7)	<0.001
Gonorrhoea	952 (10)	26	4.3 (2.9-6.3)	<0.001
Genital warts	286 (3.1)	4	2.2 (0.8-6.0)	0.97
Syphilis	181 (1.9)	8	7.1 (3.5-14.2)	<0.001
Genital herpes	131 (1.4)	2	2.3 (0.6-9.4)	0.93
Total	**9,309**	**136**	**2.3 (1.9-2.7)**	

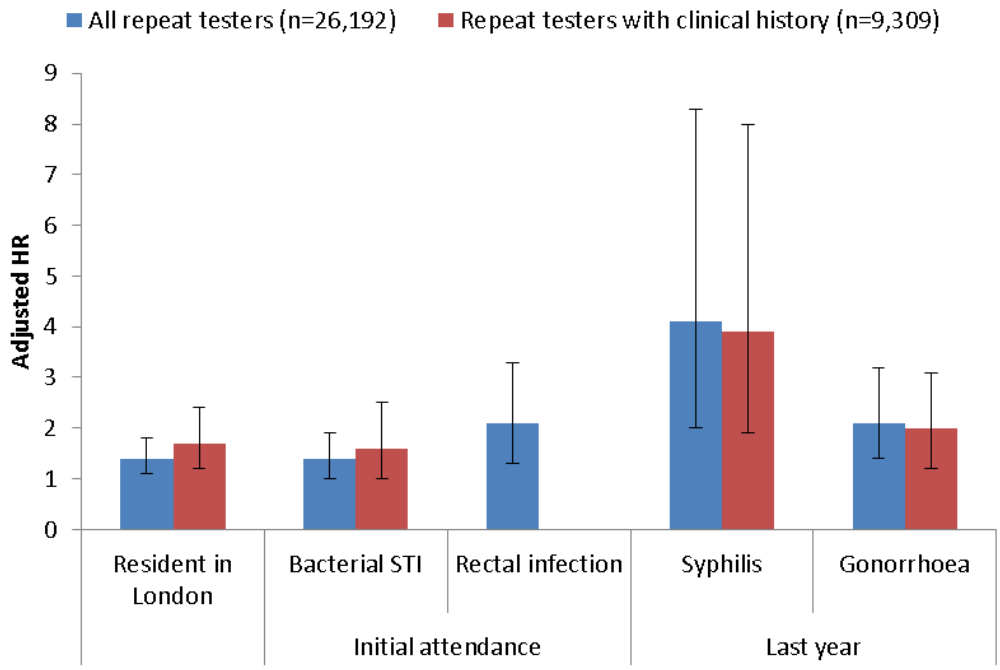
[a] Bacterial STI includes: Chlamydia, gonorrhoea, syphilis (primary, secondary and early latent), lymphogranuloma venerum (LGV), non-specific genital infection (NSGI), chancroid, and donovanosis

[b] Acute STI includes all the above and first episode of genital warts and herpes

[c] Rectal sites for gonorrhoea, chlamydia, NSGI and LGV are reported

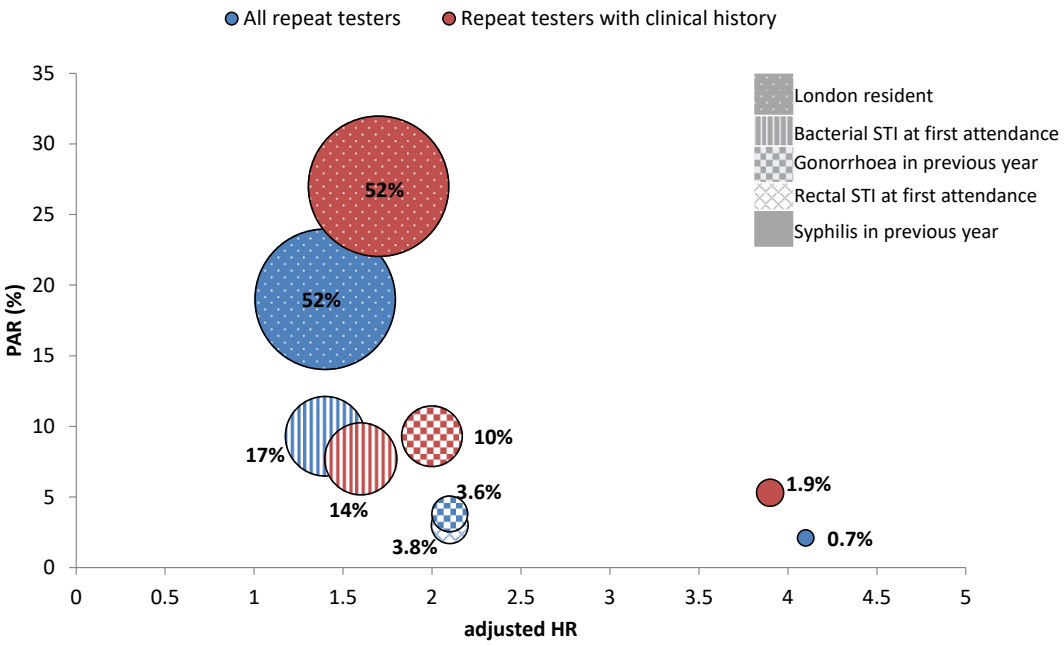
The same risk factors were identified for MSM with clinical history as were for all repeat testers with the exception of a rectal bacterial infection at the initial attendance which was only identified for all repeat testers (Figure 5.6). The magnitude of effect of each factor was no different for the two groups.

Figure 5.6 Predictors of HIV acquisition among repeat testing MSM attending GUM clinics in England, 2012



While a previous syphilis infection was most strongly associated with a subsequent HIV infection (aHR: 3.9 95%CI 1.9-8.0), it only accounted for a small proportion of infections (5%) due to its low prevalence among repeat testers (1.9%) (Figure 5.7). A gonorrhoea infection accounted for almost 10% of all the infections that occurred in the population. The four factors in total accounted for almost half of all infections (49%). The main difference between PARs among all repeat testers and those with clinical history was that PARs relating to clinical history (e.g. gonorrhoea and syphilis infections) were higher for MSM with clinical history due to the greater population prevalence of the factors (Figure 5.7).

Figure 5.7 Population attributable risk, adjusted hazard ratios and prevalence of predictors of HIV acquisition, among repeat testing MSM attending GUM clinics in England, 2012



*Size of bubble is the population prevalence of the factor (data value shown as percentage)

5.8 Comparison of repeat and non-repeat testers

Of all MSM not known to be HIV positive (n=85,505), 14% (n=11,687) did not test for HIV at the first attendance in 2012 or in the following 12 months and 56% (n=47,626) tested for HIV once (Figure 5.3). These two groups were classed as non-repeat testers (n=59,313) and were compared to repeat testers (n=26,192). The demographic profile differed by age (≥35 years: 39% vs 34%, respectively, p<0.001), birth in the UK (69% vs 66%, respectively, p<0.001) and residency in London (46% vs 50%, respectively, p<0.001) (Table 5.4). Eighty per cent of both populations were of white ethnicity.

Table 5.4 Characteristics of HIV negative MSM, by repeat testing status, 2012

Characteristic	Non-repeat	All repeat	P value

	testers (%)	testers (%)	
Age group			<0.001
15-24	15,424 (26)	7,271 (28)	
25-34	20,876 (35)	10,003 (38)	
35-49	16,876 (28)	6,779 (26)	
50+	6,114 (10)	2,123 (8)	
Unknown	23 (0.04)	6 (0.02)	
Ethnicity			<0.001
White	47,636 (80)	20,826 (80)	
Black	1,876 (3)	1,018 (4)	
Other	6,486 (11)	3,305 (13)	
Unknown	3,315 (6)	1,043 (4)	
UK born			<0.001
Yes	40,694 (69)	17,193 (66)	
No	14,577 (25)	7,556 (29)	
Unknown	4,042 (7)	1,443 (6)	
Residence			<0.001
London	27,484 (46)	13,039 (50)	
Outside London	29,444 (50)	12,233 (44)	
Unknown	2,385 (4)	920 (4)	
Clinic location			<0.001
London	30,714 (52)	14,182 (54)	
Elsewhere, England	28,599 (48)	12,010 (46)	
At initial visit in 2012:			
Bacterial STI[a]	9,020 (15)	4,380 (17)	<0.001
Acute STI[b]	10,965 (18)	5,032 (19)	0.012
Total	59,313	26,192	

[a] Bacterial STI includes: Chlamydia, gonorrhoea, syphilis (primary, secondary and early latent), lymphogranuloma venerum (LGV), non-specific genital infection (NSGI), chancroid, and donovanosis

[b] Acute STI includes all the above and first episode of genital warts and herpes

For 48% of testers, this was first recorded attendance at the clinic (since 2008) compared to 61% of non-repeat testers (p<0.001). At the first attendance in 2012, 17% of repeat testers were diagnosed with a bacterial STI compared to 15% of non-repeat testers. Fifteen per cent of repeat testers who had also tested for HIV at least once in the previous year were diagnosed with a bacterial STI at the first attendance compared to 12% of non-repeat testers (p<0.001). A tenth of repeat testers were diagnosed with an acute STI in the previous year compared to 6% of non-repeat testers (p<0.001).

A comparison of the HIV testing history between repeat and non-repeat testers showed 33% of repeat testers had tested for HIV at least once in the prior year ("regular testers") compared to 17% of non-repeat testers ($p<0.001$) (Figure 5.8). Sixty-six per cent of repeat testers only tested once compared to 81% of non-repeat testers ($p<0.001$). There were up to eight HIV tests among repeat testers and seven among non-repeat testers (Figure 5.9). A similar proportion of both groups had tested more than a year ago ("non-regular testers").

Among repeat testers, HIV incidence was lowest among those who had never been to the clinic before (0.9/100 py) and highest among regular testers (2.3/100 py) (Figure 5.8). However the confidence intervals for all groups overlapped indicating no significant difference in incidence by previous HIV testing or attendance history. Incidence non-significantly increased with the number of HIV tests in the previous year.

Figure 5.8 Previous HIV testing history and HIV incidence among HIV negative MSM, by repeat testing status, 2012

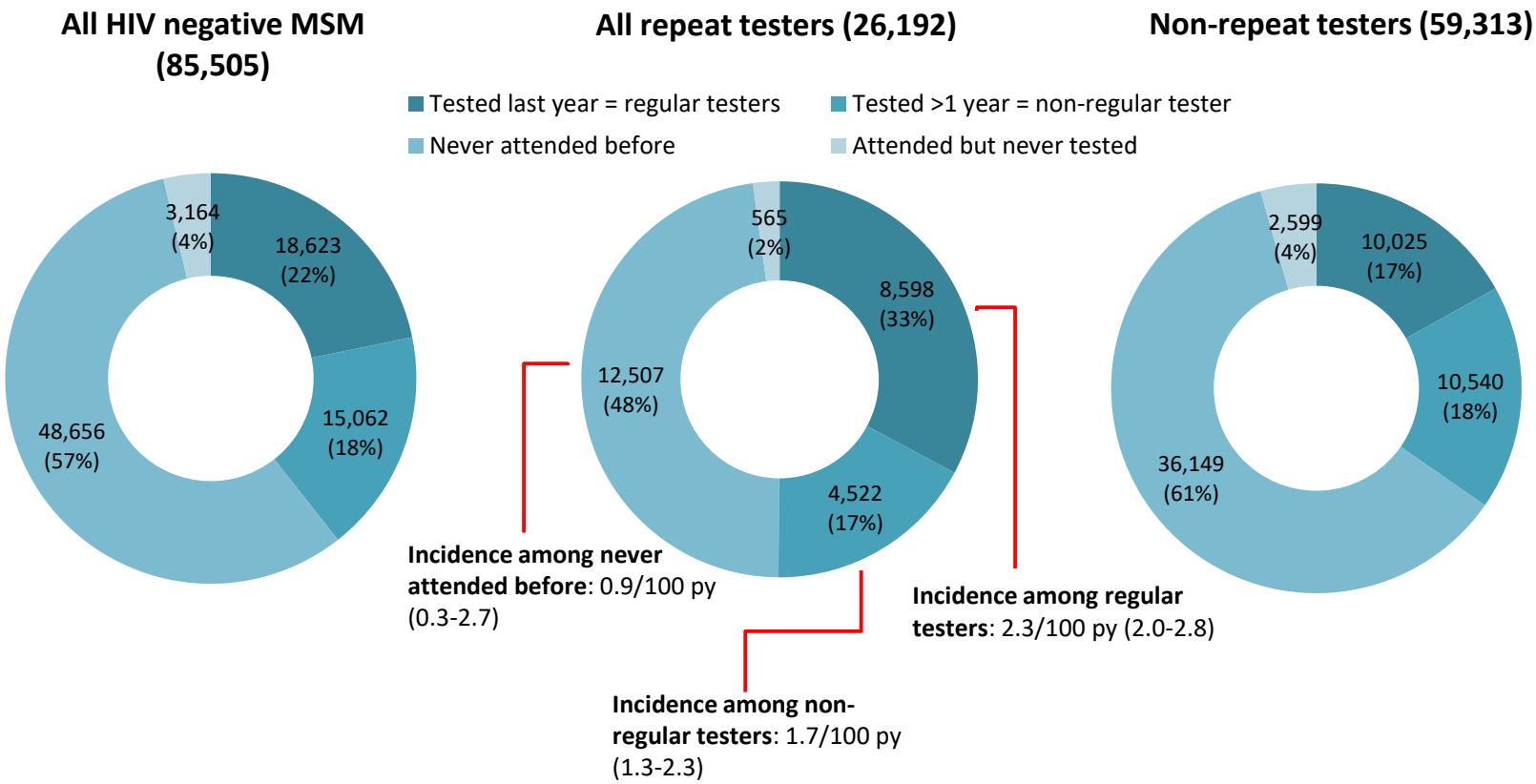
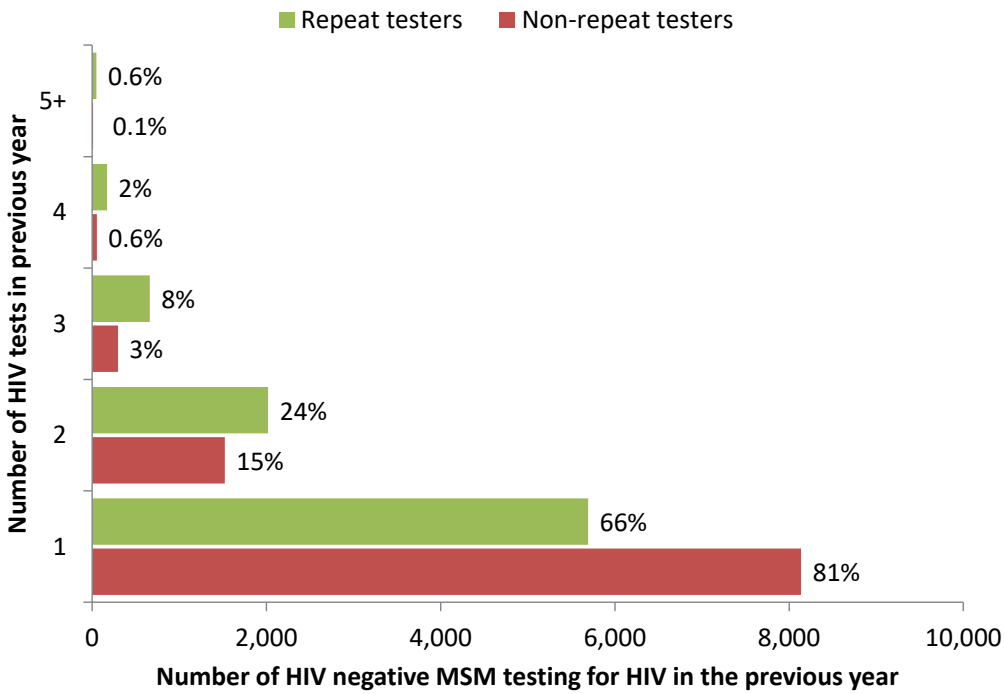


Figure 5.9 Number of HIV tests among MSM testing in the previous year, 2012



*Data values are percentage of repeat and non-repeat testers with number of HIV tests

5.9 Key Findings

In 2012, 85,505 MSM who were not known to be HIV positive attended a GUM clinic in England and of these 31% repeat tested for HIV during a one year period. HIV incidence was high at 2.0/100 py among repeat testers and highest among MSM diagnosed with a rectal STI in the prior year (5.4/100 py). Men diagnosed with a rectal STI at the initial attendance were twice as likely to acquire HIV in the subsequent year as were men diagnosed with gonorrhoea in the previous year. MSM diagnosed with a syphilis infection in the previous year were four times more likely to subsequently acquire HIV. A previous chlamydia diagnosis or HIV testing history were not associated with infection. The combined population attributable risk for HIV infection was 37%; that is, 37% of all infections occurring among repeat testers could be attributed to one of the five

risk factors identified in the study. Conversely, almost two-thirds of infections could be not accounted for by any of the routinely collected information.

Sensitivity analyses suggest that using the mid-point of seroconversion as the end date has little impact on HIV incidence. Similarly, increasing follow-up by a month to one year and month allows more men the opportunity to repeat test but without impacting HIV incidence. Incidence was significantly lower if men were right censored at exactly one year after their first HIV negative test rather than their last attendance date.

Repeat testers were younger and fewer were born in the UK than MSM who were not included in the study cohort. The proportion with previous attendance, previous HIV testing history and STI diagnosis was also higher among repeat testers. Among those testing at least once in the previous year for HIV, the frequency of testing was higher among repeat testers with 34% testing more than once compared to 19% of non-repeat testers. HIV incidence non-significantly increased with more frequent prior HIV testing among repeat testers.

5.10 Strengths and limitations

The main strength of this analysis is that it incorporated a large MSM population. Assuming that approximately 90% of MSM in the UK live in England, the men in the overall analyses represented over 10% of HIV negative MSM in England and the men included in the incidence analyses constituted almost 5%. Further, a standardised open cohort analysis allowed MSM to enter and leave the cohort at different time points during the study period.

I show that a relatively simple secondary data analysis can be performed and repeated routinely to produce robust and timely HIV estimates among MSM attending GUM clinics. These timely incidence estimates will enable continuous monitoring of the HIV epidemic in this population as well as within key sub-groups. Equally, the timeliness of the estimates is a great asset when the aim is to inform clinical and public health practice.

There are two sets of limitations in this study: i) those associated with the data source (GUMCAD), which are discussed below and ii) those arising from the methodology used to calculate HIV incidence, which are discussed as part of the general discussion on the appropriateness of the methodology (section 5.11.4).

There are three GUMCAD specific limitations. Most importantly the data can only be used to follow individuals within but not between clinics. The patient identifiers are clinic-specific and anonymised so patients can only be linked longitudinally and followed within a clinic. Hence GUMCAD cannot track the movement of individuals between clinics and in urban areas like London such movement is likely to be common. Recent data collected from a small number of GUM clinics estimated 9% of MSM attended another GUM clinic in the previous year (247). This constraint affects this analysis in two ways: 1) without the ability to identify individuals attending more than one clinic, the study population in 2012 may have been overestimated 2) these analyses will exclude MSM who according to GUMCAD had only one HIV test within the analysis timeframe but who had in fact repeat tested for HIV at another clinic and would have been included in the study cohort if movement between clinics was known. If MSM at higher risk of HIV acquisition are also more likely to attend more than one clinic for HIV testing, then the HIV incidence estimates presented here may be underestimated.

Though movement between clinics may be a limited phenomenon, I was unable to conclusively ascertain the impact on incidence from the available data.

Secondly, when these analyses were conducted, GUMCAD only captured information from GUM clinics; testing and diagnoses in other sexual health services e.g. enhanced general practitioner services will not be captured in this analysis. However, since sexual health care is mostly provided in GUM clinics for MSM, the impact on observed incidence is likely to be minimal. The majority (over 85%) of new HIV diagnoses among MSM are made in GUM clinics (28).

Thirdly, assuming that 85% of all new HIV diagnoses among MSM were made in GUM clinics, there were approximately 2,390 new HIV diagnoses in England reported to national HIV surveillance in 2012 compared with 2,000 to GUMCAD (21). Therefore, a small number of seroconversions may be missing from this analysis. The discrepancies between the two surveillance systems are probably attributable to the differences in the reporting pathways.

5.11 Reflections

The analysis approach was dictated by nature of the dataset. As a surveillance scientist, I had access to GUMCAD and it seemed appropriate to use this readily available data source to measure HIV incidence among GUM clinic attendees, especially as I expected the predominant burden of infection to be among clinic attendees. The strength of this approach was the availability of a national dataset rather than a sample of the population. However, as these data were not collected for the purpose of calculating incidence, the data items were not tailored for the project. For example, a prospective cohort study would have

allowed me to assess HIV status at regular intervals (e.g. 6 monthly or annual) rather than relying on men to return to the same clinic and have a test. This may have overcome some issues with loss to follow-up. However, conducting a cohort study is resource intensive and costly particularly as a large sample size would have been required for sufficient HIV endpoints. Alternatively, the literature review identified RITA as a method by which HIV incidence can be calculated. This approach is under investigation as part of another PhD. Finally, I could have followed my cohort for a longer period of time and used multiple imputation techniques to determine the date of infection between two tests. This would have reduced selection bias from using one year of follow-up but would also hamper the production of timely incidence estimates.

5.12 Discussion

5.12.1 Comparison of incidence with other UK studies

Our incidence estimate is consistent with other studies among MSM clinic attendees in England from 2001 (2.5/100 py, 95%CI 1.7-3.5) (26) and 2004 (3%, 95%CI 1.9-4.6) (155). These two studies employed a different methodology to estimate incidence but results suggest incidence has remained relatively stable and high over the past 10 years among men attending STI clinics (248). To estimate HIV incidence among the general MSM population, different mathematical models have been developed. These have reported incidence rates of 0.9%, (95%CI 0.5-1.3%) in the general MSM population aged 15-44 in England and Wales, in 2007 (6), mean annual incidence of 0.5% between 1998-2010 among MSM in the UK (5) and approximately 0.3% (2,500 new infections) among MSM in England and Wales in 2010 (7). These estimates highlight that incidence in clinic attending MSM is approximately two- to seven-fold higher than

in the general MSM population and underlines the high risk nature of this population.

5.12.2 Risk factors and PAR

As well as identifying risk factors for HIV acquisition, the population attributable risk was calculated to better understand what impact the removal of the risk factor in the population would have on HIV transmission. The analysis had discriminatory power to identify strata of MSM who were at high risk of HIV acquisition. Previous gonorrhoea and syphilis infections have been reported as predictors of infection (92, 135, 137, 249) and were also shown here to increase the risk of acquiring HIV two- to four-fold. Although syphilis and gonorrhoea were strongly associated with HIV infection, they occurred relatively infrequently in the population, and as the PAR is dependent on the prevalence of the variable in the population, the resulting PARs for previous STIs were small. However, as discussed it should be noted that the PAR is likely underestimated as men not attending in the prior year may have been diagnosed with a STI elsewhere. Nevertheless, while preventing these infections remains an important strategy at the individual level; their removal will likely only have a small impact on reducing population level HIV incidence.

Rectal infections were also associated with HIV acquisition, similar to the results of a study in New York (136). Rectal infections reflect the practice of risky sexual behaviours including CRAI. The estimated per-act probability of acquiring HIV when engaging in CRAI is 138/10,000 exposures to an infected source; the highest probability associated with any sexual exposure (129). This probability is likely to be even higher when the HIV positive partner is also infected with another STI. STIs can facilitate transmission of HIV during condomless sex by

increasing the shedding of HIV in the semen (250, 251). The presence of genital ulcer dieaese also increases the relative risk of acquiring HIV. As well as being strongly associated with HIV acquisition, sexual risk behaviours can occur more frequently in the population than STIs. They will, therefore, also have a higher PAR (124), which implies their reduction will be necessary to have a significant impact on HIV transmission.

Geographic location was the only socio-demographic factor associated with incidence with London residents at higher risk than residents elsewhere in the UK. This is likely due to high HIV prevalence and the sexual behaviours of MSM residing in London. HIV prevalence is significantly higher in London (2013: 132/1,000 aged 15-59 years) than the rest of the UK (39/1,000) (252), thus although the proportion of MSM living in London unaware of their infection is lower than outside London, onward transmission of HIV is likely to be higher in London. Further, the proportion of undiagnosed MSM who had tested for HIV in the past year in London has significantly increased since 2000 suggesting that in recent years a greater number of infections in this population were acquired in the year following the last HIV test (20). Trend data from community samples of MSM in London indicate that the proportion of MSM reporting CAI in the last year increased from 43% to 53% between 2000 and 2013 (20). MSM living in other cities in the UK reported less risky behaviours such as numbers of sexual and anal partners than MSM from London (46, 253). There is also some evidence to suggest that recreational drug use has increased among London MSM (254). The PAR for residing in London was the largest and reflects the high risk behaviours practiced among men residing in London.

Behavioural information would be more useful than the currently available clinical outcomes for better identification of high risk MSM in clinical settings and for guiding better decision making for HIV prevention (255). To enable monitoring of the impact of behaviours on HIV incidence, behavioural data first needs to be collected. A clinical audit indicated that routine collation, nationally, of this information should be possible as the majority of GUM clinics do collect recent sexual behaviours for MSM (11).

5.12.3 Repeat testers

Repeat testers are a diverse population of men seeking HIV testing services for different reasons; while some men may test frequently due to ongoing risk, others may test as a reassurance mechanism. Thus for some men, attendance at GUM for testing may be related to their risk whereas for others it will not be. Results in this chapter add to the evidence-base that repeat testers are likely to be a higher risk population than MSM who either don't test or only test once for HIV during a year. They attended the clinic more frequently and had higher frequency of prior HIV testing and STI diagnoses than non-repeat testers. There was a non-significant association between frequency of prior HIV testing and subsequent incidence with those testing more also reporting higher incidence, which further supports the hypothesis that seeking frequent testing is not independent of risk of infection.

Others also suggest frequency of HIV testing is related to risk behaviours. McDaid *et al* (253) reported 57% of MSM were regularly tested as part of their sexual health check compared to 36% who tested following a risk event. Men reporting at least four tests in the last two years were more likely to report at least 10 sexual and 10 anal intercourse partners than those testing 0-1 times

indicating a higher risk population of frequent testers. In Amsterdam, MSM who repeat tested reported significantly more casual partners and numbers of partners than MSM who only had a single test (256). Similarly, repeat testers from a cohort study in San Diego reported more partners and CRAI than single testers (251). This study also found an increase in risky behaviour that was associated with increased testing.

In recent years, repeat testing has increased among MSM and if this trend continues and scales up considerably it is possible that the differences observed here between repeat and non-repeat testers may decline over time. However, until we reach those levels of repeat testing, behavioural data could be useful to infer motives for HIV testing and determine if sexual behaviours are higher among repeat testers compared to non-repeat testers.

5.12.4 Appropriateness of methodology

The limitations of the retrospective cohort study design employed have already been discussed (see 4.6.1.1). The most important consideration is the possibility of selection bias. Surveillance data collected for other purposes are likely to overestimate population incidence because the reasons why a person returns to a clinic for testing are unlikely to be independent from their risk of HIV as evidenced from this analysis. Men may have symptoms during seroconversion, they may be a partner of someone newly diagnosed with HIV or they may have had a risky sexual encounter; all of these increase their risk of HIV infection and consequently lead to a clinic visit for HIV testing. This is even more apparent when estimating annual incidence using data from one year because those at risk return for testing in a shorter period of time and are thus favoured for

selection in the cohort compared to MSM without symptoms who are unlikely to return to the clinic for a second HIV test in a one year period.

The approach could be improved by using more than one year's data to measure annual incidence (242). The results from this chapter show that allowing an extra month for MSM to repeat test annually as per national guidelines so that follow-up was one year and one month had not impact on incidence estimates. Instead, increasing the number of years will increase the amount of follow-up each individual has, reduce the bias introduced by different health seeking behaviours and result in lower, more accurate estimates. Longer follow-up periods was adopted by the majority of retrospective cohort studies in the literature review and one study showed the impact of lengthening follow-up on incidence (183). The disadvantage of employing this method is that HIV incidence estimates would no longer be timely; a time lag of up to four years could occur. For example, to calculate incidence for 2012, data for the years 2012 to 2015 would be required and estimates would not be available until 2016. Such a lengthy delay would not be acceptable as incidence estimates are necessary to inform and evaluate clinical and public health practice and national HIV prevention programmes and policy.

The use of the mid-point of seroconversion as a sensitivity analysis reduced follow-up time but had no impact on incidence. It is possible that in this population, the date of infection is closer to the date of diagnosis than the midpoint because men had a reason to get tested and actively sought a test at the clinic in response to risk or because they are regular testers, both of which would shorten the interval between the infection and diagnosis. The method

would have a greater impact on incidence and be more appropriate for studies where follow-up is longer than one year.

Men were also right censored exactly one year after entering the study based on the assumption that testing is related to risk and failure to re-attend means men have remained HIV negative beyond the last date of attendance. This would be a reasonable assumption given that repeat testers in these analyses were a higher risk population and testing was likely to be related to risk. However, we cannot discount the possibility that MSM who did not return to the same clinic were newly diagnosed with HIV elsewhere during the study. Thus, assuming MSM who could no longer be followed also remained HIV negative for the duration of the study may underestimate incidence. This is important because the increased follow-up time by almost 10,000 person years had a large impact on incidence. This will be a larger assumption for those whose last attendance was closer to the first HIV negative test than for men who last attend towards the end of the year.

Thus it is likely that censoring at last date of attendance will overestimate incidence and censoring at one year after the first negative test will underestimate it. True HIV incidence probably lies between 1.2/100 py (95%CI 1.1-1.4) (365 days later) and 2.0/100 py (95%CI 1.8-2.2) (date of last attendance).

In order to ensure all repeat testing MSM could be included in multivariable analyses, I made the assumption that MSM with no clinic attendance in the prior year were similar to MSM with prior attendance but with no HIV tests or STI diagnoses and treated them as one group. This assumption was based on the

comparable HIV incidence estimates between the two groups. This assumption only impacted the population attributable risk calculations. PAR relating to clinical history may be underestimated in the primary analysis because the inclusion of all repeat testers will reduce the prevalence of the factor. For example, a prior syphilis diagnosis will only occur among those who attended in the previous year yet all repeat testers are included when calculating the population prevalence of syphilis. Further, some MSM with no prior attendance could have been misclassified; they may have attended another clinic in the prior year and been diagnosed with an STI. This approach was, however, conservative and any misclassification would increase the similarity between this combined group and the comparison group of MSM attending in the prior year and with a STI diagnosis. The resulting bias would be towards an underestimation of the true effect of prior history on HIV risk. It may be more appropriate to make no assumptions about men who did not attend in the prior year and create a separate category to include these men in multivariable analyses.

Ideally, prospective studies where men routinely return to the clinic for a HIV test would be implemented to measure incidence as HIV testing would be independent to risk and selection bias would be minimised. However, prospective studies are expensive and unfeasible for routine measures of HIV incidence. In the absence of this option, retrospective cohort studies using national clinical service data are a good alternative as long as the data are interpreted in light of the limitations. Currently, incidence estimates available from this study cannot be generalised beyond the population of MSM who repeat test at the same clinic. However, with increases in repeat testing, testing should become less related to risk and more related to routine testing, which will greatly benefit the representativeness of these analyses.

Finally, in order to calculate incidence in subgroups I calculated a sample size with the inclusion of five components: the expected incidence in the unexposed group, assumed relative risk, ratio of unexposed to exposed, desired significance level and desired power. I calculated the sample size to compare incidence between those with and without previous syphilis history. I chose this variable because history of syphilis is one of the few variables available in GUMCAD that is strongly associated with HIV acquisition. It also potentially required the largest sample size due its low prevalence in the population. A large sample size would facilitate investigation of the association of HIV with other variables collected by GUMCAD. To calculate the sample size I used the command "sampsi" in STATA and the two sample comparison of proportions option to estimate the sample sizes for the exposed and unexposed group.

The sample size calculation was based on an anticipated incidence of 1% in the unexposed population (without a previous syphilis diagnosis), which reflects incidence in the general population of MSM attending GUM clinics, a relative risk for previous syphilis of 3 (based on literature review findings), prevalence of 1% of the exposure (giving a ratio of 0.01), significance level of 0.05 and 80% power. Using these parameters, the required sample size for the unexposed group (no syphilis) would have been 34,055 and for exposed (with syphilis) it would have been 341.

Table 5.5 Sample size calculation for each population subgroup with α=0.05 and 80% power

Population subgroups	Expected incidence (%)	Relative risk	Prevalence of exposure (%)	Ratio of unexposed to exposed	Sample size
No previous syphilis	1	3	-	0.01	34,055

(unexposed)					
Previous syphilis (exposed)	3		1		341

In total, a sample of 34,096 MSM would have been required including 341 exposed (with a previous syphilis diagnosis) men to have good (80%) power to detect a relative risk of 3. As there were only 25,313 MSM with this information available in the analysis, the sample would not have had good power to detect a significant difference in incidence between the two groups. The actual sample size would have had 80% power to detect an effect size of 3.2 or greater using $\alpha=0.05$ (calculated using the "Cohort power" option in EpiSheet by Ken Rothman). However, the actual effect size was bigger than what has been documented in the literature and what was used to determine the sample size. The adjusted hazard ratio for syphilis was 4 and a significant association was detected.

The confidence interval of the hazard ratio for syphilis was, however, wide (2.0-8.3). To reduce the width of the confidence interval and hence increase the precision around the effect size estimate would require a larger sample size. Variables including gonorrhoea and PEP use, which have been linked with increased likelihood of HIV acquisition had statistically nonsignificant adjusted hazard ratios, wide confidence intervals and high (2 or above) upper bounds of the confidence intervals (CI 0.6-2.4 and CI 0.3-2.0, respectively) in this analysis. These results suggest that clinically important differences cannot be ruled out and in these cases the study was underpowered to examine the associations. It is thus not possible to surmise from these results that there is no association between these variables and HIV acquisition. This analysis used the entire GUM attending MSM population in England that repeat tested for HIV and to increase

the sample size to examine the underpowered subgroup associations would require increasing the number of years of data included in the analysis. The disadvantage of this approach is that it would not be possible to produce timely incidence estimates to monitor the current HIV epidemic among MSM.

5.12.5 Utility

HIV incidence estimates can be used by different groups including public health specialists and clinicians for a number of different purposes. The estimates can be used for surveillance purposes where the data facilitates timely monitoring of the epidemic among this MSM population and allows identification of highest risk MSM.

Further, incidence estimates especially when measured over time can be used to evaluate clinical and public health practice. Changes in HIV incidence from 'before' and 'after' could be used to evaluate whether public health interventions such as HIV testing initiatives or initiation of ART soon after HIV diagnosis have been successful at reducing transmission among GUM clinic attending MSM.

The results may also be particularly useful to clinicians who should consider targeting HIV prevention services to repeat testers and core sub-groups among repeat testers. While HIV prevention services should be offered to all MSM attending GUM clinics, identification of a core group such as MSM with previous syphilis or gonorrhoea infections enables more resource intensive services to be targeted to these men.

Our results may also support policy makers developing guidelines for individuals eligible for PrEP in the new PrEP Impact trial. Approximately 2,500 repeat testing

MSM were diagnosed with a bacterial STI in the prior year, which is a number which could reasonably be offered PrEP as part of a comprehensive HIV and STI prevention programme.

5.12.6 Implications for thesis

As hypothesised in the discussion of the literature review, this secondary data analysis has highlighted that HIV incidence is high, though stable, since the last available estimates among MSM attending GUM clinics. It is important to recognise repeat testers are unlikely to be representative of MSM attending GUM and incidence estimates presented may be an overestimate. This Chapter has added to the evidence base for high risk MSM in the UK by also identifying risk factors for HIV infection. Clinical and demographic risk factors are not sufficient to improve risk stratification of MSM and guide decision making for HIV prevention. Therefore it is important to move beyond these data and explore the additional utility of behavioural information for risk stratification. To this end, I next explore whether behavioural data can be collected from GUM clinics and whether the data collected are better predictors of HIV acquisition.

6 Behavioural study among HIV negative MSM attending GUM clinics

6.1 Introduction

In the previous chapter, I demonstrated that routinely collected clinical data can be used to estimate HIV incidence and that some clinical markers are predictive of HIV acquisition and could be used to identify strata of MSM who were at high risk of HIV acquisition. However, these results also highlighted that clinical factors only account for a small proportion of the HIV infections that occurred and while identifying infections may be important at the individual level, preventing them will have a negligible impact on population level HIV transmission. Ultimately, the public health utility of a clinical risk prediction tool solely based on clinical indicators will be limited; the addition of behavioural data may improve the clinical utility of a tool.

Sexual behaviours such as condomless anal sex (217) and numbers of partners (81, 92, 177) are associated with HIV acquisition among MSM. Engagement in CRAI has the highest per act probability of acquiring HIV associated with any sexual exposure (129). As well as being strongly associated with HIV acquisition, sexual risk behaviours are likely to occur more frequently in the population than STIs as not all condomless sex acts will result in the acquisition of a STI. The PAR is dependent on population prevalence and strength of association (124); therefore sexual behaviours will have higher PARs than STIs and will account for a greater proportion of the observed HIV infections. Therefore a reduction in sexual risk behaviours in the population will be necessary to have a significant impact on HIV transmission.

MSM engage in a range of sexual behaviours. Some that increase their risk of HIV (e.g. CRAI with partners of a different (serodiscordant) or unknown HIV status (174, 192) and others that may be protective such as CIAI with negative partners (177) or adoption of seroadaptive behaviours. Seroadaptive behaviours are strategies employed to reduce the risk of HIV transmission and require knowledge of the partner's HIV status as well as one's own. There is evidence of adoption of seroadaptive practices among MSM in the UK (20, 65, 240). Common strategies include serosorting, where CAI is only practiced with partners of the same HIV status and seropositioning, where only CIAI is practiced with HIV positive partners. There is considerable debate surrounding the effectiveness of seroadaptation. Serosorting can reduce the risk of HIV seroconversion (257) when compared to engagement in CAI with serodiscordant partners, which increases risk (125, 128, 257) but is a higher risk behaviour than consistent condom use. The evidence for seropositioning is more limited with evidence suggesting that men practicing seropositioning are at increased risk of infection compared men engaging in CIAI with HIV negative partners (177). Thus both strategies may have a limited role to play in risk reduction because success depends on knowing the partner's HIV status and data suggest this is not well known (240).

The supplementation of behavioural data to the routinely collected clinical data would greatly improve our understanding of the prognostic factors associated with HIV seroconversion among a cohort of MSM who attend GUM clinics in England. It would also be an opportunity to understand the nuances in behaviours and categorise behaviours to reflect the range of protective and risk-based behaviours men engage in. A behavioural study was conducted in five GUM clinics to collect standardised sexual behavioural data from HIV negative

MSM and determine whether this behavioural data could better predict HIV infection. The results of this study are presented in this chapter with an in-depth description of the methods available in section 3.3.

6.2 Aims and Objectives

The aim of the study was to collect standardised sexual behavioural information from HIV negative MSM in GUM clinics. The specific objectives were to:

- Evaluate feasibility and acceptability of using the standardised behavioural questionnaire in clinics
- Document prevalence of sexual behaviours including, where possible, seroadaptive behaviours among MSM attending GUM clinics
- Report HIV incidence and behavioural risk factors for acquisition

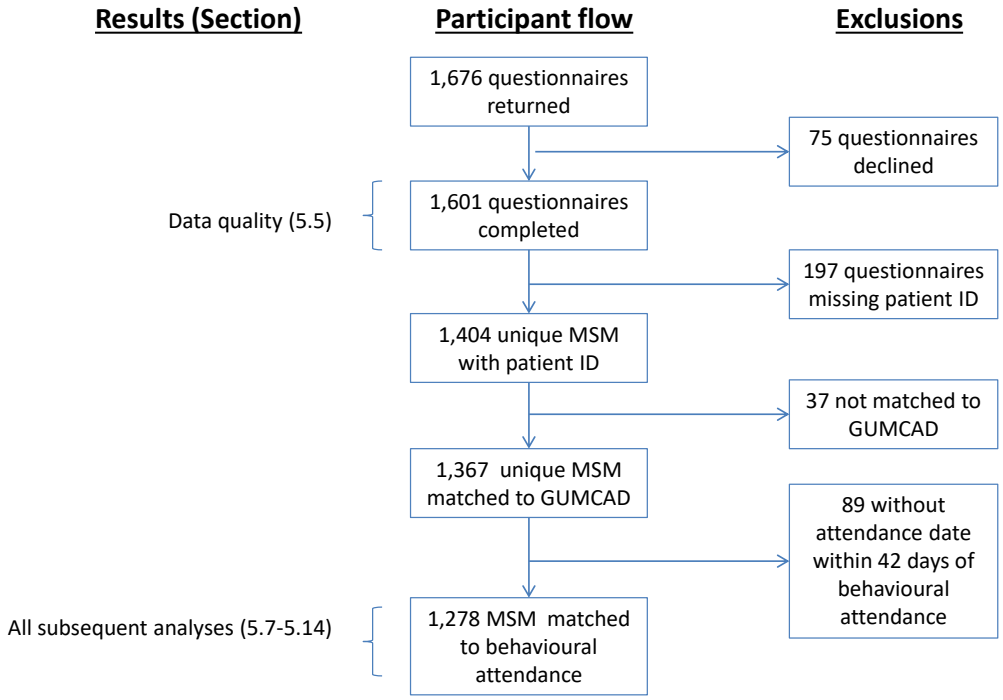
6.3 Overview of methods and analyses

A cross-sectional behavioural study where a sexual behavioural questionnaire was completed by HIV negative MSM was run in five GUM clinics. The responses were categorised into three behavioural groups: safer sex (No CAI, monogamy), seroadaptation (top only, serosorting, seropositioning) and no risk reduction strategy. Completed questionnaires were linked to clinical records to enable clinical outcome analyses (e.g. HIV incidence) to be conducted. Further details of the methods can be found in section 3.3.

I have included a flow chart to present the impact of missing information and the linkage process on how I arrived at the final analysis population (Figure 6.1). Analyses have been conducted in two key populations: i) the overall population of 1,601 MSM who completed a questionnaire and ii) 1,278 MSM who completed

the questionnaire and whose questionnaire could be linked to clinical records with a matched date of attendance.

Figure 6.1 Flow chart to present exclusions and relevant HIV negative MSM populations



6.4 Questionnaire acceptability

6.4.1 Recruitment rates

The study was too large and clinics could not feasibly document the number of MSM that were offered a questionnaire and without this information it was not possible to measure response rates. Instead the recruitment rate which is defined as the number of questionnaires returned from all MSM not known to be HIV positive was measured. In total, 1,676 questionnaires were returned to HPA/PHE during the study period from a potential 20,900 HIV negative MSM who attended the five clinics, giving an overall recruitment rate of 8%. The numbers of HIV negative/not known to be HIV positive MSM who attended one of

the five clinics during the study period were determined after linkage to GUMCAD. The numbers of men who attended and completed a questionnaire improved after the first month and the study was most efficient after I visited each clinic and presented the latest results including recruitment rates. The highest recruitment rate (25%) was achieved by Manchester (clinician-led clinic) and Royal Sussex (Table 6.1). In the remaining clinics rates of 4-11% were achieved over the recruitment period.

Table 6.1 Number of MSM attending the clinic during the study period and the number recruited, by clinic of attendance

Clinic name	Number of HIV negative/not known to be HIV positive	Recruitment rate (%)
Dean St, London	12,701	593 (4.7)
John Hunter, London	1,249	143 (11)
Manchester Royal Infirmary	1,414	356 (25)
MMC, London	3,889	168 (4.3)
Royal Sussex, Brighton	1,647	416 (25)
Total	**20,900**	**1,676 (8.0)**

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6.4.2 Declined questionnaires

The study had planned to measure acceptability as the number of questionnaires that were offered and declined. However, MSM were also not systematically asked to return empty questionnaires. I assumed that empty questionnaires or those that only had the date and patient id fields completed were declined questionnaires. In total, 75 of the 1,676 (4.5%) questionnaires were declined. Half (56%; 42) of these questionnaires came from Royal Sussex, where towards the second half of the pilot the clinic began asking men more consistently to return declined questionnaires. Another 32% were from Dean St, 9% from John Hunter and 3% from Manchester. The true proportion of MSM declining to participate is probably greater than that reported here.

6.5 Data quality

6.5.1 Data completeness

Completion of questions was over 70%, with some variation between questions (Table 6.2). The majority of questionnaires had a completed patient identifier field, which is essential for linkage to clinical records; although proportions were lower at MMC and Royal Sussex where only 83% and 74%, respectively, of questionnaires had this information. Completion of this field did increase during the study.

Table 6.2 Completeness of data overall and by clinic among HIV negative MSM recruited from five GUM clinics, England, 2012-2013 (n=1,601)

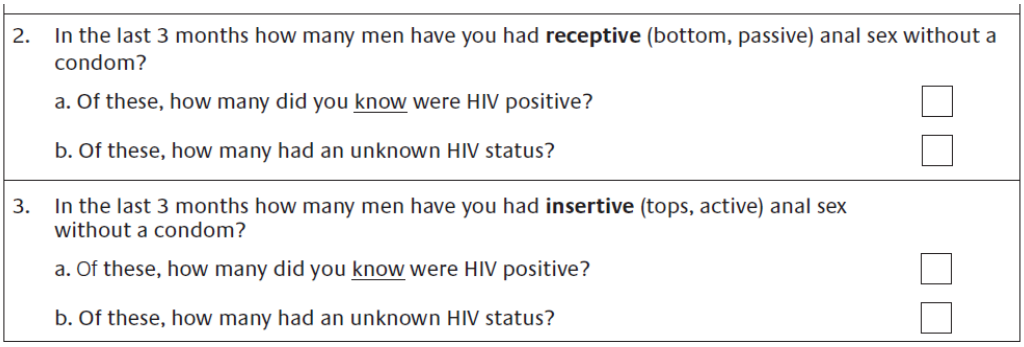
Question	Number completed (%)	Number completed (%) Royal Sussex	Number completed (%) Manchester	Number completed (%) London clinics
Patient Identifier	1,404 (88)	277 (74)	334 (94)	793 (91)
No. of partners	1,563 (98)	368 (98)	352 (99)	843 (97)
No. of new partners	1,482 (93)	353 (94)	347 (98)	782 (90)
No. CRAI*	1,112 (69)	**112 (30)**	**203 (57)**	797 (91)
HIV positive	1,472 (92)	342 (91)	331 (94)	799 (92)
Unknown status	1,443 (90)	336 (90)	317 (90)	790 (90)
No. CIAI**	1,106 (69)	**106 (28)**	**201 (57)**	799 (92)
HIV positive	1,438 (90)	342 (91)	328 (93)	768 (88)
Unknown status	1,423 (89)	336 (90)	316 (89)	771 (88)
Last CRAI*	1,526 (95)	363 (97)	339 (96)	824 (94)
Person status	1,163 (73)	279 (75)	279 (79)	605 (69)
Reason[$]	850/1,247 (68)	268 (72)	-	582 (67)

*condomless receptive anal intercourse (CRAI)
**condomless insertive anal intercourse (CIAI)
[$]Manchester did not ask for reasons for not using a condom at last CRAI

The lower completion rates for the number of CRAI and CIAI partners in the last three months were likely due to an error in the questionnaires sent to Manchester and Royal Sussex. The early questionnaires to Manchester were missing a response box for these two questions, which was later rectified (Figure 6.2).

Royal Sussex had the same problem, and although corrected questionnaires were sent to the site late during the pilot, they were unfortunately not adopted. Completion was between 28-30% for the two questions from Royal Sussex and 57% for Manchester (Table 6.2).

Figure 6.2 Questions 2 and 3 missing the response box on questionnaires sent to Royal Sussex and Manchester (questionnaire screen shot)



Where there was missing information on partners of CRAI and CIAI I used information provided in the other questions to make some assumptions about these two questions. If the numbers of CRAI partners of HIV positive and unknown status (i.e. questions 2a and 2b) was '0', I assumed that total numbers of CRAI partners was also '0' (i.e. question 2) as long as total numbers of partners (question 1) was not greater than four. I replace the missing information with '0' for this question. The full assumptions are described in 3.3.4.

Based on these assumptions the amount of missing information on numbers of CRAI partners reduced from 31% to 14% (total complete = 1,380) and for CIAI partners from 31% to 16% (total complete = 1,338). Completion for questionnaires from Royal Sussex increased from 30% to 71% and from 28% to 66% for the two questions, respectively. Completion for questionnaires from Manchester increased from 57% to 83% and 80% for the two questions,

respectively. There were no significant changes to the London clinics. The assumptions have been carried forward and used in all subsequent analyses.

6.5.2 Data discrepancies

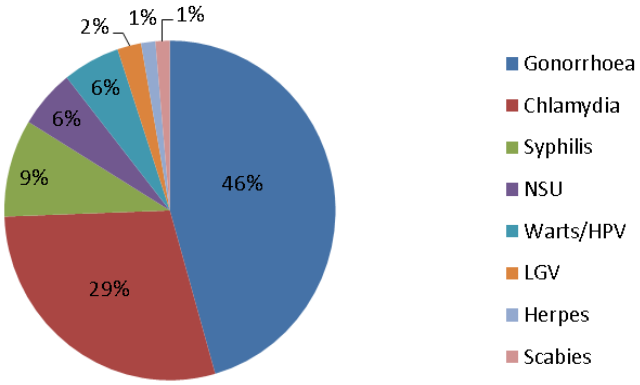
The majority of the completed data was of good quality with few discrepancies between answers in the different sections of the questionnaire. A small minority of completed patient identifiers were invalid (1.4%). The validity of some answers was cross-checked by comparing responses to different questions. For example, there were 21 men who reported never engaging in CRAI yet reported at least one partner with whom they had CRAI in the last three months in an earlier section of the questionnaire. Conversely, another 18 men (1.1%) reported no partners with whom they had CRAI in the last three months but then went on to say they had had CRAI in the last three months. One hundred and two men (6.4%) reported never having CRAI but then went on to respond to the question on the HIV status of the partner whom they last had CRAI and 28 (27%) of them also reported the reason why they didn't use a condom. As it was not possible to identify which of these responses were correct, the responses were excluded.

There were misunderstandings with the questionnaire. The largest misunderstanding related to the last five questions, which were to only be completed by men who had never attended that clinic before. The first of these questions asked men if they had attended another clinic before and if they did the name of that clinic. Overall, 54% of men who completed this question reported the same clinic as their current clinic and was as high as 68% among men attending Royal Sussex. It is likely these men misread the instructions and completed this section of the questionnaire even though they were not new attendants at the clinic.

6.6 Previous GUM attendance and clinical history

After excluding men who erroneously completed the section for new attendants (attended the clinic for the first time), 771 MSM were designated as new attendants. Over half (59%) had attended another clinic in the last year, 29% more than a year ago and 12% had never been to a GUM clinic before. There were no significant differences between clinics. A total of 756 men completed information on STIs in the previous year. A quarter of men reported 215 STIs in the last year with gonorrhoea the most common (98, 46%), followed by chlamydia (62, 29%) (Figure 6.3).

Figure 6.3 Diagnosed STIs in the last year reported by HIV negative MSM who were new attendants, England, 2012-13 (n=215)



Sixty-three per cent (471/753) tested for HIV in the last year, 21% tested 1-5 years ago and 12% had never tested before. In comparison, only 15% had ever taken PEP and of those that had, 39% took it in the last year.

6.7 Data linkage to clinical records

In order to obtain clinical and demographic information for recruited men, I linked the behavioural data to clinical records using the clinic name and patient id fields

in the questionnaire. Of the 1,601 complete questionnaires, 197 (12%) were missing patient id and could not be included. Of the remaining 1,404 men, all but 37 were linked to their clinical GUM records (Figure 6.1). Linked men include those for whom the patient id was partly missing or partly correct but who were matched using fuzzy matching criteria (n=81).

In total, there were 17,463 clinical records between 2008 and end of March 2014 for the 1,367 men, giving an average of 13 records per individual. Only 8,880 records (51%) pertained to different attendance dates; the remainder were multiple records for the same day to record the services and diagnoses received. On average, an individual attended on six different days during this time period.

The majority of men (n=1,278, 93%) had a behavioural attendance (an attendance that was within 42 days of completing the questionnaire) in their clinical records. This means I could match the date when the behavioural questionnaire was completed with a date of attendance at the GUM clinic. For the remainder, although they had clinical records, none matched with the date the behavioural questionnaire was completed. These men were excluded from any further analyses.

6.8 Sample characteristics

At the baseline attendance (date of recruitment/questionnaire completion), 43% of the 1,278 MSM were aged 25-34 years and 56% were white and UK-born (Table 6.3). Half of the men attended one of the three London clinics. Less than half of men (n=581) had attended the clinic in the year prior to their baseline

attendance. Among these, 96% had tested for STIs and/or HIV and 37% were diagnosed with at least one acute STI.

Three quarters of men who attended the clinic on the date of recruitment attended for a HIV test (73%). Three per cent (n=35) refused a test and for another 4% (n=47) a HIV test was not considered appropriate at the behavioural attendance. Other frequent reasons and outcomes were gonorrhoea related: a gonorrhoea test (8%), diagnosis (11%) or being a contact of a gonorrhoea case (6%). In total, 24% were diagnosed with a bacterial STI at this attendance.

Table 6.3 Characteristics of HIV negative MSM recruited from five GUM clinics, England, 2012-2013 (n=1,278)

Characteristic	All HIV negative MSM (%)	Dean St (%)	John Hunter (%)	MMC (%)	Manchester (%)	Royal Sussex (%)
Age group						
15-24	274 (21)	73 (14)	24 (21)	11 (19)	98 (30)	68 (25)
25-34	546 (43)	239 (47)	41 (35)	29 (51)	147 (45)	90 (33)
35-49	367 (29)	166 (33)	38 (32)	14 (25)	64 (20)	85 (31)
50+	91 (7.1)	28 (5.5)	14 (12)	3 (5.3)	16 (4.9)	30 (11)
Ethnicity and birthplace						
White UK-born	717 (56)	211 (42)	48 (41)	22 (39)	244 (75)	192 (70)
White European	233 (18)	128 (25)	28 (24)	14 (25)	23 (7.1)	40 (15)
White non-European	110 (8.6)	65 (13)	21 (18)	5 (8.8)	5 (1.5)	14 (5.1)
Non-white UK-born	77 (6.0)	35 (6.9)	3 (2.6)	8 (14)	23 (7.1)	8 (2.9)
Non-white born abroad	117 (9.2)	58 (11)	15 (13)	6 (11)	22 (6.8)	16 (5.9)
Other/Unknown	24 (1.9)	9 (1.8)	2 (1.7)	2 (3.5)	8 (2.5)	3 (1.1)
Bacterial STI at baseline	305 (24)	123 (24)	22 (18)	11 (19)	100 (31)	49 (18)
HIV testing/STI screening previous year*	559 (96)	254 (97)	46 (94)	20 (100)	120 (95)	119 (95)
Acute STI previous year*	213 (37)	81 (30)	19 (37)	6 (30)	57(45)	52 (42)
Total	**1,278**	**506**	**117**	**57**	**325**	**273**

*Among the 581 MSM who attended in the previous year

The recruited population differed demographically by clinic; a greater proportion of MSM recruited from Manchester were aged 15-24 years (30%) compared to the other clinics (14-25%) (Table 6.3). More men recruited outside London (Manchester (75%) and Royal Sussex (70%)) were of white ethnicity and born in the UK compared to London MSM (Table 6.3). Between 24-25% of MSM attending the London clinics were of white ethnicity and European born. Attendance in the prior year was highest among Dean St MSM (52%) and lowest among those attending MMC (34%) and among those that attended, the proportion diagnosed with a STI was highest at Manchester (45%) and lowest at Dean St and MMC (30% each). The prevalence of a bacterial STI at baseline was also highest among MSM at Manchester (31%).

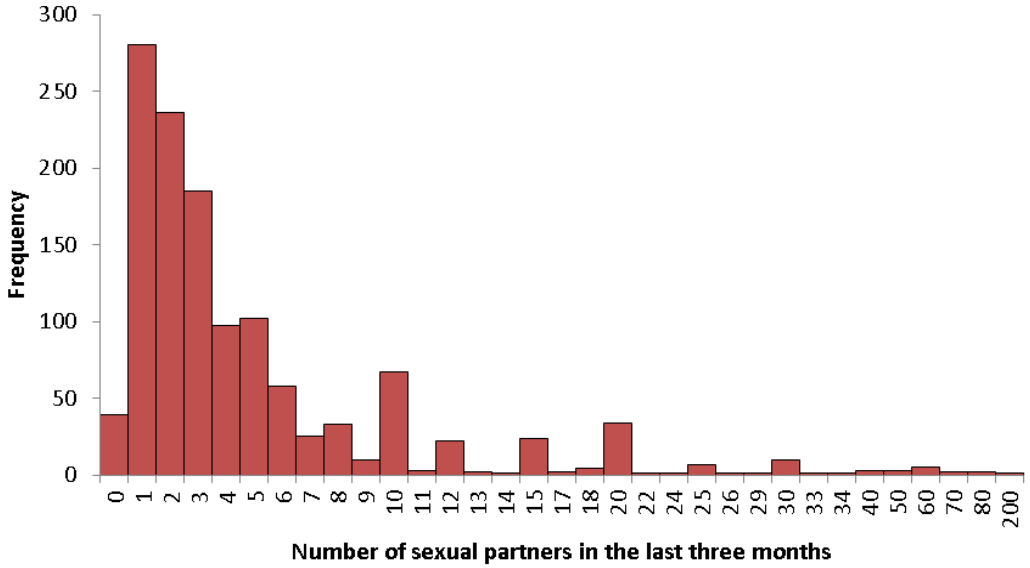
6.9 Total sexual partners

I only present the distribution of sexual behaviours in this and subsequent sections for MSM who were successfully linked to their clinical records (n=1,278).

6.9.1 Sexual partners

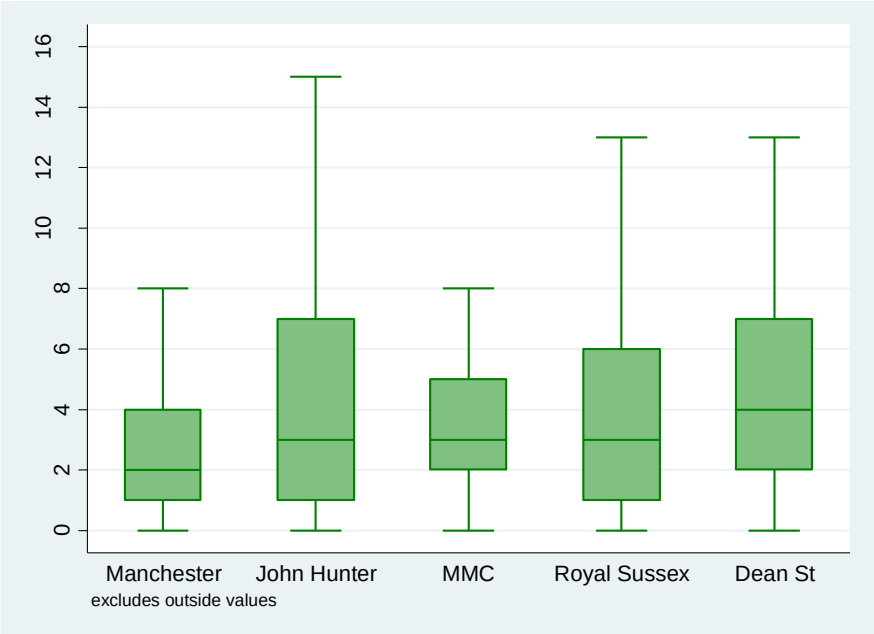
In total, 1,250 MSM reported 6,805 sexual partners, defined as any partner with whom the individual reported oral and/or anal sex in the three months prior to completing the questionnaire. Thirty-nine (3.1%) men reported no sexual partners in the last three months. The majority of the remainder reported between 1-10 partners (1,083, 87%) (Figure 6.4), with 34% reporting more than four partners and 10% more than 10 partners.

Figure 6.4 Distribution of total numbers of anal and oral partners in the last 3 months reported by HIV negative MSM attending five GUM clinics in England, 2012-13 (n=1,250)



The numbers of reported sexual partners differed between clinics, with MSM attending Manchester reporting significantly fewer partners than men from Dean St and John Hunter. The median numbers from Manchester were 2 (IQR 1-4) compared to 3 or 4 in the other clinics (Figure 6.5). Fewer men reported five or more partners at Manchester (20%, 95%CI16-25) compared to the other clinics (30-43%, p<0.001) (Table 6.4).

Figure 6.5 Median (Interquartile range) number of sexual partners by clinic



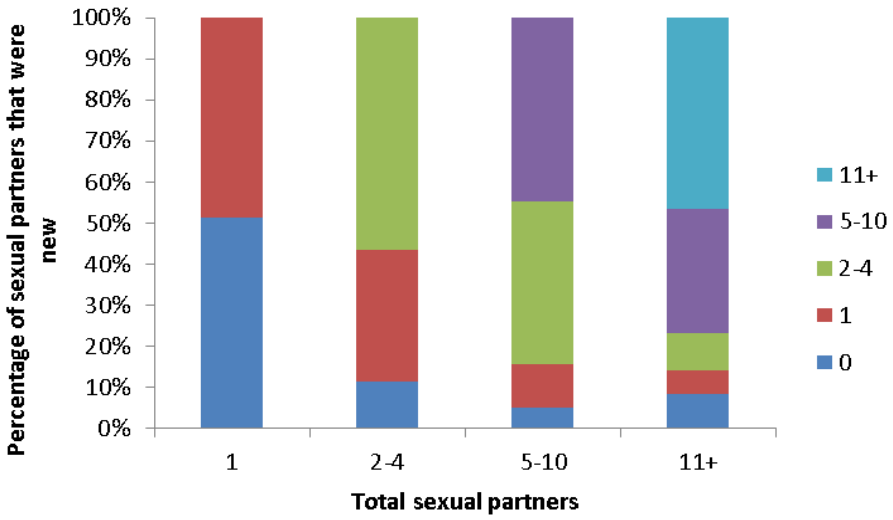
As well as clinic of attendance, the number of sexual partners differed by demographics. The proportion of men reporting five or more partners increased with age; 25% (95%CI 20-30) of 15-24 year olds compared to 42% (95%CI 38-48) of 35-49 year olds (p<0.001) (Table 6.5). Overall, there was no difference between partner numbers and ethnicity and country of birth. However, fewer MSM of white ethnicity born in the UK reported 5 or more partners (30%, 95%CI 26-33) compared to white MSM born in Europe (43%, 95%CI 36-49) (Table 6.6). Among MSM attending in the previous year there were no differences in partner numbers by HIV testing or STI screening history (p=0.43) or previous STI diagnosis (p=0.92).

6.9.2 New partners

Twenty-one per cent of men reported that none of their sexual partners were new while 75% reported that between 1-10 partners were new partners. Overall, 1,139 men who reported total sexual partners also completed information on new

number of partners in the last three months. Total numbers of partners and new partners were categorised into four groups; men who reported one partner, 2-4, 5-10 or more than 10 partners. Within each group of total partner numbers, between 45-57% reported that the majority of their partners were also new partners (Figure 6.6). For example, of the 492 men who reported 2-4 sexual partners, 57% reported 2-4 of those partners were new.

Figure 6.6 The relationship between total and new sexual partners, by total sexual partners, reported by HIV negative MSM, England, 2012-13 (n=1,139)



The cognitive interviews did, however, highlight the confusion around the question on new partners. It is thus unclear how men interpreted this question; whether they meant partners that were new 'ever' or just new for the last three months.

Table 6.4 Overview of sexual behaviours reported by HIV negative MSM by clinic of recruitment

Behaviour	Dean St	John Hunter	MMC	Manchester	Royal Sussex	P value	All
Number of sexual partners (%)							
Number*	491	109	57	323	270	<0.001	1,250
0	8 (1.6)	3 (2.8)	1 (1.7)	17 (5.3)	10 (3.7)		39 (3.1)
1	99 (20)	26 (24)	9 (16)	82 (25)	61 (23)		277 (22)
2-4	174 (35)	41 (38)	30 (53)	158 (49)	112 (41)		515 (41)
5-10	151 (31)	22 (20)	10 (18)	50 (15)	58 (21)		291 (23)
10+	59 (12)	17 (16)	7 (12)	16 (5.0)	29 (11)		128 (10)
Median sexual partners, last 3 months (IQR)	4 (2-7)	3 (1-7)	3 (2-6)	2 (1-4)	3 (1-6)	<0.001	3 (1-6)
Percentage reporting ≥5 sexual partners, last 3 months (95%CI)	43 (38-47)	36 (27-46)	30 (18-43)	20 (16-25)	32 (27-38)	<0.001	34 (31-36)
Percentage reporting condomless anal intercourse (CAI), (95%CI)							
Number*	468	104	53	253	165		1,043
CAI, last 3 months	63 (58-67)	51 (41-61)	47 (33-61)	46 (40-53)	33 (26-40)	<0.001	52 (49-55)
Percentage reporting condomless receptive anal intercourse (CRAI), (95%CI)							
Number*	477	108	55	311	265		1,216
CRAI, last year	53 (48-57)	41 (31-51)	38 (25-52)	52 (46-57)	51 (45-57)	0.095	50 (48-53)
Number*	481	105	54	272	193		1,105
CRAI, last 3 months	43 (38-47)	29 (20-38)	26 (15-40)	36 (30-42)	26 (20-33)	0.001	36 (33-39)
≥2 CRAI partners, last 3 months	12 (9.5-16)	8.6 (4.0-16)	7.4 (2.1-18)	8.8 (5.7-13)	8.3 (4.8-13)	0.512	10 (8.4-12)
Percentage reporting condomless insertive anal intercourse (CIAI), (95%CI)							
Number*	471	105	54	260	175		1,065
CIAI, last 3 months	50 (45-55)	41 (31-51)	41 (28-55)	35 (30-42)	25 (19-32)	<0.001	41 (38-44)
≥2 CIAI partners, last 3 months	19 (15-23)	14 (8.2-22)	15 (6.6-27)	12 (8.6-17)	8.6 (4.9-14)	0.016	15 (13-17)

*refers to the denominator in each category

Table 6.5 Overview of sexual behaviours reported by HIV negative MSM by age group

Behaviour	15-24	25-34	35-49	50+	P value
Number of sexual partners (%)					
Number*	267	532	362	89	
0	11 (4.1)	15 (2.8)	8 (2.2)	5 (5.6)	<0.001
1	65 (24)	125 (24)	68 (19)	19 (21)	
2-4	125 (47)	224 (42)	133 (37)	33 (37)	
5-10	53 (20)	122 (23)	99 (28)	17 (19)	
10+	13 (4.9)	46 (8.7)	54 (15)	15 (17)	
Median number, last 3 months (IQR)	2 (1-4)	3 (1-5)	4 (2-8)	3 (1-8)	<0.001
Percentage reporting ≥5 sexual partners, last 3 months (95%CI)	25 (20-30)	32 (28-36)	42 (37-48)	36 (26-47)	<0.001
Percentage reporting condomless anal intercourse (CAI) (95%CI)					
Number*	226	457	297	63	
CAI, last 3 months	52 (45-58)	56 (52-61)	47 (41-53)	44 (32-58)	0.05
Percentage reporting condomless receptive anal intercourse (CRAI) (95%CI)					
Number*	267	519	348	82	
CRAI, last year	60 (54-66)	55 (51-60)	39 (34-44)	35 (25-47)	<0.001
Number*	240	483	312	70	
CRAI, last 3 months	39 (33-46)	41 (37-46)	28 (23-33)	27 (17-39)	<0.001
≥2 CRAI partners, last 3 months	12 (8.2-17)	10 (7.8-13)	9.0 (6.0-12)	7.1 (2.4-16)	0.541
Percentage reporting condomless insertive anal intercourse (CIAI) (95%CI)					
Number*	233	461	304	67	
CIAI, last 3 months	38 (32-45)	44 (40-49)	39 (33-45)	37 (26-50)	0.316
≥2 CIAI partners, last 3 months	12 (8.5-17)	15 (12-19)	16 (12-20)	18 (9.6-29)	0.654

*refers to the denominator in each category

Table 6.6 Overview of sexual behaviours reported by HIV negative MSM by ethnicity and birthplace

Behaviour	White UK born	White European	White non-European	Non-white UK born	Non-white born abroad	P value
Number of sexual partners						
Number *	706	228	104	75	113	
0	26 (3.7)	7 (3.1)	0	1 (1.3)	2 (1.8)	0.09
1	171 (24)	42 (18)	20 (19)	15 (20)	25 (22)	
2-4	300 (42)	82 (36)	43 (41)	36 (48)	46 (41)	
5-10	139 (20)	68 (30)	27 (26)	17 (23)	31 (27)	
10+	70 (10)	29 (13)	14 (13)	6 (8.0)	9 (8.0)	
Median sexual partners, last 3 months (IQR)	3 (1-5)	4 (2-8)	4 (2-7)	3 (2-6)	3 (2-6)	
Percentage reporting ≥5 sexual partners, last 3 months (95%CI)	30 (26-33)	43 (36-49)	39 (30-49)	31 (21-42)	35 (27-45)	0.004
Percentage reporting condomless anal intercourse (CAI) (95%CI)						
Number*	568	202	91	64	97	
CAI, last 3 months	46 (42-51)	52 (45-59)	69 (59-78)	59 (46-71)	62 (51-72)	<0.001
Percentage reporting condomless receptive anal intercourse (CRAI) (95%CI)						
Number*	694	214	107	70	111	
CRAI, last year	49 (45-53)	56 (49-62)	55 (45-65)	40 (28-52)	50 (41-60)	0.097
Number*	609	208	95	68	104	
CRAI, last 3 months	34 (30-38)	38 (31-45)	39 (29-49)	37 (25-49)	40 (31-50)	0.482
≥2 CRAI partners, last 3 months	8.2 (6.2-10)	12 (7.9-17)	12 (5.9-20)	15 (7.3-25)	13 (6.8-20)	0.131
Percentage reporting condomless insertive anal intercourse (CIAI) (95%CI)						
Number*	580	203	96	65	99	
CIAI, last 3 months	35 (31-39)	40 (34-47)	56 (46-66)	54 (41-66)	51 (40-61)	<0.001
≥2 CIAI partners, last 3 months	11 (8.4-14)	16 (11-22)	18 (11-27)	28 (17-40)	22 (14-32)	<0.001

*refers to the denominator in each category

6.10 Condomless anal sex

6.10.1 Condomless anal intercourse

Although the questionnaire did not include a question on number of CAI partners, I determined whether men had CAI in the last three months based on what was reported for numbers of sexual partners (question 1) and condomless partners (questions 2 and 3). Men who reported CAI were those had at least one CRAI or CIAI partner and those that reported no CAI were those who reported no CRAI and CIAI partners or those who reported no sexual partners in the last three months. It was not possible to determine the number of CAI partners as questions 2 and 3 are not mutually exclusive and therefore the total number of insertive and receptive partners does not equate to total number of CAI partners.

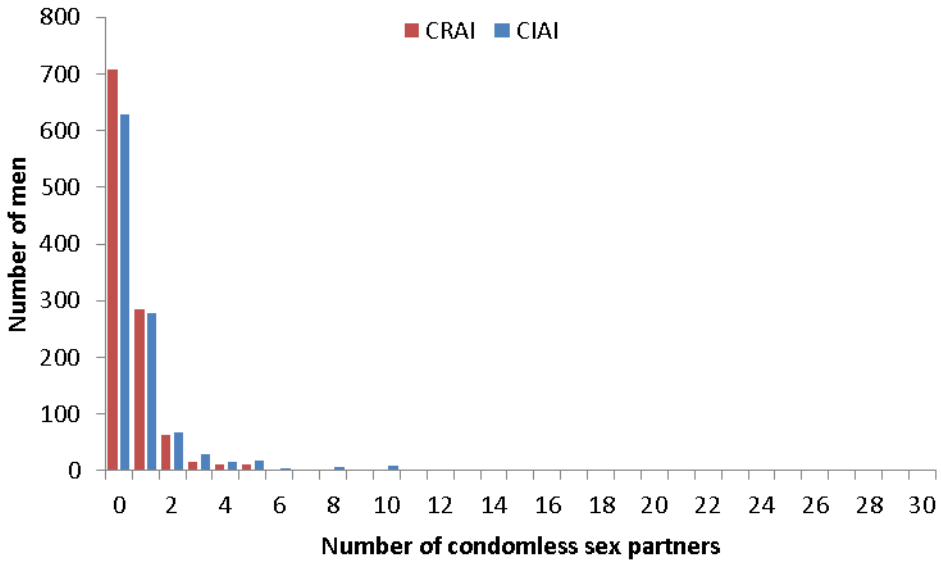
In total, 52% (543/1,043) (95%CI 49-55) reported CAI in the last 3 months. More men from Dean St reported CAI in the last three months (63%, 95%CI 58-67) compared to men from Manchester (46%, 95%CI 40-52) and Royal Sussex (33%, 95%CI 26-40) (Table 6.4). In contrast to total sexual partners, younger men were more likely to report CAI in the last three months; half of 15-24 year olds reported CAI compared to 44% (95%CI 32-57) among 50+ year olds (p=0.05) (Table 6.5). As with sexual partners, fewer white MSM born in the UK reported CAI (46%, 95%CI 42-51) compared to other groups (Table 6.6).

6.10.2 Condomless insertive and receptive anal intercourse

In total, 1,105 MSM completed the question on numbers of partners with who they engaged in CRAI and 1,065 on CIAI partners. Seven hundred and eight (64%) men reported having no CRAI in the last 3 months and 629 (59%) reported no CIAI (Figure 6.7). Therefore 36% (95%CI 33-39) reported CRAI and 41%

(95%CI 38-44) CIAI. A further 285 and 278 reported one CRAI and CIAI partner, respectively (26% each). Between 8% and 11% of men reported 2-4 partners. Very few men reported CRAI and CIAI with more than 10 partners (n=5, 0.5% and n=7, 0.7%, respectively).

Figure 6.7 Distribution of numbers of partners with whom HIV negative MSM engaged in condomless receptive (n=1,105) and insertive (n=1,065) anal intercourse in the last 3 months, England, 2012-13



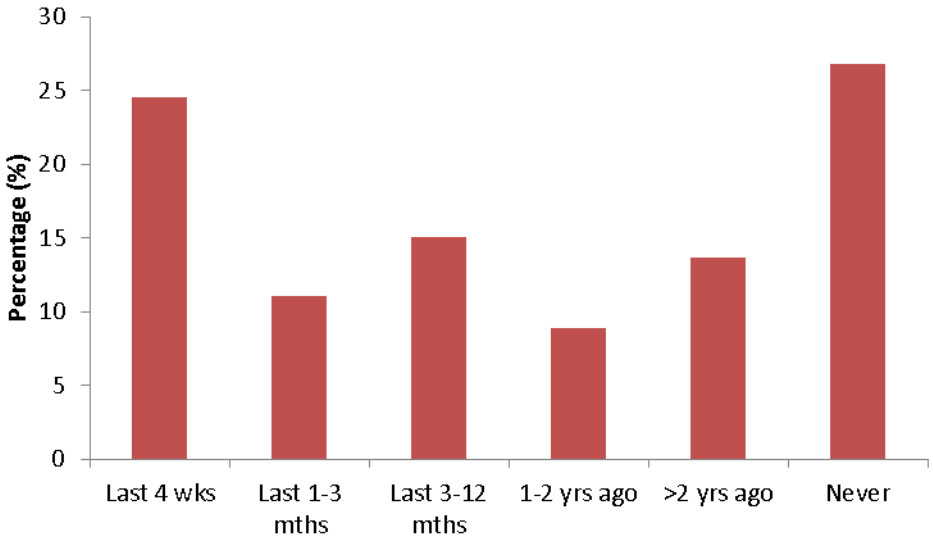
Men attending Dean St were significantly more likely to report CRAI (43%, 95%CI 38-47 vs 26-36%, p=0.001) and CIAI (50%, 95%CI 45-54 vs 25-41%, p<0.001) than men attending the other clinics (Table 6.4). The proportions reporting two or more CRAI partners did not significantly differ between clinics though CIAI partners did between Dean St (19%, 95%CI 15-22) and Royal Sussex (8.6%, 95%CI 4.4-13) (p=0.016). The only differences by age were for engagement in CRAI; it was higher among younger MSM. In line with the general trends reported thus far, CIAI was less common among UK-born MSM of white ethnicity than all other groups except white European MSM (Table 6.6).

Of the 402 MSM who reported CRAI with at least one partner, 323 (80%) completed both questions relating to the HIV status of their partners (questions 2a and 2b). Half reported that none of their partners were HIV positive or of unknown status (i.e. their partner was HIV negative) and the remainder had CRAI with MSM of different HIV status. Seventy-nine per cent (349/441) completed both questions relating to the HIV status of their CIAI partners with a similar proportion reporting only HIV negative partners for CIAI (49%).

6.10.3 Condomless receptive anal intercourse at last act

A quarter (300/1,216) (95%CI 22-27) of men reported engaging in CRAI in the last month, 50% (95%CI 48-53) in the last year and 27% (95%CI 24-29) reported never having CRAI (Figure 6.8). The proportion reporting CRAI in the last year did not differ by clinic or ethnicity. However, 60% (95%CI 55-67) of 15-24 years olds reported their last CRAI act to be in the last year compared to 35% (95%CI 25-46) of men aged 50+ years (Table 6.5). For each of the categories, between 64-74% reported the partner to be HIV negative and the majority of the rest didn't know the HIV status of the partner. Only 4% reported their partner to be HIV positive and on treatment.

Figure 6.8 Last act of condomless receptive anal intercourse reported by HIV negative MSM, England, 2012-13 (n=1,216)



The most common reason for not using a condom at the last act of CRAI was because the individual was in a monogamous relationship (27%), followed by being under the influence of alcohol (18%) (Table 6.7). Very few men reported not using a condom because they were on PrEP (n=2) or because they planned to get PEP after sex (n=4). The low numbers on PrEP is not surprising as the results of the PrEP trials (10) had only recently been published.

Table 6.7 Most commons reasons for not using a condom at last act of condomless receptive anal intercourse reported by HIV negative MSM, England, 2012-13 (n=651)

Reason	Frequency (%)
Monogamous relationship	177 (27%)
Under influence of alcohol	120 (18%)
To feel closer to partner	86 (13%)
Only use condoms with other partners	85 (13%)
Condoms weren't discussed	81 (12%)

Fifteen per cent of men (n=97) also gave reasons other than those listed; the most common among these was being in a relationship or only having CRAI with

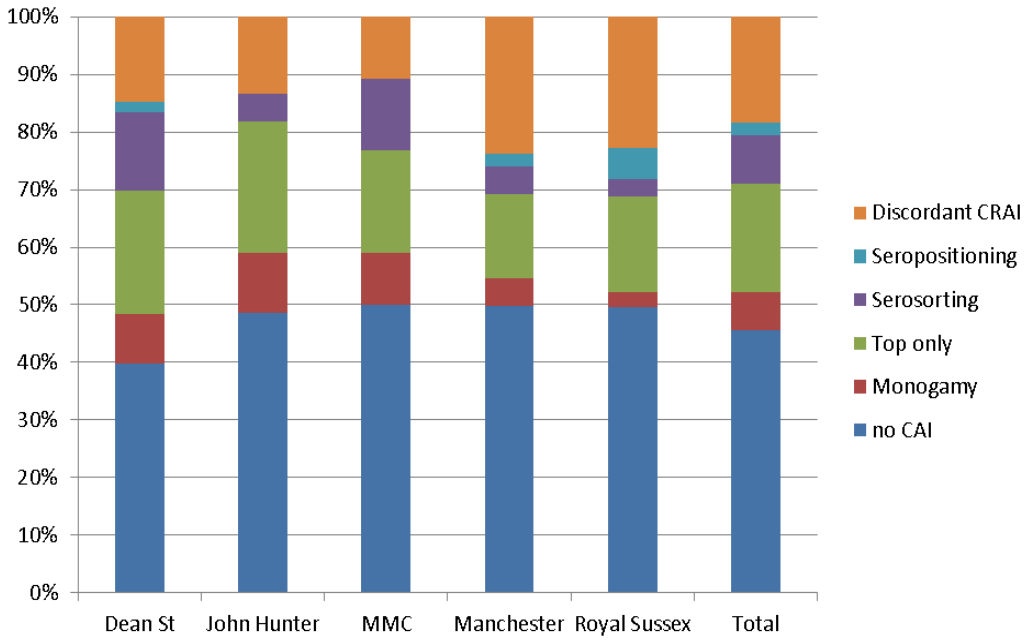
a regular partner (17%) and the condom breaking or slipping off (17%). A quarter of men gave multiple reasons for not using a condom.

6.11 Seroadaptation

I assigned 1,109 (87%) MSM to one of the six mutually exclusive hierarchical seroadaptive behaviours (Figure 6.9). Data completeness was not sufficient for the remainder to be categorised. Around half the population from each clinic reported CAI in the last three months. Overall, 7% were classed as monogamous, 19% being top (CIAI only), 8% serosorting, 2% seropositioning and 18% reported no risk reduction strategy in the last three months.

Men attending Royal Sussex reported significantly less monogamy than the other clinics (3% vs 5-10%, $p=0.03$) and serosorting was more common among attendees at Dean St and MMC (14% and 13%, vs 3-7%, $p<0.001$). Men attending Manchester and Royal Sussex reported no risk reduction strategy more frequently than men attending other clinics (24% and 23%, vs 11-15%, $p<0.001$).

Figure 6.9 Seroadaptive behaviours among HIV negative MSM by clinic of attendance, England, 2012-13 (n=1,109)



As the numbers in some categories were small, they were further collapsed into three behavioural categories: i) safer sex (no CAI, monogamy), ii) seroadaptation (top only, serosorting, seropositioning) and iii) no risk reduction strategy (CRAI with serodiscordant or unknown status partner). Fifty-two per cent reported safe sex, 29% seroadaptation and 18% no risk reduction strategy (Table 6.8). There were no differences in categorisation by age group whereas significantly fewer white MSM from Europe (including the UK) reported seroadaptation compared to non-European white MSM (25% vs 46%, $p<0.001$). With increasing numbers of partners, men were more likely to employ no risk reduction strategy and less engaged in safe sex. Fourteen per cent of MSM reporting one partner in the last three months had engaged in CRAI with partners of HIV positive or unknown status compared to 17% of MSM with 2-4 partners and 24% of MSM with more than four partners ($p<0.001$).

Clinical outcomes at baseline were associated with behavioural categorisation; 24% of MSM diagnosed with a bacterial STI and 36% with a rectal diagnosis or syphilis reported no risk reduction strategy in the previous three months (p<0.001) (Table 6.8). A similar association was not observed for clinical history. An acute STI in the last year was not associated with behavioural classification.

Table 6.8 Behavioural categorisation of HIV negative MSM by demographics and clinical history, England, 2012-13 (n=1,109)

Characteristic	Safe Sex	Seroadaptation	No risk reduction strategy	P value
Age group				0.43
15-24	132 (53)	68 (27)	50 (20)	
25-34	240 (51)	134 (29)	95 (20)	
35-49	169 (53)	102 (32)	49 (15)	
50+	38 (54)	23 (33)	9 (13)	
Ethnicity and birthplace				<0.001
White UK-born	345 (55)	155 (25)	124 (20)	
White European	118 (59)	55 (27)	28 (14)	
White non-European	36 (38)	44 (46)	16 (17)	
Non-white UK-born	28 (43)	27 (42)	10 (15)	
Non-white born abroad	44 (43)	38 (37)	21 (20)	
Other/Unknown	8 (40)	8 (40)	4 (20)	
Attendance at clinic				0.001
London	286 (51)	196 (35)	83 (15)	
Outside London	293 (54)	131 (24)	120 (22)	
Partner numbers				<0.001
0*	39 (100)	0	0	
1	168 (68)	43 (17)	35 (14)	
2-4	241 (53)	136 (30)	79 (17)	
>4	125 (35)	144 (40)	87 (24)	
Unknown	6 (50)	4 (33)	2 (17)	
At baseline:				
Bacterial STI				<0.001
No	472 (56)	234 (28)	141 (17)	
Yes	107 (41)	93 (36)	62 (24)	
Rectal infection/syphilis				<0.001
No	549 (54)	301 (29)	172 (17)	
Yes	30 (34)	26 (30)	31 (36)	
In the previous year:**				
HIV test/STI screen	247 (50)	146 (30)	100 (20)	0.67
Acute STI	95 (52)	46 (25)	42 (23)	0.26
Total	**579 (52)**	**327 (29)**	**203 (18)**	

*MSM reporting no partners were included because there were clinical outcomes in this group.
**comparison group to calculate p value are men who attended in the prior year but were not diagnosed with a STI or did not have a HIV test/STI screen.

6.12 New HIV diagnoses at baseline

Eight (0.6%) MSM were newly diagnosed with HIV at the behavioural attendance. Due to the small number of outcomes, I only examined univariate associations between variables and infection. While no associations were significant, a greater proportion of men diagnosed with gonorrhoea in the prior year were diagnosed with HIV at baseline (2.1%, OR: 4.7) (Table 6.9). Odds of HIV infection were also higher among men reporting seroadaptation (OR: 1.8) and no risk reduction strategy (OR: 2.9) compared to men practising safe sex. However, there were two HIV diagnoses among men reporting safer sex in the last three months.

Table 6.9 New HIV diagnoses at baseline and subsequent incidence among HIV negative MSM by demographics and clinical history, England, 2012-13 (n=1,278)

	New diagnoses at baseline		HIV Incidence	
	Number of infections (%)	Unadjusted OR (95%CI)	HIV incidence/100 py	Unadjusted HR (95%CI)
Age group				
15-24	2 (0.7)	1	5.6 (2.1-14.9)	1
25-34	1 (0.2)	0.25 (0.02-2.7)	3.7 (1.7-8.2)	0.5 (0.1-2.0)
35-49	4 (1.1)	1.5 (0.3-8.5)	1.0 (0.16.8)	0.2 (0.02-1.5)
50+	1 (1.1)	1.5 (0.1-17.0)	0	-
Ethnicity and birthplace				
White UK-born	5 (0.7)	1	3.6 (1.6-8.1)	1
White European	1 (0.4)	0.7 (0.1-5.2)	3.6 (1.2-11.3)	1.3 (0.3-5.3)
White non-European	0 (0)	-	2.4 (0.3-16.9)	0.8 (0.1-7.2)
Non-white UK-born	0 (0)	-	0	-
Non-white born abroad	1 (0.9)	1.2 (0.1-10.6)	3.0 (0.4-21.4)	1.0 (0.1-8.8)
Attending a London clinic				
No	8 (1.3)	-	3.6 (1.1-11.0)	1
Yes	0 (0)	-	2.9 (1.5-5.9)	0.8 (0.2-3.1)
Gonorrhoea last year				
Attended, no gonorrhoea	2 (0.4)	1	2.2 (0.8-5.9)	1
Attended, gonorrhoea	2 (1.9)	4.7 (0.7-33.7)	10.0 (3.7-26.5)	6.0 (1.3-26.9)
Did not attend	4 (0.6)	1.4 (0.3-7.6)	2.2 (0.7-7.0)	1.3 (0.3-6.7)

Table 6.9 continued	New diagnoses at baseline		HIV Incidence	
	Number of infections (%)	Unadjusted OR (95%CI)	HIV incidence/100 py	Unadjusted HR (95%CI)
Syphilis last year				
Attended, no syphilis	4 (0.7)	1	3.3 (1.6-6.9)	1
Attended, syphilis*	0 (0)	-	11.8 (1.7-83.9)	-
Did not attend	4 (0.6)	0.8 (0.2-3.3)	2.2 (0.7-7.0)	0.7 (0.2-2.6)
Behavioural group				
Safe sex	2 (0.4)	1	1.3 (0.3-5.3)	1
Seroadaptation	2 (0.6)	1.8 (0.2-12.7)	2.2 (0.9-8.9)	4.4 (0.5-42.8)
No strategy	2 (1.0)	2.9 (0.4-20.5)	5.7 (1.8-17.6)	8.5 (0.9-81.4)
Bacterial STI at baseline				
No	6 (0.7)	1	2.2 (1.0-5.0)	1
Yes	2 (0.6)	1.1 (0.2-5.4)	5.8 (2.4-13.8)	3.0 (1.0-10.5)

* There are no HIV diagnoses at baseline among MSM diagnosed with syphilis in the previous year and only one in the subsequent year. For this reason, syphilis results in the incident risk factor analysis were unstable and are not included

6.13 HIV incidence

There were 641 MSM who re-attended the clinic after the baseline attendance. Among these men, there were 11 new HIV infections during 356 years of follow-up; equating to an incidence of 3.1/100 py (95%CI 1.7-5.6 py). There were no differences by demographics (Table 6.9). HIV incidence was significantly higher among men diagnosed with gonorrhoea in the previous year (10.0/100 py, HR: 6.0, p = 0.02) compared to men who were not (2.2/100 py). Incidence non-significantly increased from 1.3/100 py among MSM practising safer sex to 2.2/100 py among MSM adopting seroadaptive behaviours and 5.7/100 py among those employing no risk reduction strategy.

Though Table 6.9 examines the association between behavioural groups and HIV incidence, I also examined the role of CAI (both insertive and receptive) and partner numbers on subsequent risk of HIV. Men reporting CRAI with at least two partners were at four times greater risk of acquiring HIV compared to men

reporting 0-1 partners (unadjusted HR: 4.9 95%CI 1.1-22.1) and having at least two sexual partners was non-significantly associated with greater risk (HR: 2.0, 95%CI 0.2-15.6) whereas there was no association with CIAI and HIV (HR: 0.6, 95%CI 0.08-5.0).

Using the unadjusted hazard ratios, the PAR for a previous gonorrhoea infection was 35% (prevalence: 11%) and for CRAI with serodiscordant or unknown status partners was 60% (prevalence: 20%). CRAI with at least two partners accounted for 32% of infections (prevalence: 12%).

6.14 Representativeness

6.14.1 MSM not offered the questionnaire

In order to examine non-response I compared MSM who completed the questionnaire ('recruited') with those that did not ('non-recruited'). There were 19,224 HIV negative MSM who attended one of the study clinics during the study period but who were not recruited. Men who were not recruited were demographically and clinically different to men who were recruited (Table 6.10). Recruited men were more likely to be young (<35 years: 64% vs 58%, p<0.001), of white ethnicity and born in the UK (56% vs 46%, p<0.001) and attending a non-London clinic (i.e. Manchester or Royal Sussex) (47% vs 12%, p<0.001) than those not recruited (Table 6.10). More of those recruited had attended the same clinic in the prior year (46%) compared to those not recruited (38%) and among these recruited men, 96% had a STI screen or HIV test. More recruited men were also diagnosed with an acute STI in the prior year (37% vs. 22%, p<0.001).

Table 6.10 Comparison of HIV negative MSM recruited (n=1,278) with those not recruited (n=19,224) by demographic and clinical variables, England, 2012-13

Characteristic	Recruited men (%)	Non-recruited men (%)	P value*
Age group			<0.001
15-24	274 (21)	2,940 (15)	
25-34	546 (43)	8,150 (42)	
35-49	367 (29)	6,451 (34)	
50+	91 (7.1)	1,683 (9)	
Ethnicity and birthplace			<0.001
White UK-born	717 (56)	8,935 (46)	
White European	233 (18)	3,820 (20)	
White non-European	110 (8.6)	2,170 (11)	
Non-white UK-born	77 (6.0)	1,116 (6)	
Non-white born abroad	117 (9.2)	2,183 (11)	
Other/Unknown	24 (1.9)	1,000 (5)	
Attendance at clinic			<0.001
London	680 (53)	16,935 (88)	
Outside London	598 (47)	2,289 (12)	
Bacterial STI at baseline			<0.001
No	973 (76)	16,876 (88)	
Yes	305 (24)	2,348 (12)	
HIV testing/STI screening previous year**	559 (96)	6,511 (89)	<0.001
Acute STI previous year**	213 (37)	1,609 (22)	<0.001
Total	**1,278**	**19,224**	

*P value of comparison of recruited men at baseline with men not recruited
**only includes MSM who attended the clinic in the previous year to the baseline attendance: 581 (45%) recruited men and 7,301 (38%) non-recruited men. For men not recruited the first attendance date where a questionnaire could have been filled in during the study was used to define the "previous year"

I also prospectively measured HIV incidence among men not recruited. Among 13,282 MSM who returned to the clinic, there were 83 new HIV infections over 18,142 person years of follow-up giving a HIV incidence of 0.5/100 py (95%CI 0.4-0.5), which was significantly lower than among men in the study (3.1/100 py, 95%CI 1.7-5.6).

6.14.1.1 Weighted analyses

Due to the large non-response, the recruited sample was not representative of all HIV negative MSM attending the five GUM clinics. Young MSM and white MSM born in the UK were over-represented among recruited men. After weighting by age group, ethnicity and birthplace and clinic location, the sample were aligned to all HIV negative MSM attending the five GUM clinics.

The proportion of MSM aged 15-24 years reduced from 21% to 15% (Table 6.11). Similarly, UK-born white MSM reduced from 56% to 47%. The weighting also impacted the distribution of behavioural groups. More men were classified as practising seroadaptation (33%) and fewer adopted no risk reduction strategy (15%).

Table 6.11 Effect of weighting on demographic and behavioural proportions among HIV negative MSM completing the questionnaire, England, 2012-13 (n=1,278)

Characteristic	Crude proportions	Weighted proportions
Age group		
15-24	21	15
25-34	43	44
35-49	29	32
50+	7	8
Ethnicity and birthplace		
White UK-born	56	47
White European	18	23
White non-European	9	12
Non-white UK-born	6	6
Non-white born abroad	9	11
Other/Unknown	2	0
Attendance at clinic		
London	53	88
Outside London	47	12
Behavioural group		
Safe sex	52	51
Seroadaptation	29	33
No risk reduction strategy	18	15
Bacterial STI at baseline		
No	76	77
Yes	24	23

I re-examined new diagnoses at baseline after weighting. The proportion newly diagnosed with HIV at baseline reduced from 0.6% to 0.001%. Weighting highlighted that the sample had over recruited men from outside London and since all endpoints were in the population outside London, the effect of weighting was to reduce the proportion to almost zero. The likelihood of being diagnosed with HIV remained non-significantly higher among MSM adopting seroadaptive behaviours and employing no risk reduction strategy (OR: 1.6, 95%CI 0.1-19.2

and 4.7, 95%CI 0.4-52.4, respectively) (Table 6.12). Similarly, MSM with a gonorrhoea diagnosis in the previous year were more likely to be diagnosed at baseline with HIV (OR: 6.9, 95%CI 0.9-50.1).

Table 6.12 Weighted unadjusted odds ratios and hazard ratios for new HIV diagnoses at baseline and subsequent incident infections among HIV negative MSM by demographics and clinical history, England, 2012-13

	New diagnoses at baseline Unadjusted OR (95%CI)	HIV Incident infections Unadjusted HR (95%CI)
Age group		
15-24	1	1
25-34	0.2 (0.02-2.5)	0.5 (0.1-2.7)
35-49	1.2 (0.2-7.7)	0.2 (0.02-1.9)
50+	2.0 (0.2-24.5)	-
Ethnicity and birthplace		
White UK-born	1	1
White European	0.2 (0.02-1.4)	1.0 (0.2-5.5)
White non-European	-	0.9 (0.1-8.3)
Non-white UK-born	-	-
Non-white born abroad	0.9 (0.1-7.7)	1.3 (0.1-11.6)
Attending a London clinic		
No	-	1
Yes	-	0.9 (0.2-3.6)
Gonorrhoea last year		
Attended, no gonorrhoea	1	1
Attended, gonorrhoea	6.9 (0.9-50.1)	9.6 (1.8-52.6)
Did not attend	1.0 (0.2-6.8)	1.6 (0.2-10.8)
Syphilis last year		
Attended, no syphilis	1	1
Attended, syphilis*	-	-
Did not attend	0.6 (0.1-2.8)	0.7 (0.1-3.5)
Behavioural group		
Safe sex	1	1
Seroadaptation	1.6 (0.1-19.2)	5.0 (0.5-47.6)
No strategy	4.7 (0.4-52.4)	3.9 (0.3-47.1)
Bacterial STI at baseline		
No	1	1
Yes	1.2 (0.2-7.0)	4.5 (1.1-18.7)

* There are no HIV diagnoses at baseline among MSM diagnosed with syphilis in the previous year and only one in the subsequent year. For this reason, syphilis results in the incident risk factor analysis were unstable and are not included

After weighting, HIV incidence dropped to 2.9/100 py and the confidence intervals were wider (1.5-6.2). A previous diagnosis of gonorrhoea remained significantly associated with HIV incidence (HR: 9.6, 95%CI 1.8-52.6) as did a bacterial STI diagnosis at baseline (HR: 4.5 95%CI 1.1-18.7) (Table 6.12). Men practicing safer sex remained at lower risk of acquiring HIV infection than men in the other two groups (although this was not a significant association). The risk of HIV increased among those practising CRAI with at least two partners after weighting (HR: 6.4, 95%CI 1.4-28.7).

6.14.2 Item non-response

Item non-response occurs when some items in a questionnaire are not completed as well as others due to question sensitivity, the respondent not knowing the answer, not understanding the question or edit failures. Among 1,278 MSM, 14% were missing information on the number of CRAI partners and 17% information on number of CIAI partners. Non-completion of these two questions is higher than for the other variables and may plausibly be due to two reasons: social desirability and the missing boxes for these two questions in the questionnaires sent to Royal Sussex and Manchester.

A comparison of men who completed these questions with those that did not showed there were systematic differences in the two populations. Missingness was related to age group, clinic of attendance and sexual behavioural variables (Appendix 8). The majority of men who did not complete the questions were from outside London (that is, from Royal Sussex and Manchester). Men who completed the question on numbers of CRAI partners also completed the

question on CIAI partners (94%) and men who did not complete CRAI partners also did not complete CIAI partners (87%). The majority of men who completed the question on CRAI/CIAI also completed the sub-questions on the HIV status of the partner and between a half to two-thirds of non-completers completed the sub-questions.

Missing data in the CRAI and CIAI questions were associated with a HIV diagnosis but not with a diagnosis of a high risk STI at baseline (defined as HIV, syphilis, rectal gonorrhoea, rectal chlamydia and LGV). The latter outcome is used for risk prediction (Chapter 8) and is therefore mentioned here to examine the suitability of MI. More men with missing information on CRAI were diagnosed with HIV at baseline (2.3%) compared to those with information (0.4%, p=0.003). The same relationship was observed for CIAI. However, 8% of men with missing information were diagnosed with a high risk STI compared to 11% of those with information (p=0.11). There was also no association with incident HIV infection and missing data (CRAI p value=0.217, CIAI p value= 0.341).

I next compared the association of CRAI and CIAI partners, where completed, with other covariates. In a multinomial logistic regression model, age and numbers of CIAI partners were significantly associated with numbers of CRAI partners (Table 10.4, Appendix 8). CRAI and CIAI partners were strongly correlated with each other suggesting men were reporting the same numbers of CRAI and CIAI partners. For example, men reporting one partner with whom they engaged in CIAI were six times more likely to also report one CRIA partner (<0.001). In addition to age and numbers of CRAI partners, attendance at a London clinic and country of birth and ethnicity were associated with numbers of CIAI partners (Table 10.5, Appendix 8).

6.15 Key Findings

This study demonstrates that collecting behavioural data is possible from clinics although the low recruitment rate indicates the method of distribution of questionnaires was a problem and using a paper questionnaire is not a long-term feasible option. The completeness of the returned questionnaires was good; between 70-98% of the behavioural questionnaires were complete. Linkage to clinical records reported to national surveillance was possible and successfully achieved. This was due to good completion of the patient ID number and the date of questionnaire completion. Only 9% of questionnaires were excluded due to issues relating to the linkage process.

After linkage, there were 1,278 MSM (80% of 1,601 MSM) who were included in subsequent analyses. Three per cent of these men reported no partners in the last three months. Half of the men reported CAI; 36% CRAI and 41% CIAI in the last three months. Older MSM (aged 50+ years) were more likely to report more sexual partners but younger MSM reported higher risk behaviours (e.g. more CAI and CRAI). The clinician-led method to administer the questionnaire at Manchester did not impact the responses as men reported behaviours similar to the other clinics except Dean St whose recruited attendees reported more risk (e.g. more CRAI and CIAI) than men at other clinics.

Half of all men reported safer sex, 29% a seroadaptive behaviour and 18% no risk reduction strategy. Though men at Manchester reported fewer partners, less CAI and CIAI than men at other clinics, more of them were categorised into the no risk reduction strategy group (i.e. reporting CRAI with serodiscordant

partners) compared to men attending London clinics. A similar picture was also observed for men recruited at Royal Sussex.

Less than 1% of men were diagnosed with HIV at baseline and a further 11 were diagnosed subsequently (incidence: 3.1/100 py, 95%CI 1.7-5.6). HIV incidence non-significantly increased from 1.3/100 py among MSM practising safer sex to 2.2/100 py among seroadapters and 5.7/100 py among those employing no risk reduction strategy. Men reporting CRAI with at least two partners were at significantly increased risk of acquiring HIV (unadjusted HR: 4.9, 95%CI 1.1-22.1) with an associated PAR of 32%.

There were some systematic differences between recruited men and non-recruited men. HIV incidence was significantly lower among those not recruited (0.5/100 py), this was a lower risk population. Further, missing data for CRAI and CIAI partners was associated with other measured variables and was not related to any of the outcomes except HIV diagnosis at baseline. Where completed, these two behaviours were also associated with some of the measured covariates. Thus data are probably missing at random although there was some evidence of missing data being associated with the outcome. There is a possibility that some unmeasured variables may also account for the differential response. Some of the bias can be reduced through multiple imputation, which will be further explored in Chapter 8.

6.16 Strengths and limitations

This is a large study examining sexual behaviours among HIV negative MSM attending GUM clinics in England. Despite the low recruitment rate, 1,601 MSM completed a questionnaire. Though sexual behavioural data is collected by

clinics, I implemented the questionnaire in five clinics and showed that collection of standardised information from MSM on a number of sexual behaviours considered important determinants of HIV infection was possible and was of value at identifying further predictors of infection. When the study was conceived and run, there were no other sources of readily available behavioural data from GUM clinics. A further strength is the longitudinal design employed. Though behaviours were collected at one time point, the data were successfully linked to clinical records to allow clinical history and subsequent outcomes to be investigated. I was able to calculate HIV incidence in different behavioural groups. This has, to my knowledge, not been conducted and reported for this setting for HIV negative MSM in England.

There are two sets of limitations to this study. The limitations associated with GUMCAD have already been discussed in chapter 5 (section 5.9) and will not be further discussed here except a mention of linkage between GUM clinics. National surveillance cannot record movement between clinics and this may be a significant limitation as the behavioural study indicated that over half of men who attended the clinic for the first time had attended another clinic in the previous year compared to the 9% reported elsewhere (247). Only 12% had never been to a GUM clinic before. The inability to link between clinics will impact incidence and other analyses where previous clinical history is important for risk stratification or determining HIV testing patterns. The next section focuses on limitations arising from the study.

There were a number of potential biases that occurred during the implementation and data collection stage of the study that limit the generalisability of the results beyond the population that was recruited. First, selection bias may have arisen

because the study was only conducted in five clinics for a six month period and therefore only MSM who attended one of the participating clinics during the study period had the opportunity to complete a questionnaire. These clinics were not selected to be representative of all MSM attending GUM clinics; they do however account for a large proportion of the source population. Further, as no seasonality is expected in relation to behaviours or clinical outcomes, no significant differences are expected between MSM who attended the clinic during the study and those that did not.

Secondly, selection bias occurred due to the low recruitment rate and incidence was lower in the non-recruited population. The low recruitment rate was largely due to operational difficulties where clinics, particularly larger clinics with more MSM attendances, found distribution of paper questionnaires a challenge. Other reasons included competing studies and forgetting to give out the questionnaire. Although the study was extended to offset the low recruitment rate, fewer MSM were recruited than anticipated. The low recruitment rate resulted in a sample size that was not large enough to power multivariable analyses. Due to the operational challenges faced, it was also not possible to assess the acceptability of the questionnaire. The volume of work that would have been required to record the numbers of men offered questionnaires would have been unfeasible for clinics. It was however likely a large number of MSM who did not complete a questionnaire were not offered the questionnaire rather than they declined it.

Thirdly, the study may have introduced some volunteer bias as those MSM who completed a questionnaire were systematically different to the population of HIV negative MSM attending the five clinics. The results of the study suggest recruited MSM were a higher risk population at greater risk of HIV infection

though incidence estimates were comparable with results from all repeat testers (Chapter 5). As a result of the non-representativeness of the sample, it is possible that the prevalence of sexual behaviours reported here overestimate that in the wider MSM population attending GUM clinics. One could, however, argue that this is the population of interest as any HIV prevention interventions will be targeted to this group and therefore the results obtained from the recruited sample are relevant.

Fourthly, in addition to the biases introduced during recruitment, bias potentially occurred during data collection. The omission of response boxes for the two questions on receptive and insertive partners on the majority of questionnaires sent to Manchester and Royal Sussex affected the analysis and interpretation of the data. Where possible this was compensated in part by using information provided in the sub-questions to make assumptions for these missing data and replace with "0" partners. For example if men reported "0" CRAI partners of HIV positive or unknown status I assumed they had no receptive partners though they may have had CRAI partners of HIV negative status. This approach may have underestimated CAI in the sample by assigning men to the no CAI group. Risk factor analyses may have also been affected; more men would be assigned to the safe sex group and if these men had engaged in CAI, this would underestimate the risk associated with seroadaptation and/or adopting no strategy and HIV acquisition. Other than these two questions, overall completion was high including for the questions that related to HIV status of CRAI and CIAI partners.

The reason for the missing data (e.g. sensitivity of question or missing box) may not be as important as whether the responses would differ systematically from

those that do answer and if so whether then the data can be predicted in an unbiased manner using the other covariates. Analyses indicated systematic differences between the observed and missing data and that CRAI and CIAI partners were related to other covariates, suggesting MI can be used to predict the missing values using the existing covariates. Without MI, these complete case analyses are potentially biased. While multiple imputation techniques will reduce bias, residual bias is likely to remain in the predicted values. I have not conducted MI in this chapter, but explore it in chapter 8 when developing risk models.

As changes could not be made to the questionnaire after the cognitive interviews, the wording of two of the questions may also have some implications when interpreting the findings. Though the results suggest about half of all partners in the last 3 months were new, it is not possible to know whether this was truly the case because men may have interpreted the question on numbers of new partners incorrectly. Secondly, the cognitive interviews highlighted that men were confused by the option “he was only dipping” as a reason not to use a condom. In the behavioural survey, this was a very uncommon response, though this may reflect that men did not understood what it meant and therefore did not select it. Thus the survey may have underestimated the number of true responses for this option. It is however reassuring that the cognitive interviews suggested that the other questions, particularly those pertaining to numbers of receptive and insertive partners, were interpreted as intended.

Finally, men were not specifically asked to report seroadaptive behaviours; instead their responses to a number of behavioural questions were used to

categorise them. Therefore the categorisation was dependent on complete and true responses from men.

As well as potential biases that arose during this study, I cannot discount the effect of confounding especially as I was unable to conduct multivariable analyses that would have adjusted for measured confounders. An example of potential confounding is the effect of STIs on HIV transmission. Although the association has been widely reported with potential epidemiologic interactions defined, sexual behaviours are potential confounders of this relationship. A confounder is a variable that is related to the outcome and exposure of interest and is not on the causal pathway of the exposure and outcome. Sexual behaviours could distort the effect measure of STIs on HIV acquisition.

6.17 Reflections

There are a number of areas of learning from the behavioural study that I would use to modify the study were I to repeat it. Firstly, I would consider making changes to the items included in the questionnaire. The questionnaire was developed to collect the minimum amount of sexual behavioural data that mimics clinical practice as closely as possible. This limited how many questions could be asked. I would add a sub-question on the numbers of partners of HIV negative status rather than surmising this information from the other HIV status questions (numbers positive and numbers of unknown status). This would have overcome the problem of replacing missing data for total numbers of partners where the box was missing and improved the quality of subsequent analyses. Though I had piloted the Word version of the questionnaire, I did not pilot the version that was formatted by the PHE publications team and which was the version with the

missing boxes. This additional pilot would have highlighted this issue. Further, I think the inclusion of a question on drug use during sex would have strengthened analyses on risk factors for HIV acquisition. Though one of the earlier drafts of the questionnaire included such a question, I removed it because it was not routinely collected information in clinics.

Secondly, the cognitive interviews were conducted after the survey rather than before, as was originally planned. It would have been better to postpone the survey until the cognitive interviews could be completed but PHE was keen to start once the clinics were recruited and I did not feel I could change this timeline. PHE were aware that the PROUD trial was starting soon, which was a driving force for the behavioural study to start too. It was anticipated that the behavioural data would feed into identifying higher risk MSM who might need PrEP and hence inform any future PrEP trial. In hindsight, there was no real urgency for the study to be rushed. At the stage when PHE wanted to start, I had not received ethical approval or my research passport. The research passport in particular was a lengthier process than I had anticipated as it required both internal and external checks. Without these approvals in place I was unable to conduct the interviews in time. I decided to go ahead with post-survey testing because the findings of the interviews would still be relevant for any future work using the questions and the findings of the interviews could aid interpretation of the survey results.

Finally, the study achieved a low recruitment rate despite my clinic visits and the different recruitment approaches adopted by clinics to improve recruitment. For some clinics this study was one of many ongoing projects or there had been other recent studies conducted with similar target populations. Clinic research

fatigue is likely to have occurred; especially as all clinics are large urban clinics often involved in research projects relating to MSM. On reflection, greater feedback to clinics and more face to face visits may have helped maintain interest and help recruitment rates especially as my one visit to each clinic did impact recruitment soon after. I could have also more regularly and closely monitored response rates as this would have highlighted recruitment issues and potentially allowed me to better monitor the offer of questionnaires. A higher recruitment rate may have also been achieved if the study was carried out as research. Research would have enabled adoption onto CRN portfolio, which would have supported recruitment with the availability of a small amount of funding. This may have provided some additional motivation for the clinic and would have been the option that I would have preferred. It may have also given me greater ownership of the work and subjected the work to more rigour. In reality, though, this may have made little difference given the reasons already discussed and the only solution may have been a dedicated research nurse to oversee recruitment. However, as the idea of the study was to mirror clinical practice as much as possible, PHE were keen to run the study as enhanced surveillance rather than a research project. As the Medical Director agreed that this work could be viewed as surveillance, I felt the study had to proceed as surveillance.

6.18 Discussion

6.18.1 Comparison with MSM recruited in other settings

A comparison of MSM recruited in this study with samples recruited online, from social venues and nationally suggests MSM attending GUM clinics engage in higher risk behaviours. The median number of partners in the past year reported

by MSM from a national probability sample was 2 (IQR: 1-5) (15); lower than the numbers reported by MSM for a three month period in this study. Just over a third of our sample reported more than 4 partners in the last three months; in comparison 23% of a nationally representative sample, 54% of men recruited in social venues in London and 58% of men recruited online reported at least five partners in the past year (61). While similar proportions had attended a GUM clinic in the previous year, more MSM in this study were diagnosed with an STI in the previous year (17%) compared to MSM recruited in a national sample, from social venues and online (5%, 12%, 10%, respectively).

The estimates from this study are however in line with estimates from other GUM samples (Table 6.13). The AURAH study showed that58% of HIV negative MSM attending GUM clinics had condomless sex and 13% had engaged in CRAI with a sexual partner of unknown or HIV positive status in the last three months (258). Fifty-nine per cent of MSM recruited at MMC to a human papilloma virus study reported CAI in the last year, which is expectedly higher than that reported in this study (259). The sample of MSM recruited in Natsal reported less CAI; however this could be expected given that these men were recruited from the general population as opposed to GUM clinics, though they had attended a GUM clinic in the past 5 years (259). MSM recruited in PROUD reported far higher numbers of partners in the last 3 months (260). Inclusion into the study included engagement in CAI in the last 3 months indicating this is a self-selected high risk population not comparable to men recruited in this study. Most recently, 55% of MSM recruited from six GUM clinics reported CAI and a median of three partners (unpublished data from RiiSH, personal communication Dr. Sonali Wayal).

Table 6.13 Comparison of sexual behaviours between the behavioural study participants and other GUM attending samples of MSM

Behaviours in the last 3 months (unless indicated)	Behavioural study (2012-2013)	PROUD trial (2012-2014) (260)	HPV in MSM (2010-2012) (259)	Natsal 3 (2010-2012) (259)	AURAH (2013-2014) (258)	RiiSH (2016) (unpublished)
Number recruited/included	1,601	540	522	43	1,484	451
CAI (%)	52%	100%	59%**	44%**	58%	55%
CRAI (%)	36%					
CIAI (%)	41%					
Median number of partners (IQR)	3 (1-6)	10 (5-10)				3 (1-7)
Median number of CRAI partners (IQR)	1 (1-2)	2 (1-5)				
Median number of CIAI partners (IQR)	1 (1-2)	2 (1-6)				
CRAI with HIV serodiscordant or unknown status partner (IQR)	18%				13%	

*in the last 6 months; **in the last year

6.18.2 Comparison of seroadaptive behaviours with other studies

The prevalence of seroadaptive behaviours (29%) in our study was less widespread than in the US. Almost half of HIV-negative MSM in San Francisco reported behaviours that could be categorised as seroadaptive strategies in 2011 (261) and 62% of men participating in HIV prevention studies in the US were categorised as seroadapters based on reported behaviours (128). Serosorting was less frequently practiced in the study sample than in other studies, which report between 25-38% of HIV negative MSM serosort (93, 261-265). In 2013,

27% of HIV negative MSM in London exclusively serosorted in the last year (20).UK-born white MSM who made up over half the sample in this study reported seroadaptive behaviours less frequently than other MSM populations. This will have impacted estimates reported here.

Seropositioning was also considerably less frequent in this sample (2%) as other studies estimate prevalence to be between 6-15% (217, 261, 262). It is very possible that seropositioning has been under-reported due the categorisation process. Some men classified as being top only (CIAI with one or more partners) may actually have been men who seroposition. Assignation of top only was lower in the hierarchical order and required less information than seropositioning, which required information on the status of the CIAI partner and whether CRAI was always with HIV negative partners. True prevalence of seropositioning in the study was probably between 2-17% (prevalence of top only).

We are unable to distinguish intentional adoption of these strategies to reduce the risk of acquiring HIV infection with unintentional practices as we did not ask men to specifically report any seroadaptive behaviours. We did, however, observe a large proportion of MSM who knowingly engaged in CRAI with a sexual partner of unknown HIV status or of positive status (18%). This is higher than among MSM sampled in London gyms in 2008 (11%) (65) although not unexpected as MSM attending GUM are likely to be a higher risk population. It is similar to the proportion that reported CAI with a sexual partner of unknown HIV status or of positive status reported in a community survey in 2013 (16%, (20)). Some of these positive partners may have suppressed viral loads and these individuals would be considered almost non-infectious (266) so the extent of HIV transmission risk in these relationships may be overestimated.

6.18.3 HIV outcomes and behavioural risk factors

HIV incidence among MSM in this study is comparable to estimates for repeat testing MSM for whom incidence was calculated in Chapter 5 (2.0/100 py, 95%CI 1.8-2.2) suggesting the recruited population is similar to repeat testers. This may however only be the case because the sample size was small and the confidence intervals wide. The point estimate is higher than among all repeat testers.

HIV incidence was significantly higher among men diagnosed with a bacterial STI at the baseline attendance (HR: 3.0) compared to men who did not have a bacterial STI. Bacterial STIs, especially gonorrhoea, are known predictors for HIV infection (Chapter 5). Men diagnosed with a STI will potentially be referred to a health advisor at the clinic to discuss risk and recent behaviours in greater depth in order to change behaviour. Yet, in this sample risk continued after potential contact with clinical staff, which is highlighted by high HIV incidence.

It cannot be determined from the results whether seroadaptation was an effective strategy for preventing HIV acquisition. The number of HIV endpoints was too few to facilitate a multivariable analysis. The non-significant increase in incidence from 1.3/100 py among MSM practising safer sex to 2.2/100 py among MSM adopting seroadaptive behaviours could imply some risk associated with seroadaptation and HIV transmission in this cohort. These could be men actively serosorting but successful seroadaptation requires knowledge of the partner's HIV status and with an estimated 13% of MSM living with HIV in the UK unaware of their infection in 2015 (12) and with inadequate levels of HIV testing (20, 253), men are more likely to be "seroguessing" rather than serosorting (265). It should

however be noted that since 2000 the proportion of HIV negative MSM testing in the past year has significantly increased (20) as has repeat testing (22) such that men are better able to participate in seroadaptive strategies and are likely to be serosorting with increased safety.

Studies have shown seroadaptation is better for HIV prevention than employing no risk reduction strategy (128, 217), and this was also clear from our study which showed that incidence further increased to 5.7/100 py among those employing no risk reduction strategy. However, despite the greater risk when no strategy is employed, seroadaptive behaviours still represent an increased risk of acquiring of HIV infection. It should, however, be noted that all sex practices carried some risk with seroconversions occurring even among men reporting only safer sex. This may reflect underreporting of CAI due to social desirability bias, failure of the condom, or in very rare cases HIV transmission from oral sex (129). It may also reflect men believing they are in monogamous relationships without realising the relationship is not monogamous. Evidence shows that significant transmission occurs within partnerships (267). Therefore including monogamy within the safer sex group could underestimate the protective effect of reporting no CAI in the last three months.

Despite the limitations of the data, they do however show that behaviours such as CRAI with two or more partners have large associated PARs (32%). PAR has been calculated using the unadjusted hazard ratios and will therefore be an overestimation but it illustrates the added benefit of behavioural data and their potential impact on HIV transmission in this population if they were to be reduced.

Evidence suggests MSM transition between periods of higher and lower risk and only a minority of men consistently practice the same behaviours (37, 38). Men reporting unsafe sexual behaviours in the three months prior to the baseline attendance could have subsequently adopted different behaviours including no CAI. In order to better assess the association between seroadaptive strategies and HIV incidence, collecting behavioural information at all clinic attendances would be far superior than using data from cross-sectional behavioural studies.

6.18.4 Long-term feasibility and utility

Regular collection of behavioural data would augment existing national surveillance in GUM clinics. However, using a paper questionnaire, as was done in this study, would render such data collection unfeasible and impractical. Clinics chose their own method of questionnaire distribution as each clinic functions differently. Additionally, I visited clinics to get feedback on how the study was running and to provide interim results to motivate staff participation. However, despite these steps to engage and motivate clinic staff, the recruitment rate remained low suggesting this mode of delivery was probably not acceptable to staff.

However, this work has been instrumental in the development of the sexual behavioural component of GUMCADv3, which is an enhancement of GUMCAD. It will collect additional behavioural, drug and partner notification information. The current sexual behavioural questions included in GUMCADv3 reflect those used in the pilot (Box 6-1) and once finalised this standardised set of sexual behavioural questions will be completed for all HIV negative MSM at every attendance at a GUM clinic in England.

Box 6-1 Sexual behavioural questions ('last 3 months') for MSM, GUMCADv3

Current questions

1. Number of MSM partners in the last 3 months?Have you had anal sex with a known HIV positive partner in the last 3 months? How many anal sex partners did you have unprotected (receptive or insertive) anal sex with?How many anal sex partners did you have unprotected receptive anal sex with?

GUMCADv3 would overcome the need for data linkage as the behavioural data would be incorporated into the electronic reporting systems and data completeness would not be an issue. Though data would no longer be self-completed it is unlikely this will have a large impact on reported behaviours. There is no indication from the behavioural study that responses significantly differed between Manchester and the other clinics. Further, formative cognitive interviews conducted with MSM indicated that men are willing to provide this information as they are used to discussing their sexual behaviours when attending GUM clinics.

The utility of collecting behavioural data will be explored in greater depth in the following chapter where the opinions of clinical staff are documented. Behavioural data, while important for surveillance, are equally vital for informing public health practice and HIV prevention programmes. While it was suggested in the previous chapter that clinical risk strata of MSM could be used to develop eligibility guidelines for PrEP, the behavioural data would allow for more nuanced stratification and identification of MSM at high risk of HIV infection. A clinical risk assessment tool could be developed based on behavioural, clinical and demographic data. A risk assessment tool is an example of a clinical decision making tool that assists decision making and prioritisation of service delivery. A risk assessment tool for MSM would stratify men by their current

sexual risk for HIV. In the US, clinical risk calculators have been developed to aid clinicians offer HIV prevention services that are tailored to an individual's risk (146, 268). A similar approach could be taken in GUM clinics whereby a risk assessment tool that incorporates recent sexual behaviour could inform an individual's current risk and identify the most appropriate HIV prevention services.

6.18.5 Implications for thesis

Despite challenges in implementing the study and recruiting HIV negative MSM, the study has importantly demonstrated proofs of concept of collecting standardised sexual behavioural data, linking them to retrospective, current and prospective clinical records and using this process to identify higher risk MSM. Broadly, sexual behaviours account for a greater proportion of HIV infections in the population than would be accounted for by clinical/demographic factors alone and therefore should be collected, at least for risk stratification. The intuitive next step would be to explore whether clinical staff consider sexual behavioural data to be useful in their practice. Since it is envisaged that the data would be used to formally risk stratify MSM, it is also important for this thesis to capture what MSM think about risk stratification and triaging of prevention services. This thesis is well placed to gain service provider and user perspectives before any changes might be suggested for clinical practice.

7 Utility and acceptability of HIV risk scores and tiered prevention services

7.1 Introduction

Standardised behavioural information can be obtained from MSM attending GUM clinics, although a paper questionnaire will not be feasible and sustainable in the long-term. As well as being useful for surveillance and public health purposes, the proposed data should also be beneficial to healthcare providers and patients. One of the potential uses of behavioural data is to risk assess MSM in clinical settings. Clinical decision making tools are widely used in other medical fields and have been developed more recently for HIV and STIs (146, 269, 270). Such tools guide clinical decisions such as establishing cut-offs for screening for infections or for offering specific services.

Evidence suggests self-perception of HIV risk could impact utilisation of services and if self-perceived risk does not equate to actual risk then men in need of services many not use them. A HIV risk assessment tool may have an added benefit of establishing actual HIV risk for the patient. It is common for MSM not to perceive themselves at high risk of HIV infection especially when they compared their risk to an average person like them (271); many may underestimate their risk. Among MSM living with undiagnosed HIV infection, 42% of young MSM between 1994 and 1998 thought they were at low risk of ever becoming infected with HIV (272) and more recently, 59% thought they were at low risk for being infected with HIV (273). Less than half of HIV negative MSM using barebacking websites said they had a slight chance of becoming infected with HIV, a third reported they had some or half a chance while another 9% and 4% said they had

a pretty good or very strong chance of acquiring HIV, respectively (274). Around 10% reported having no chance.

There are a number of factors associated with risk perception including partnership status, numbers of partners, age, ethnicity and risk behaviours. Partnered MSM felt safer; although sizable proportions of both single and partnered MSM said their chance of contracting HIV was 0% (24% and 48%, respectively) (275). The role of numbers of sexual partners was often underestimated with three-quarters of MSM who perceived themselves at low lifetime risk were, in fact, at substantial risk as almost half reported 20 or more lifetime partners (276). Ethnicity could also be an important factor as young black MSM in the US were more likely to acquire HIV but perceive themselves at similar lifetime risk of HIV as white MSM (276). Younger MSM, those engaging in receptive anal sex and men under the influence of alcohol and/or drugs during sex were groups of MSM who perceived their risk of acquiring HIV to be high (274). Knowledge of HIV transmission does not necessarily correlate with self-perception of HIV risk as knowledge has been shown to be relatively high in groups with low and high self-perceived risk of HIV (274). As well as considering practices and knowledge, other factors such as desire and fear also play important roles in determining risk. Fear of HIV acquisition could prevent some men from taking any risk while other men may be willing to take some/considerable risk in order to gain pleasure (277).

Further, HIV negative MSM perceive risk differentially, whereby some condomless anal acts were considered to have greater risk of transmission (278) and certain risk reduction strategies such as engaging in insertive anal intercourse were considered safe (277) or low risk behaviour (279). It could be

surmised that men who adopt risk reduction strategies also believe themselves to be at lower risk. MSM diagnosed with HIV were surprised at their diagnosis because they considered themselves to be low risk as they only engaged in low risk activities (e.g. oral sex, condom use with HIV positive partners) (280).

Low risk perception is a documented barrier to HIV testing (35, 280, 281) although even among MSM who rated themselves as 'greatly' at risk or 'at quite a lot' of risk of HIV a significant proportion had not tested for HIV in the past year suggesting awareness may not always result in service utilisation (35). Acceptance and usage of PrEP among MSM is also linked to self-perception as men who perceived themselves at low risk did not see themselves as potential candidates for PrEP (282, 283) whereas men reporting HIV risk behaviours were more likely to be interested (9, 284).

To facilitate better acceptance and use of triaged services, it may be useful for MSM to first know their actual HIV risk especially if there is disconnect between what they perceive their risk to be based on their behaviours and experience and what their actual risk is. A HIV risk assessment tool would achieve this for the patient while also being useful to the clinician. The question remains whether clinical staff would utilise the behavioural data and whether MSM would find it acceptable to be triaged into risk groups and subsequently into tiered HIV prevention services. Therefore, to determine whether a clinical risk assessment tool and routine behavioural data collection is wanted and acceptable to both service providers and users I undertook interviews with both groups. Service providers were asked about their views on the utility of standardised behavioural data, while MSM were asked about their self-perception of risk and how acceptable a formal HIV risk assessment would be to them.

7.2 Aims and Objectives

The aim of this piece of research was to explore the utility of sexual behavioural data in GUM clinics from the perspective of service providers and the acceptability of using behavioural data to develop personalised risk assessment scores for MSM. Specifically, the objectives were:

- To understand the clinical utility of routinely collected standardised behavioural data for MSM from a service provider perspective
- To understand how HIV negative MSM view their risk of HIV and the factors that are taken into consideration
- To learn whether formal HIV risk assessment and tiered HIV prevention services would be acceptable to MSM and whether acceptability is linked to self-perception of risk.

The first objective was addressed through semi-structured interviews conducted with clinical staff from the GUM clinics involved in the behavioural study (section 3.4.1). The last two objectives were investigated through semi-structured interviews with MSM attending two GUM clinics in London and Brighton (section 3.4.2). The next sections present the results of both sets of interviews.

7.3 Semi-structured interviews with clinical staff

In total, eight clinical staff were interviewed from four of the five clinics that participated in the behavioural study. The interviews took place between March and August 2013. The number of staff interviewed at each site by their clinical grade is presented in Table 7.1.

Table 7.1 Semi-structured interviews with clinical staff participating in the behavioural study

Clinical staff	Clinic name				
	Manchester	John Hunter	Dean St	Royal Sussex	Total
Consultant	1	0	0	0	1
SpR*/HIV specialist	0	1	1	0	2
Health advisor	0	1	0	1	2
Nurse	1	1	0	0	2
Support staff	1	0	0	0	1
Total	**3**	**3**	**1**	**1**	**8**

*specialist registrar

7.3.1 Purpose of national behavioural data

All interviewed staff expressed positive views that supported standardising the collection and collation of behavioural data nationally. Two key themes emerged from the interviews: service provision, which included the planning, delivery and evaluation of services, and guidance to clinical practice. Each are discussed more fully below.

7.3.1.1 Service provision

Some service providers suggested that clinics were not always good at providing sexual health promotion and key to improving sexual health provision was to improve the evidence base. Collecting evidence and presenting it in a systematic manner could advocate for an improvement in the provision of sexual health services including promotion services.

> [Data collected] to put a bit more weight behind health promotion because if you think about health promotion in England at present, it's exceptionally low….When the information is collected and is presented in a tangible way, it gives evidence as to why our practice has to change to make sure we capture the correct information to truly assess risk.
>
> Nurse

> I think it's [sic] what it does is give you a baseline for the people that…because everyone is, 'Oh we're seeing lots more people with lots more risk', I think it helps to have that information quantified rather than a perception, 'Oh we're seeing loads more infections, oh yes we're seeing lots more people taking drugs'. It gives you a baseline to start thinking 'well how are we going to pilot interventions for these patients in clinic?
>
> Health adviser

Local service provision could also be strengthened if a more comprehensive picture could be built of the local population. Behavioural data could make an important contribution to achieving this goal as it provides additional information to what is clinically known about service users. Knowledge of behaviours individuals engage in locally may drive provision of certain services. The data could also help plan and promote outreach activities in the community for populations at higher risk of HIV.

> I think we need to know about our local patients…knowing your local patients it helps you understand what they need.
>
> Specialist registrar/HIV specialist

In the life cycle of service provision, behavioural data plays an important role in identifying the needs and baseline characteristics of the local population. Further, these data would also feed into the evaluation of services. Therefore, subsequent to service implementation, the same behavioural parameters could be collected and used for service evaluation. Changes in behaviour, and in particular, reductions in risk behaviour, would be important indicators used to highlight the impact and justify the need for the particular service.

> Our commissioners want to know more and more, which is a good thing about behaviour and how we're going to change behaviour and we need a baseline and that often doesn't exist…We haven't got a baseline for behaviour and PEP [post-exposure prophylaxis] use and whether you knew whether your partner was HIV positive or not.
>
> Health Adviser

> If you're trying to demonstrate why we do what we do, you need to show an outcome. So for example, if we're screening lots of people and there's no behaviour change at all, the rate of infections are continuing to rise then we're not doing something right. And is it because we're not doing the health promotion, not giving condoms or whatever the sequalae of that may be. You have to have clinical outcomes linked back to what we do.
>
> Nurse

Systematically collected behavioural data could also help reinforce services and funding needs for providers. With the extra behavioural information, service providers could go back to commissioners with evidence that additional funding was required for higher risk populations with greater needs and for trained staff to deliver specific prevention services including motivational interviewing.

> [I could] make the case for a counsellor or more health advising. I could make the case for availability of PrEP [pre-exposure prophylaxis] if it was found to be effective…If you have a large number of patients with high scores then you would expect more funding to deal with the increased risk cohort that you have.
>
> HIV consultant

Nationally, standardised behavioural information from all GUM clinics in England facilitates comprehensive population and service provision comparisons between clinics. Service providers could compare their local situation with other service providers serving similar populations.

> It might be interesting in terms of looking at the clinics which had a higher risk behaviour group and just looking at whether or not that correlated with a number of new HIV diagnoses….I'd imagine that we have quite a lot of high risk behaviour among our patients.
>
> Specialist Registrar/HIV specialist

6.3.1.2 Clinical practice

Regular behavioural data collection could aid clinical practice in a number of different ways. The majority of service providers noted that sexual history was already taken for patients although it was also noted history taking was not as

systematic as it should be and the data quality was at times too poor to be used. A national standardised behavioural questionnaire would ensure a uniform approach to clinical history taking which would be comparable and impartial for all patients within the clinic but also between clinics.

> Ask the questions, every time, for everybody who comes. And not us decide 'well they look quite nice they probably don't inject'.
>
> Nurse

> To uniform the way we approach some patients….but it is like something is not written anywhere, it's something that you acquire with your experience. So it would be eventually good to have at some point written down and standardised.
>
> Specialist Registrar/HIV specialist

A standardised approach could particularly be beneficial to staff joining sexual health without any prior experience. For these new members, discussing sexual health may be difficult so the availability of set behavioural questions could guide discussions around potential risk behaviours.

> We have lots of new doctors every six months because we have a rotation of GPs, we have new registrars…and if they weren't working in sexual health before they get lost because they don't know anything about all this. It's kind of a new topic for them…can be useful for the new doctors who are starting having that guideline of how to approach about a MSM patient.
>
> Specialist Registrar/HIV specialist

Regardless of whether the staff are new, the process of collecting behavioural data could initiate discussions around risk and was seen as an opportunity to reflect back to the patient and discuss behaviours in greater depth to increase awareness and determine the drivers of behaviours. Some men may be aware of their actions but need a greater discussion on what are causing those actions.

> We tend to think of risk in terms of window periods… we don't tend to think 'are you happy with the sex you're having, what is pushing your

> buttons in terms of the fact that you've come for PEP two or three times in the last six months'
>
> Health adviser

> When you're doing outreach you could actually say, 'Look, you're having unprotected sex here, there is a lot of infections that come from this sauna; you need to be aware of that and you need to be using condoms'… A lot our patients aren't aware that they go to these saunas and they're like having multiple partners with no condoms and it's rife…In saunas there's syphilis, HIV and we're just trying to prevent them passing it on basically.
>
> Nurse

Different clinical grades of providers spoke of using behavioural data to inform clinical decision making. At the most basic level, support workers could use behaviours such as engagement in condomless anal sex as a marker to refer male patients to health advisors. More senior clinical staff (e.g. registrars, HIV consultant) spoke more broadly of how patient care could be streamlined to ensure patients are referred onto appropriate services. Streamlining services in this manner would allow better targeted care.

> If they were to complete it as part of the patient history [it] would prompt people to maybe refer more to specialist clinics and you actually might end up spending a bit more time seeing patients you need to see….you might think 'how would this [behavioural] information help us develop resources and actually stream patients in to slightly different services'.
>
> Health Advisor

The HIV consultant spoke further about using behavioural data for making clinical decisions. The data could be used to quantify risk taking or assign some level of risk to MSM and this is discussed in more detail in the following section.

> If it's longitudinal it can help us quantify how many people are risk takers, and who eventually becomes HIV positive or diagnosed with say a sexually transmitted infection, and whether we need to be more targeting those groups...[the most use is for] quantifying risk factors in your cohort.
>
> HIV consultant

As well as the positive aspects and utility of behavioural surveillance a few staff members also spoke of potential challenges that would require some thinking. In order for behavioural data collection to be a viable long-term option, it cannot be administered as a paper questionnaire as was done in the behavioural study. Data collection would work better as an electronic mechanism whether through online surveys or via the clinic's electronic recording system.

> It would be quicker and easier and more effective for the administration and management of the outcomes.
>
> Nurse

Further, the impact of data collection on time was mentioned. As there could be some duplication of sexual history taking for behavioural surveillance and for case notes, this would mean longer consultations, especially if using paper questionnaires. Proformas used by some clinics include additional non-sexual behavioural data collection (e.g. drug and alcohol use), which means they could not be entirely replaced.

7.3.2 Uses and utility of risk assessment tool

Quantification of risk taking was raised unprompted by the HIV consultant; other service providers were specifically asked about the usefulness of formally stratifying MSM into different groups based on their reported risk behaviours. The responses were classed as utility from the provider's perspective and from the patient's perspective.

7.3.2.1 Clinical perspective

The greatest benefit of a risk assessment tool was its ability to objectively stratify MSM into risk groups so that the same reported behaviours resulted in the same

risk profile, regardless of which clinic MSM attended. Consequently, risk stratification could also positively impact service provision for MSM as HIV prevention interventions could be offered based on the level of identified risk and thus on need. Rather than all services being available to all men, individuals would only receive services they needed as defined by their risk profile. Potentially men would also be eligible for the same set of interventions regardless of where they attended.

> You could make clinical decisions based on the risk score, so if they are between one and five refer for behavioural interventions, and the standard PEPSE and all that. And if it's between five and ten consider PrEP.
>
> HIV consultant

> I think what would be helpful is an objective score where if you score this, then this is what has to happen or this is the recommendation that we have…because at the moment it's a bit free for all and we probably see lots of high risk people who maybe we should be offering more interventions.
>
> Health adviser

A potential HIV risk score was compared to other scores used in HIV clinics. The Framingham (risk of cardiovascular disease), Frax (risk of fractures) and alcohol scores all tell providers what to do with the score results and a HIV risk score should similarly tell providers what to do. A clear set of interventions or next steps should be available to providers to recommend to MSM based on their risk score.

Clinical staff thought the tool may be more appropriate for certain grades of staff to use in their work. The tool could be beneficial to support staff and health advisors; both groups are not medically trained and the score could guide them especially if they are unsure on whether a referral is required. Support workers can be the first member of staff to see a patient and a standardised risk tool would make referral pathways clear and easy. Health advisers could, in

particular, benefit as they are charged with having lengthier and more in-depth discussions with men regarding their behaviours and are therefore more likely to triage men to further services.

> I think the thresholds would be different really. I think that the doctor's thresholds for referring someone to have a high risk point of case test or if they're a high risk then a discussion with the health adviser would be pretty low…whereas maybe the health adviser might have different [thresholds].
>
> Specialist registrar/HIV specialist

As well as guiding clinical decisions the risk tool could be an important first step towards behaviour change, especially among MSM at high risk of HIV. The score presents an opportunity to move beyond telling people how to behave and provide feedback and ask men how they would feel about getting HIV at some point based on their risk score. An actual score value and the corresponding implications may have the desired effect on the individual.

> If you know that someone has had lots of partners in 3, 6, 12 months then...[it might be] the right time for you to say, 'I notice you've had lots of sex and potentially at some point you're going to get HIV or syphilis – what do you feel about that?' If you acknowledge it for them to bounce back because sometimes no one has ever asked that question.
>
> Nurse

> We know lecturing doesn't work and I don't do it anymore. People get told to stop smoking and they don't do it, so you just show look this is your risk with smoking, this is your risk without smoking. How important is it to you that you don't get a heart attack especially, and you let them go home and think about it…So I wonder if you can do it [for HIV].
>
> HIV consultant

All the benefits of a risk tool discussed up to now are at the individual level where the tool can be used to promote service utilisation and behaviour change. The HIV consultant also discussed population level benefits where monitoring of scores at a population level over time could be used to evaluate HIV prevention

interventions because any improvements in behaviour and risk as a result of interventions would reduce average risk scores.

7.3.2.2 Health care workers view of the patient perspective

There were mixed views on the utility of a risk score from a patient's perspective. While some staff reported an actual number could help men better understand their risk others believed that rather than knowing the exact number, patients who, for example, are high risk may find it more useful to be told what they need to do next to reduce their risk.

> A lot of them say, 'What's the risk, can you give me a percentage?' I think that'd be quite useful in terms of prevention…I think sometimes if you put it in terms of numbers it makes them feel better.
>
> Nurse

> The score is probably more for doctors than for patients…It's impossible for patients to understand [the Framingham score] so it's the same like you have 15% chance to develop to get HIV in the next 2 years and then the patient will be like probably a bit lost. Because it's so difficult for me to understand what this means, so I just want to know if based on the score we need to do something or not.
>
> Specialist registrar/HIV specialist

Although some providers thought they could initiate behaviour change, when considered from the patient's perspective they were less certain that a risk score would be sufficient for the patient. A cut-off that determines risk would not necessarily be effective because behaviour change also depends on the individual wanting to change their behaviours and a risk score may not be sufficient to motivate this change. Therefore the score should be interpreted in the context of the individual's desire to change otherwise the likelihood of service uptake and subsequent success at motivating behaviour change will be low.

> Some guys would go, 'I don't give a fuck'. Then you'd be like, 'Okay have you thought about the other things that you could pick up'…a lot of guys

> are not particularly worried about HIV but they're frightened to get syphilis because they know the injections are painful.
>
> Nurse

> I would have thought if someone is high risk, if they're not really open to the idea of changing or they don't really want to, then they're not going to be that suitable for motivational interviewing. So it would have to be looked at along with other factors. It wouldn't just be a cut-off point.
>
> Specialist registrar/HIV specialist

> I think it depends on a person...because sometime you could still tell somebody something and they would still go and do something different.
>
> Support worker

In conclusion, systematic collection of behaviours from MSM attending all GUM clinics in England would be beneficial to service providers for a number of reasons including for service provision and to guide clinical practice. Specifically using behavioural data to create a risk tool that stratifies MSM into risk groups based on recent behaviours would additionally provide a powerful and objective method by which MSM could be assigned appropriate HIV prevention services. Service providers disagreed on whether MSM would benefit from being told their risk score. In the next sections I explore what MSM thought about their risk of acquiring HIV, being given a risk score and also examine how they felt about being offered triaged services.

7.4 Risk perception, risk scores and tiered HIV prevention services

Semi-structured interviews were conducted with HIV negative MSM from two GUM clinics to understand how men assess their own risk of HIV acquisition and to determine whether being formally risk assessed for HIV was an acceptable method to direct HIV prevention services.

7.4.1 Overview of sample

Twenty semi-structured interviews were conducted with MSM from the MMC in London and the Claude Nicol Centre in Brighton. Of these 20, one interviewed man from Brighton was HIV diagnosed and was excluded from the analysis and results. All men identified themselves as gay or bisexual. The age group quotas proposed in the sampling strategy were achieved (age range: 21-68 years) and most men were white British (63%) (Table 7.2).

Table 7.2 Characteristics of interviewees (n=19)

	Clinic location	
	London	**Brighton**
Age group		
16-25	4	3
26-50	3	2
>50	3	4
Sexual Orientation		
Gay	8	9
Bisexual	2	0
Ethnicity		
White British	3	9
White Other	3	0
Black British	2	0
Black Other	1	0
Other (Chinese)	1	0
Total	**10**	**9**

7.4.2 Self-perception of HIV risk

Overall, two men considered themselves to be at high risk of HIV infection and their perceived risk likely reflected their actual risk as one spoke of his “addiction to sex” and the other was interested in taking PrEP. Another four said that in comparison to their risk of STIs, their risk of acquiring HIV was lower. A couple of men compared their risk to others and reported having the same risk as an average gay man. The remainder described their risk as being low or even zero.

Five themes were identified in relation to perceived HIV risk from the interviews: partnerships and trust, intentions to be safe, contextual factors, HIV knowledge, and othering (Table 7.3). Partnerships and trust, contextual factors and othering were emergent, other themes were predefined in the topic guide. The interviews identified the majority of factors that impacted an individual's risk perception were individual and interpersonal.

Table 7.3 Themes and sub-themes arising from the data

SEM	Themes	Sub-themes
Individual	Intentions to be safe	Condom use Frequency of HIV testing Normal behaviours vs those that were unintentional
	HIV knowledge	Impact on behaviours Importance of pleasure
Interpersonal	Partnerships & trust	Long-term versus casual relationships HIV status of partner
	Contextual factors	Alcohol-fuelled events Experience of HIV Background/occupation Fluctuation in risk over life course
	Othering	Risk associated with younger age and partner
Societal	Othering	Experience of HIV campaigns in early years of epidemic

7.4.2.1 Intentions to be safe

Perception of risk was driven by behaviours that men classed as usual and intentional behaviours. Condom use was frequently spoken of to explain perceived risk and it was synonymous with safe sex, that is, the use of condoms during anal intercourse. Twelve of the men with low perceived risk used condoms

during anal intercourse and cited it as one of the main reasons for their perception. Personal preference, fear of HIV and the belief that condomless sex could only be practised within monogamous relationships, where the likelihood of acquiring HIV would be negligible, were all positive determinants of condom use.

> It would be with a monogamous partner and we've been tested at three month intervals as well. So your chances are less, of the transmission of HIV, if you are both deemed negative.
>
> 26-50 year-old 'White British' man

Condom use was believed to mitigate other behaviours and risks including sex with men they did not know as well (especially in terms of their HIV status) and with large numbers of men. One man, spoke of his personal preference to always use a condom and therefore expressed a relaxed attitude to engaging in casual sex.

> I think there is an increased status [of acquiring HIV] because I may meet people for casual sex and I think there is always an increased risk with that, as there is an increased risk of getting run over by a bus if I walked out on the street.
>
> 26-50 year-old 'White British' man

Despite intentions to be safe, when probed further, it became apparent that inconsistent condom use was not uncommon in sexual encounters. Condomless sexual encounters fell into two categories: those where men knowingly engaged in condomless sex and those that occurred by accident. Men in the former group rationalised their encounters and were willing to take these calculated risks because the associated risk was perceived to be low.

> I nearly always use a condom. I have protected sex but there is the odd chance that it could happen because there is some people that I have had unprotected sex with.
>
> >50 year-old 'Black British' man

> I know the risk, there are times for the foreplay or the beginning of the sex, sometimes I don't use a condom, but we always put a condom on later. But I understand that there's still a risk for, I don't know, pre-cum, or for HIV that is not significant.
>
> 16-25 year-old 'Chinese' man

For the respondent addicted to sex, although he preferred sex with a condom, due to the large numbers of partners, the chances were higher for the condom to break, come off or be taken off by the partner. The other high risk respondent was not asked about his non-use of condoms.

While some men reported using condoms regardless of the type of relationship they were in, two men actively did not use condoms because they were both in closed monogamous relationships. To minimise their risk of HIV acquisition, one tested with his partner to know they were both HIV negative while the other was in a relationship with a HIV positive partner who he ensured had a suppressed viral load before engaging in condomless sex. Due to their relationship status and the protective steps they took to minimise their chances of HIV acquisition, both felt unlikely to get HIV.

Partner numbers was infrequently considered when gauging risk but among those who did and who also used condoms, there was the belief that having large numbers of partners did not increase risk as sexual acts were protected with a condom. However, since some of these men used condoms inconsistently they were likely placing themselves at risk while believing their use of condoms sufficiently off-set the large partner numbers.

A number of men tested to confirm they were being safe or as a reassurance mechanism. The frequency at which men tested and the events leading to the

testing episode were specific to the individual and were driven by perceived risk. The respondent who was addicted to sex and knew his chance of getting HIV was high tested almost every month to monitor his HIV status. The remaining men perceived themselves to be at low risk of HIV and this influenced their testing practices. Some tested episodically in response to a specific event such as condomless sex, which suggests men were aware of the risk but in retrospect.

> I had an incident about a month ago where I ended up having unprotected sex with someone I didn't really know. And…Yes, the worry of that has got to me a bit and so I ended up coming here a week later.
>
> 16-25 year-old 'White British' man

This individual, who was still waiting for his HIV test result after his one night stand, described his perceived risk of HIV to be low which was incongruent with his feelings of anxiety over the results. Men in this group considered themselves to generally be at low risk and these episodes, which did not necessarily occur frequently, were not reflective of their usual behaviours.

Others tested for HIV as part of their routine check-up every 6 months, year or two years. These men tested because they felt they should rather than because they were at any real risk. The test provided reassurance and confirmation that their behaviours were not putting them at risk. One respondent attended the clinic for the first time in two years for a test because he engaged in CAI with his regular partner (his only partner with whom he has sex).

> In fact we came the other day mainly because we had sex without a condom. We were talking about it, and again even though we're regular partners it's really not a good thing to do, so we just came today and had an HIV test as well….[later in the conversation] I was quite confident of the HIV result because I hadn't really done anything that would warrant any change in that status.
>
> >50 year-old 'White Other' man

> I get tested, you know, every once in a while, because I just feel like supposed to, but I'm not like too worried about it.
> **Interviewer: What is every once in a while?**
> Once a year, or like once every time I get really worried about STDs.
>
> 16-25 year-old 'White other' man

These results indicate that perceived risk influences HIV testing where men who think they are at high risk of HIV test more frequently than men who do not believe themselves to be at risk. Risk perception may also impact uptake of other HIV prevention services, which I discuss when examining men's views on being risk assessed and given services based on their risk score.

HIV testing within partnerships also provided reassurance, as noted above, and allowed men to adopt HIV risk reduction strategies such as serosorting where men engage in CAI with partners of the same HIV status. However, worryingly men did not always continue to test especially when in partnerships where a condom was not used. Irregular testing was a feature of many, although not all, long-term partnerships.

> We've been together for about three years, and we've been tested together and gone through the whole process as well.
> **Interviewer: Do you do it routinely?**
> Well, we've been, sort of, a couple of times before we were looking at, sort of, you know, using condoms and things like that, so…because we're both…we're both a little bit paranoid about catching anything anyway...[later in conversation] so obviously going into a relationship where you're not using condoms, it's not something that I'd, that either of us take lightly.
>
> 26-50 year-old 'White British' man

Men spoke of avoiding behaviours they considered high risk including sharing toys, fisting, activities that shed blood and involving other men in partnerships. Only one respondent, aged >50 years, reported complete abstinence after being highly sexually active as a younger man. He did not state whether the abstinence

was related to HIV risk or due to other personal reasons. As well as avoiding high risk behaviours, men actively engaged in activities they believed posed a lower risk for HIV infection and which contributed to low perceived risk of HIV. A couple of men reported being the top partner during anal intercourse because it was recognised to have a lower risk for HIV infection.

Although drug use is known to be associated with high risk sexual behaviours, it was not reported by any of the interviewed men. A couple of men specifically reported not taking any hard drugs, sharing needles or using drugs recreationally because it was regarded as risky behaviour.

7.4.2.2 HIV knowledge

General knowledge and awareness of HIV including the transmission routes was high among all respondents regardless of age and perception of risk and it was often reported to be better than knowledge of other STIs. Knowledge was, therefore, not necessarily linked to self-perception of risk. HIV was reported to be difficult to transmit both anally and orally because it has to be transmitted through body fluids and blood. Based on the knowledge that HIV is less easily transmitted than STIs, most men perceived themselves to be at low risk of HIV and a few described their risk to be lower for HIV than for other STIs.

> HIV is something people are so conscious of. Especially gay men…I almost feel like I could inadvertently catch other things because I'm just less educated about them and I'm not thinking about them as much.
>
> 16-25 year-old 'White British' man

> I think I have low risk for HIV.
> **Interviewer: Do you think that's directly related to your sexual behaviour or is it just because you think that it's less likely to transmit?**
> HIV has to be transmitted through body fluids and blood which is different than chlamydia and gonorrhoea because they can transmit through skin contact…I think statistics wise, there are less people that has [sic] got HIV, compared to the number of people who has got gonorrhoea or chlamydia.
>
> 16-25 year-old 'Chinese' man

HIV knowledge did appear to impact practice and engagement in certain behaviours known to be associated with higher risk. One respondent who worked as a paramedic and was knowledgeable about health and sexual health spoke of always using condoms when engaging in anal sex and his knowledge of HIV was reflected when he listed the activities he did not engage in (e.g. sex with people from high prevalence areas, sex work). As mentioned by one of the men above, HIV statistics played a factor when considering risk; the concept of prevalence was related to an individual's risk because areas with a higher prevalence of HIV were also areas where the probability of meeting someone with HIV was higher.

> I think there is always a risk out there, especially in an area of a higher risk, or a high prevalence of STIs, HIV etc which is Brighton and London, because of the increased numbers of gay people in Brighton there's a higher prevalence of HIV in Brighton than other parts of the country that I have lived in.
>
> 26-50 year-old 'White British' man

> One of eight don't know are not aware of them having HIV, so that's quite a high number and many people that don't know. So I think there's a higher risk of getting HIV than other STIs.
>
> 16-25 year-old 'White Other' man

The latter quote is from a man who had recently moved to London and reported that his chances of HIV acquisition had increased because compared to where he came from there were more men in London with HIV and therefore a higher chance of a potential partner also having HIV.

Understanding HIV risk also directly impacted men's choices to have sex with HIV positive partners. A few men asked their partners their HIV status for fear of having sex with a HIV positive person and there was some suggestion of discrimination associated with being positive when considering partner choice. Men were not willing to have sex, even with a condom, with a HIV positive partner because the risk of HIV transmission was too great. This is despite them knowing that HIV positive men may be on treatment and have an undetectable HIV viral load.

> **Interviewer: Do you think you are prejudiced, not wanting to have sex with a man with HIV?**
> It is stopping someone based on an illness really isn't it? So that's bad…but I just need to think of myself. I know the viral load, they can be low and stuff like that, undetectable and everything. I know that. But yes, I don't want to put myself at that risk.
>
> 16-25 year-old 'White British' man

> I think I wouldn't really want to have a long term relationship with a positive…HIV positive person. I don't want to really have sex with them, because I think you'll be…even though, if I use, obviously, protection, there will be a higher chance for me to acquire HIV with a positive person in a relationship.
>
> 16-25 year-old 'Chinese' man

The practice of oral sex without a condom was unanimously reported by men for two reasons; low likelihood of HIV transmission from oral sex and the lack of 'appeal' of using a condom. The only time men considered using a condom for oral sex was if the partner was HIV positive because of the possibility of transmission with bleeding gums.

> **Interviewer**: Would you say you use condoms all the time?
> Yes, but not for oral sex. But you're still supposed to, but nobody really does…[later in the conversation] My understanding is that it's far less likely, it's super rare to get HIV through oral sex.
>
> 16-25 year-old 'White Other' man

> I suppose if you want to be really clever, you would use a condom with all forms of sex, but oral sex with a condom just doesn't appeal.
>
> >50 year-old 'White British' man

Despite understanding the risk of STI transmission increased during condomless oral sex (even if HIV may rarely be transmitted), the role of sexual pleasure in oral sex outweighed any potential risks from not using a condom. In fact, most men perceived their STI risk to be higher than for HIV because of engaging in condomless oral sex.

7.4.2.3 Partnerships & trust

Relationship status was a key determinant of perceived HIV risk for many men and was closely aligned with trust where much of an individual's risk or lack of was apportioned to the partner. A number of typologies were described and compared to being single, men who spoke of having a boyfriend or partner believed being in a relationship mitigated risk to some degree. Some were in long-term partnerships that were either monogamous or open relationships but regardless of this distinction, these men spoke of the importance of trust and consequently men in these partnerships perceived their risk to be low.

> We are very, very trusting of each other in our relationship…We do have sometimes open relationships where we do involve other people in our sexual activity but throughout the time we'll always make sure that we use protection.
>
> 26-50 year-old 'Black British' man

> If you have a regular partner and you can have mutual trust then it [speaking of HIV risk] should be zero either way.
>
> >50 year-old 'White other' man

For those in open relationships, trust and not wanting to cause harm to the sexual health of the partner were important parameters that ensured the partnerships remained safe for both men. However, boredom was cited as a

reason to venture out and by doing so men were increasing their chances of acquiring HIV because they were potentially exposing themselves to risky situations, sometimes by engaging in condomless sex, and potentially sharing the infection with their partner.

Despite mutual trust, men in long-term relationships did not necessarily engage in condomless sex, which could reflect the risk adverse nature of respondents. In relationships where condomless sex was practiced, mutual trust contributed largely to engaging in condomless sex.

> My partner and I are not in any open kind of relationship and we don't really have that kind of relationship…and we've been tested together.
>
> 26-50 year-old 'White British' man

> Also there's a semi trust thing, you know, it's about somebody says they're regularly tested, you might therefore, if you are doing the same, you might regard that as an opportunity to have unsafe sex…
> **Interviewer: And trust them?**
> And trust, and trust.
>
> >50 year-old 'White British' man

In short-term partnerships, partners were only spoken of in relation to trust when there was also an element of durability to the relationship. Having a single partner during any one time point was a behavioural strategy used to reduce the chances of getting HIV infection and which contributed to a lower perceived HIV risk. Having multiple partners was viewed as risky behaviour and having a partner who could have multiple partners was avoided.

> On the personal section of Craigslist…I tend to browse through the ads and if there are people who are constantly on there then I don't make any contact even if I'm interested because it kind of says well they're having too many partners.
> **Interviewer: What would be too many partners for you?**
> Too many, that's a good question. That's like asking how long is a piece of string. I suppose if you have more than one regular partner.
>
> >50 year-old 'Black British' man

As with long-term relationships, condomless sex was acceptable within some non-long term regular partnerships and this sex was not viewed as risky because the partners were specifically chosen for condomless sex. Partners who avoided concurrency and who were described as not being 'reckless' or high risk were chosen.

> There is some people that I have had unprotected sex with, fortunately, they don't always have a history of many partners.
>
> >50 year-old 'Black British' man

In contrast to the potential stability afforded by partnerships, single men recognised their single status increased their risk of HIV because outside of relationships, engagement in casual sex was not uncommon. References to casual sex were sexual encounters with someone who you did not know or did not know as well and/or where men were met in venues such as clubs and saunas.

There were two aspects of casual sex that influenced self-perception of HIV risk: not knowing the partner and particularly the HIV status of the partner and the numbers of unknown partners. The large numbers of partners was, not unexpectedly, a common feature of casual sex and increasing partner numbers increased the probability of acquiring HIV.

> The higher volume of people, random people, you get with, the chances are through the roof, really.
>
> 16-25 year-old 'White British' man

In some instances, men did not understand or underestimated the potential risk they placed themselves in until after having sex. For example, one man did not discover until after that his partner took drugs, went to sex parties and had sex

with multiple partners. In recognition of this information, he took PEP very soon after the incident. Men who did understand their risk, despite acknowledging casual sex could increase the likelihood of getting HIV, often expressed a relaxed attitude, which was reflected in their own self-perception of risk.

> I think there is an increased status because I may meet people for casual sex and I think there is always an increased risk with that, as there is an increased risk of getting run over by a bus if I walked out on the street.
>
> 26-50 year-old 'White British' man

> If you are having casual sex, and you are always safe there's no great worry involved. There's always a risk. There's never really a great worry.
>
> 16-25 year-old 'White British' man

They expressed this attitude because they used condoms and valued the safety it offered them (even if a condom was not consistently used). One man said casual sex was 'ingrained' and he expected to always engage in it. Even though he knew the quantity and type of people with whom he had sex probably increased his risk, he minimised his risk through other behaviours (e.g. always using a condom, not engaging in full penetrative sex). His behaviours reiterate the significance men place on pleasure and that men are willing to take certain calculated risks in the pursuit of pleasure.

Interestingly, an increase in people meeting for casual sex was noted and attributed to the accessibility of social apps and media. Meeting through this environment amplified the 'unknown' factor of the partner because you were unlikely to discuss your current sexual health status with men through this medium.

Knowledge of the partner's HIV status, regardless of partnership status or engagement in casual sex was taken into consideration when speaking of their

own risk by some. Among those engaging in casual sex, the respondent addicted to sex never asked the HIV status of partners; all of whom were met in clubs and saunas. Despite being fully aware of his HIV risk, sexual desire was the overriding factor that drove his actions and although operating at a much higher level of risk, this respondent was willing to take these risks to achieve sexual gratification. In contrast, others always asked the HIV status of their partner because if both are tested and both are HIV negative then the chances of acquiring HIV are low.

When in longer lasting relationships, the HIV status was often established at the beginning through HIV testing but men did not necessarily test together, they relied on honesty to disclose HIV test results. While honesty was integral to long-term relationships, men in new partnerships or in casual encounters unanimously felt they could not entirely trust the response of their partner especially when the partner stated being HIV negative. Being told by the partner they were negative was not considered evidence; men could actively lie, mislead or they may not know themselves while assuming to be HIV negative. However, men still asked because believing the partner to be HIV negative provided some degree of reassurance. One man treated all partners as being HIV positive as a strategy to protect himself because it was safer than assuming the partner was negative. The uncertainty of the partner's status was reflected when judging one's own risk.

> Yes, my chances of catching HIV are probably lower [than a STI], but at the same time I can't say that.
> **Interviewer: Why do you say it's low?**
> Because I am basing it on me saying people I have sex with are telling me they are HIV negative, but that is based on them saying it, it could be a lie, so at the same time, I can't give an answer to that question.
> 16-25 year-old 'White British' man

> When you're single you tend to, although I still take precautions and be careful, you're at higher risk, I would say purely because you don't know, when you meet someone, you might go out for a while, then sex is always inevitable, and you don't know what their status is, and you could ask someone, are you HIV positive or negative, they might say negative but they don't know because they haven't had the check-up.
>
> >50 year-old 'White British' man

In contrast, others were willing to consider sex with HIV positive people and one man reported engaging in condomless sex with his positive partner. He believed his risk of HIV was low because they were in a monogamous relationship and they had waited until the partner's viral load was undetectable. Trust was an important factor in this relationship. Even outside relationships, sex could be safe and responsible and possibly safer than sex with someone who says they are HIV negative. This is another example of calculated risk; knowing that your partner is HIV positive and therefore knowing the potential risks helped make an informed decision, which led to sex that was not perceived as risky.

> So there was a time I was getting with a guy in a club and we were about to catch a taxi back to my place and he…you know it's actually, thinking back to it was probably irresponsible, there are probably other people I have had sex with who are HIV positive that wouldn't have told me. But he felt he had to tell me before he got into a taxi with me. And we had safe sex and it was fine and I didn't really see an issue with it because I was aware that someone's on treatment and the kind of person who is responsible enough to tell you they are HIV positive is the kind of person that is responsible enough to be taking their medication and I didn't see it as…We used a condom but I didn't see it as something risky.
>
> 16-25 year-old 'White British' man

> Are you safer having sex with protection with somebody with an undetectable HIV than you are with somebody unknown…if you are using correct protection etc, you're probably as safe as somebody if they didn't have HIV.
>
> 26-50 year-old 'White British' man

These two examples provide an insight into how some men rationalise their sexual decisions with positive partners. Men considered sex with HIV positive

men who are positive but on treatment and knowing your partner is HIV positive could promote trust between the partners. This is in contrast to others who could not have sex with positive partners because of the associated risk.

7.4.2.4 Contextual factors

Contextual factors included the influence of alcohol, experience of HIV and fluctuations in risk over the life course. Alcohol-fuelled incidents, which were associated with loss of inhibition and 'going with the flow' resulted in condomless sex. In hindsight, men acknowledged these to be risky events.

> The first time I met a boy in a club and I was really drunk, really drunk, and he, yes, it was stupid, didn't use a condom.
>
> 16-25 year-old 'White British' man

These episodes sometimes resulted in acquisition of other STIs such as gonorrhoea and were therefore clearly high risk episodes. Alcohol-fuelled incidents were only reported by young men in the sample but as these events were accidents and not reflective of their usual behaviours, they were not factored into assessments of HIV risk. In contrast, older men reported drinking less for the very reasons cited by young men as leading to condomless sex.

> I don't go on the gay scene in Brighton, I don't go to the pubs or anything like that….and when I see the people there standing on the streets every night drinking, even at teatime...I just think, god....they're drunk.
>
> >50 year-old 'White British' man

> I'm that type of person that is cautious in lots of things, but in particular with sex…I know some people who, once they've had one or two drinks, their inhibitions, they go. With me, I don't allow that to happen because I've mentally built that in. It's my protection. We all have a protection, don't we?
>
> >50 year-old 'White British' man

These views highlighted that older men drank less because they did not want the alcohol to make them vulnerable, to lower their inhibitions and place them in risky situations.

For some men, it was the sudden proximity of HIV in their lives that made them reconsider their practices and likelihood of getting HIV. First-hand experience of HIV from knowing someone living with the infection or someone who had died from an AIDS-related illness altered an individual's own perception of risk because HIV was no longer something that happened to others. It was something that could happen to you and for some men these experiences impacted their sexual behavioural practices.

> My partner had a very bad experience with his life in the past where his sister died of HIV back in Africa. So he's very very strict about using protection, both with me and with other people there. So we specifically look for people who only use safe sex.
>
> 26-50 year-old 'Black British' man

> When you meet other young people that are HIV positive, another case was an ex-boyfriend, this ex-boyfriend was 20 when he got HIV, just like he was really quite a fanciable guy, it's just and you realise it could happen to anyone at any age, It's not just something that just affects guys in their 40s with piercings and tattoos.
>
> 16-25 year-old 'White British' man

> I was at risk up until about 20 years ago and then a friend of mine got HIV and I became very careful after that….I began to practice safer sex because I felt that I didn't want to catch HIV, I didn't want to be in the same state he was. I wanted basically to live a happy life and not be restricted by drugs.
>
> >50 year-old 'White British' man

For others, experience of the gay scene affected risk perception. A man spoke of the effect of working in gay bars had on him and his own sexual risks:

> In the gay scene there is a lot of promiscuity, I am not saying all gay men are like that, but in general a lot of them are. So our risk is higher and I work in a gay club so I see it every Saturday night, where you see they are being promiscuous and all that. So that obviously scares me because I observe it so much and I see it happening all the time, sharing partners and all that stuff. So that's another reason why, because I can see it happening before my eyes, so I just don't want to take the risk really.
>
> 16-25 year-old 'White British' man

Although he stated that gay men were at higher risk, he perceived his risk to be low because of his experiences and his intention was to be safe. However, his beliefs did not reflect his behaviours and practices because he reported engaging in considerable sexual activity and not always using a condom.

HIV risk was spoken of fluctuating over the life course due to changes in an individual's circumstances. One individual spoke of his self-esteem shaping his behaviour and influencing the likelihood of engaging in unsafe behaviours. When he had low self-esteem he cared less about who he was with; he just wanted to be with somebody.

> If your self-esteem is quite low, it's quite possible to engage in unsafer practice than if your self-esteem is quite high. There's a big link.
>
> 26-50 year-old 'White British' man

Changes from sexual debut to gaining more experience were also associated with risk. A young gay man reported started out as having unsafe sex because he knew no better and because the porn industry played a role in his condom use. As condom use is not common practice in the porn industry he did not consider condoms 'sexy'. Intermixed with sexual debut was young age where younger individuals think that nothing can threaten them; akin to watching kids jump out of trees. However with experience he also began to use condoms. Young age was also linked to causal sex in our sample. The majority of men who

spoke of engaging in casual sex were aged less than 35 years and some young men referred to casual sex as occurring during a time limited period in their life when they wanted to party and have fun before settling into a relationship. These attitudes further highlight the influence of sexual pleasure and fun in decision making when faced with the opportunity to engage in what may be considered higher risk sex.

7.4.2.5 Othering

The final theme, othering, was an emergent theme linked to other themes discussed here and refers to situations where men reasoned they were safe and therefore at low risk while other men were not safe. For example, older men associated greater risk with younger age for two reasons: 1) young MSM did not live through the fear of the early years of the HIV epidemic and the public health awareness campaigns and 2) an element of invincibility. Living through the early years of the epidemic had attenuated older men's behaviours because they had lived through the fear of dying if infected with HIV and had experienced the awareness campaigns used in the early years. These campaigns were suggested to be effective at attenuating behaviours at the time. In contrast, young men might be less concerned with their health and with factors that could potentially harm or threaten their health especially with the availability of treatment. As already noted, younger men may perceive risk and HIV infections to be more common among older men as one young man noted he was surprised to find that men other than those in their 40s could be HIV positive. Older men spoke of their risk being lower than that of younger men because they were less likely to engage in unsafe sex or take drugs.

> Its sharing, not just drugs, its sharing needles and things. You don't know what these kids do these days because they're all into these…their inhibitions have gone.
>
> >50 year-old 'White British' man

> They are young, the thing was that when it [HIV] first surfaced it was deemed and was for so many a death sentence…now there is that sort of perhaps safety thing, that if I get caught out then I can take medication. And also, if you're young, you're young aren't you? I think you are perhaps, more prone to do things and if you're under the influence, if you're out partying on either alcohol and drugs.
>
> >50 year-old 'White British' man

Secondly, in casual encounters, risk was almost unanimously attached to the partner because the partner was not as well known. Disassociation between their engagement in casual sex and that of the partner was apparent for while men did not necessarily think they were being risky, they did think that partners who were willing to have random sex were likely to be higher risk individuals.

> If you went out and met someone in the street and had sex with them, didn't know anything about them…you could assume that someone like that would have…would be at more risk, if they're more open or more willing just to sort of have sex with anyone.
>
> 16-25 year-old 'White British' man

> My knowledge is fairly high in terms of making sure of using appropriate condoms etc, to ensure safety. I think there's just a risk of who you interact with, who your sexual partners are.
>
> 26-50 year-old 'White British' man

In summary, risk perception was complex and often based on the interplay of a number of factor operating at the personal and interpersonal levels. In general, intentions to be safe were the main drivers of risk perception as they reflected normal behaviours while unintentional behaviours, which were less frequent, were also less likely to be factored into risk assessments though these behaviours could be considered risky.

7.4.3 Risk scores

Men communicated mixed views when asked what they thought about being given a risk score based on their recent behaviours. These views are examined in greater detail below.

7.4.3.1 Clinical staff – trust and challenging assumptions

An important feature of the score was that it was tailored to the individual rather than being generic. For one individual this was particularly important because as well as confirming his perceived low risk as his actual risk, the risk score could challenge assumptions made about gay men, potentially by staff.

> I feel like they're actually listening to the circumstances and not just looking at, like, a demographic as a whole and saying, oh, you know, you're between 30 and 40 and you're male and you live in London and you're gay, so you're therefore, like, 99% at risk of catching everything.
>
> 26-50 year-old 'White British' man

In contrast, the trust placed in clinical staff to provide reliable information meant others were more willing to heed advice provided by doctors regardless of whether it confirmed their own views. As men thought it the role of clinical staff and health advisors to provide information and advice, these individuals were regarded as figures of authority that were respected. The information they gave would not be taken lightly and would more likely have some impact on the individual than information provided by others (e.g. peers).

> If I am told certain things by a person who I respect, and I find the people here are very confidence-inducing, I would then listen.
>
> >50 year-old 'White British' man

7.4.3.2 Awareness and behavioural impact

Almost all men suggested that being given a risk score would in some way impact their knowledge and awareness. A personalised risk score that is based on individual circumstances (e.g. recent behaviour) was perceived as likely to resonate better with men and ultimately lead to greater behavioural change by increasing awareness, in the first instance. Men unaware of their risk would likely be given a score that indicated their risk was higher than their own perception, and this new information was likened to knowing someone who acquired HIV.

> **Interviewer: What do you see as the advantage of getting a score?**
> Well, a bit like the HIV my friend got, it's sort of a wake-up call
>
> >50 year-old 'White British' man

The experience could serve to increase awareness of one's own actions and where necessary rouse an individual to stop engaging in behaviours that placed them at risk. This is particularly relevant as a number of men while expressing their own perceived risk to be low, then described behaviours and practices that were incongruent with their assumption. Being informed that they were at high risk may illicit feelings of alarm or concern when the individual believed their risk to be low; men might feel scared when told they were at high risk of acquiring HIV should they continue to engage in current practices. These feelings were, however, spoken of positively and any anxiety caused was offset by the knowledge gained from being told of the potential risks that one was exposed to.

> [I] probably would have been alarmed actually…Because if I'm going to be indulging in high risk activities that would be worth someone telling me…If they tell you high risk then it could be because I was a bit silly, or a bit stupid I suppose in your activities or it's things that you're not aware of.
>
> >50 year-old 'White Other' man

No one voiced concerns or negative sentiments at being told their actual risk even when it was higher than perceived risk. This may be attributed to the fact that the risk tool was objective in deriving the score and because of this, the results of the risk assessment process was considered the truth. Men reported that knowing this truth could not only increase awareness it could also empower them to act on the information and enable positive changes to their lifestyles and behaviours.

> Any information is power and you can use it for your own good. I think it's important for people to be made aware of their own risks…[later in conversation] When indeed you know, you have a lot of empowerment to decide on what to do in the future.
>
> 26-50 year-old 'Black British' man

Men said they would accept being told their actual risk is high and higher than their perceived risk, and even if initially there was little intent to listen to the information, the score was likely to remain in the back of one's mind. In effect, once the individual has had time to consider and digest their actual risk, there is the possibility that positive behavioural change may still occur later.

In contrast to those unaware of their actual risk, one man said the score could also challenge his personal assumptions of being gay and young, where you assume you are high risk.

> I think being a young, gay man these days you just assume you're a high risk, you know…as a single gay man it's, like…you feel like you're playing Russian roulette every day
>
> 16-25 year-old 'White British' man

For others, who already know their behaviours or some of their behaviours increase their risk of HIV, a score could be used to remind or reiterate risk.

> I'm glad they told me or reinforced it, maybe you probably already know, or some people do know and some people are not aware of it, but to reinforce it to someone like myself or someone else, it brings it home more so it sticks in there.
>
> >50 year-old 'White British' man

MSM perceived at high risk did not think the score would be harmful or necessarily useful. The actual score value was not considered important and although a high risk score may serve as a warning it may not modify sexual behaviours. For these men, it was the subsequent interventions that were important, for example, a conversation to discuss the implications was considered more meaningful as it could potentially have a lasting impact. In particular, it could be an opportunity to promote the use of condoms and other prevention methods.

Having an individual's low risk perception confirmed was associated with happy and pleasant feelings. However, although men might feel pleased about being low risk, there was some fear that the confirmation could inadvertently promote complacency and greater future engagement in risky behaviour. It was suggested by one man that an appropriate, well-devised message should be provided for men who are assessed to be at low risk score to prevent any increase in future risk.

Increasing awareness and highlighting risk may not be sufficient to impact on behaviour especially among those who are fully aware of their risk and situation because a risk score does not and cannot account for the wider context. As pointed out by two men, an individual's situation may not permit behaviour change and a risk assessment score would, in these situations, make no difference. However, the process of risk assessing could initiate discussions that

aim to better understand the circumstances and what could work for the individual.

> They told me, well, you are high risk, I don't think I actually cared at all, which I know is terrible but I think…
> **Interviewer: Is there a reason why you didn't care?**
> Well, partly because I couldn't because of...what I was doing couldn't change, you know; I was doing it for a reason, I was between a rock and a hard place.
>
> 16-25 year-old 'White British' man

Further, behaviours are likely to change independent of risk scores. One man expressed the view that people transition between risk behaviour stages so that engagement in risk behaviours in the last few months is not necessarily reflective of behaviours in the last year or in the future. As risk can be linked to relationship status, men could transition from being single and at greater risk to being in more stable relationships were risk may be minimal. Therefore a risk score based on behaviours in the recent past does not necessarily reflect the future and future HIV risk.

> So you can't base just that two months of where there was a lot of sex going on where they did get some STIs, as a generalisation of what the future is going to be because people aren't the same, they change with time.
>
> 16-25 year-old 'White British' man

7.4.4 Tiered HIV prevention services

7.4.4.1 Targeted services

Gay men due to their sexual orientation are used to being targeted for HIV prevention and most people do not think twice about targeting MSM. For this reason, it was acceptable and normal to receive targeted services. However, when asked whether MSM should receive services and interventions that were based on the results of the risk score, mixed views were expressed. Men in

favour of targeting services suggested that services and interventions should be based on need rather than being freely available to everyone. Men should only be referred to services they need but as this may not be current practice, people's mind set would need to first change before targeted interventions could be normalised into clinical practice.

> **Interviewer: So you're not at risk at all, so you wouldn't get anything, what would you feel?**
> I think that's just general health isn't it really, because you go to a GP, actually no, you've not got white stuff on your tonsils, you don't need antibiotics, the big antibiotic myth, it's a similar thing. The expectation of the public is that they're going to get x, y, z service, but that's what they expect, but actually, they don't need that, so they're not going to get it.
> 26-50 year-old 'White British' man

An advantage of needs-based services is better accessibility to and streamlining of sexual health as waiting times could be reduced and resources better allocated. In practice, if men were identified as high risk, they would clearly benefit from any extra support offered whereas being identified as low risk would suggest no extra support was required.

Others found targeting of services unacceptable and were of the opinion that services should be offered to everyone, regardless of the risk score and an individual's risk. One man said that as people transition between risk levels, an individual currently identified as low risk may become high risk and it would be safer to offer all interventions to all men so that they are fully equipped to manage their risk. Patient choice was integral to patient care when attending sexual health services and men were accustomed to having the opportunity to speak to someone if they wanted to even if it was not clinically indicated. This opportunity was considered necessary as it provided reassurance to the patient.

> I think everybody regardless of perceived risk should be offered a one to one with a professional.
> **Interviewer: Why?**
> Because you don't know what they're hiding, what they don't know themselves, how they might not be aware how risky they've been.
> 26-50 year-old 'White British' man

Finally, there might be the possibility that responses to the risk assessment questions would not be honest if men knew their responses would determine offered services. Answers may alter depending on what men want to receive. This view was, however, only expressed by one respondent suggesting it was not a commonly held opinion.

7.4.4.2 Behavioural change

Seven men voiced mixed opinions on how effective the prescribed interventions would be in facilitating behaviour change. There was the potential for the interventions to positively impact behaviours because they offered the opportunity to learn and improve sexual practices in the future. If the score was high, then it was clear support was required and it would gratefully be taken; gratitude was expressed for any help that would be given to reduce HIV risk especially if it involved talking to someone about behaviours, for example, a health advisor or a counsellor.

> **Interviewer: How did you feel about someone talking to you about wanting to change behaviour?**
> Good. I felt good about it, to talk about, because someone that's not within your social life, friends and such, someone outside that…to talk about and make yourself conscious about what you're doing.
> 16-25 year-old 'White other' man

Conversely, the interventions may have little effect. There are those who know what they are doing and if they do not want to change or stop engaging in practices that increase HIV risk, then encouraging those men to accept an

intervention or once accepted, ensuring the intervention has an impact might be difficult. This is similar to the opinions of service providers who felt it may be difficult to ensure high uptake of services. For example, men who want to engage in bare back sex are unlikely to want to change, so rather than trying to change their behaviour, it may be more effective to advocate and push for frequent HIV testing.

> I think it would work with some individuals, it can't work with all, because some people will already know exactly what they're doing and therefore changing an established pattern would be more difficult.
>
> >50 year-old 'White British' man

This sentiment was echoed by one of the high risk men. He was strongly against any attempt to change his behaviour. He believed it was an infringement of his free will and such interventions could even have the opposite effect. It is possible that the more an individual is told not to engage in risky practices, the more they will engage in them.

> At the moment it is what I want to do or what I feel desire to do. If anybody is going to interfere in my free will, it's like, you know, they're going to try to stop me from doing what I want to do.
>
> 26-50 year-old 'Black other' man

One young respondent felt he did not require any interventions to help monitor and control his behaviours. If he were told he was high risk, he would prefer to be responsible for his own behaviours and manage them by himself. The offer of interventions to address his behaviours would imply that he was a 'sex addict', which made him feel uncomfortable.

As with the risk assessment process, triaging of HIV prevention services should also take into consideration personal circumstances and the wider context as

they may be relevant and could determine whether interventions will be successful at modifying behaviour. Men may want to engage in risk behaviours despite knowing they are at increased risk or they may not be in a position to change their behaviours. In these circumstances behaviour change will be difficult because success is dependent on the offer of appropriate services and the willingness of the recipient to engage and accept the service.

> If you are in the middle of a really difficult situation the last thing you need is to feel vulnerable when you need to be strong, you know.
>
> 16-25 year-old 'White British' man

Older age was associated with acceptance of interventions. Some related the fear they felt living through the beginning of the HIV epidemic to a greater likelihood of using offered services (if it was deemed necessary) while others felt that as they were older they were better informed, less casual about their sexual practices and therefore less likely to need and use such services.

7.4.4.3 Risk perception

There was no clear evidence that risk perception would affect the likelihood to accept interventions based on risk scores. Only one respondent who said his chance of HIV was incredibly unlikely also stated that he did not need or would not use services. In contrast many men who thought they were at low risk stated they would be willing and grateful to receive help if their actual risk was higher than their perceived risk.

7.5 Key Findings

The service provider interviews highlighted the benefit of routine behavioural data collection for local delivery and evaluation of needs-based services and providing

guidance in making clinical decisions. The latter of which was viewed as applicable to all staff grades though with health advisors as the greatest beneficiaries as it is their role to motivate behaviour change and refer men to further services. In particular, the value of a quantitative risk assessment tool and its ability to objectively stratify and direct service provision based on need was recognised by providers. Service providers disagreed on whether employing a risk assessment tool would facilitate change in patient behaviour.

The interviewed sample of MSM was, in general, a risk adverse population with low perceived risk. Risk perception was complex and the results suggested some potential discord between perceived risk and actual risk. Importantly, men rarely judged their risk based on engagement in risky behaviours (e.g. condomless sex, casual encounters) or the context of those behaviours (e.g. influence of alcohol) but on their intention to be safe even if their actual behaviours would not always be considered safe, and on the status of their relationships. There were distinct relationships; those that were long-term and associated with trust and those that were casual. Trust contributed to low perception of risk whereas casual relationships were not linked to trust unless there was some sense of durability. HIV knowledge was, as expected, high in the sample and was not associated with HIV risk perception. Men were willing to take calculated risks, risks that potentially elevated their actual risk, but that were acceptable trade-offs in exchange for sexual pleasure.

Broadly, being risk assessed was acceptable due it its objectivity. Being given a risk score could be a wake-up call or a reminder that may or may not have positive impacts on behaviour. There was no indication that men who perceived their risk as low would be unwilling to accept services if they found out their

actual risk was high. The greatest debate centred on the availability of interventions based on patient demand rather than patient need. It was also unclear whether interventions could really change behaviours as it also required engagement from the patient and the desire to change.

7.6 Strengths and limitations

A major strength of this component of the thesis is that I conducted interviews with both service providers and users to capture clinical and patient perspectives. Both groups would be affected if behavioural data collection became routine and if a new clinical decision making tool were introduced into clinical practice and referral mechanisms. These results provide insights into the views of a HIV negative MSM population attending GUM clinics in England and add to the evidence base on factors that contribute to HIV risk perception.

The study findings from both sets of interviews may be limited by the number of interviews carried out. For the service provider interviews, I only interviewed, for example, one consultant and one support worker and it was apparent from the interviews that staff grade level did impact responses. It is therefore unlikely I reached saturation in the service provider interviews. Similarly, the service user interviews did not reach saturation for all the topics. Topics such as partnerships and trust, intentions to be safe and views on interventions and risk scores reached saturation whereas other topics such as risk reduction strategies and partner numbers and how they influenced risk perception were not discussed by many men. However 20 interviews were chosen to ensure a mix of ages and experiences and as a pragmatic approach.

Further, the views expressed by MSM attending these two large GUM clinics may not capture the range of views of MSM attending other clinics in other parts of England. The views of MSM who do not attend GUM clinics or chose not to participate were not included. Both these groups may have different perceptions of risk.

We used a relatively structured topic guide to conduct the service user interviews. During the analysis of the interviews it became apparent some discussions could have benefited from further probing but they were not as the topic may not have seemed relevant at the time or followed the structure of the guide. Though I used the SEM for data analysis, I did not explore the impact of policy and organizational factors on risk perception and men did not spontaneously speak of any factors on these levels that contributed to their perception.

Finally, while it was the aim of the research to captures views on utility from service users and providers, I have not captured the wider voice on utility of systematically collecting behavioural data from stakeholders such as data analysts and scientists involved in data cleaning, management and analysis at PHE where national surveillance data are held.

7.7 Reflections

I wonder if being a female non-clinical interviewer may have impacted the responses men gave me during the service user interviews. Although men are used to speaking of their sexual behaviours during consultations with clinical staff, they were being asked to disclose similar information for research purposes. It is possible that men felt uncomfortable sharing details especially

explicit sexual behavioural details in this context or if they did share their experiences, they may have underreported sexual behaviours that may be considered unsafe. It was difficult to know how men may have related to me and what impact this may have had on the topics discussed. Additionally, I was noticeably pregnant during the interviews, which may have further affected men's perceptions of me and what they felt comfortable talking about. I personally did not feel uncomfortable and tried my utmost to make men at ease and to ensure that they did not feel judged for anything they shared. I had also piloted the topic guide with a member of the patient and public involvement group and was given feedback on discussion style and body language to try and ensure a non-judgmental and open discussion approach.

I had not expected stories of people who had died from HIV during the early stages of the epidemic. These were not always easy stories to recount or listen to but men spoke of these experiences openly to explain their own perceptions and actions and I hope I did justice by listening well.

I had originally planned to conduct all 20 interviews myself but as the objectives of the SANTE project were similar to my research, I split the interviews with the SANTE researchers. On reflection, the advantage of doing all the interviews would have been the additional experience gained and ensuring the interviews were conducted in the same manner. Further, SANTE was focused on all STIs and on recruiting MSM regardless of their HIV status. These differences impacted the HIV content of some interviews and subsequent analysis as the HIV related questions were asked in a slightly different manner than originally planned and elicited responses where men spoke of their risk perception of HIV

in relation to their risk of STI. As a result it was, at times, difficult to interpret risk perception.

7.8 Discussion

Consistent with the social ecological premise that individual and environmental factors shape an individual's experiences, the interviews found that intentions to be safe and relationships heavily influenced perceived HIV risk. Men in the sample generally intended to be safe in their sexual practices such that virtually all men reported their risk to be low. They frequently reported condom use and HIV testing as protective practices. However, on further probing, there was evidence of inconsistent condom use, which was linked to alcohol use and other contextual factors. As these events could be rare and not reflective of normal behaviour, they were rarely factored into risk assessments. Observing inconsistencies between what men think and what they do is not unique to this study (285).

As well as individual level factors, factors operating at the interpersonal level were important contributors to risk perception. Trust was hugely influential on appreciation of risk, and in long-term partnerships it contributed to low perceived risk. The nature of the relationship with the partner was important and in particular an idea of not causing harm to the partner. However, men in long-term relationships did not regularly test for HIV and did not test with their partner. These findings concur with what men reported in the cognitive interviews in relation to HIV testing being a personal experience. Men spoke of testing at the beginning and this may not be sufficient, particularly in open relationships. Evidence suggests that half to three-quarters of HIV transmissions are from main sexual partners due to the greater number of sex acts and lower condom use

(267). The remaining infections were due to sex with men in casual relationships. In relationships where condoms were not used, the absence of condoms could be seen as an expression of trust (286) rather than any certainty that the partner was HIV negative. An important feature of open and casual relationships was that men do not necessarily know the HIV status of their partners, which is what made these relationships particularly risky. Trust and engagement in condomless sex may also play a role in determining uptake of other HIV prevention measures such as PrEP (287).

The apparent disconnect between what men believed and perceived risk with what they actually did suggests men cannot objectively determine their HIV risk. Consistent with other studies (273, 274), MSM may underestimate their risk of HIV because they believe they engage in low risk behaviours or take actions to minimise any potential risks. However, men who incorrectly appraise their risk miss benefiting from effective HIV prevention services, especially if their actual risk is high. The interviews suggested some link between perception of risk and HIV testing. Men aware of their high risk tested more frequently than those believing themselves at low risk and these latter men were more relaxed and tested less frequently for confirmation or reassurance rather than from any real fear of being infected. Therefore low risk perception may pose a barrier to HIV testing as reported by others (35, 272, 280, 281). Men who believed themselves at low risk of HIV may not utilise prevention services because they do not think it necessary. It therefore becomes imperative to identify the men who should be offered interventions.

'Othering' was an emergent theme from the interviews where participants distanced themselves from their actions and implied that the partner was

responsible for risk not themselves. This theme was less so about individual risk perception and related more to with what others do. Othering was apparent when speaking of the types of people who engage in sex with partners that were not well known and when discussing the HIV status of the partner. As men did not test together, they could never be certain what the HIV status of their partner was and it's likely that these men were seroguessing rather than knowing the status of their partner. Some men appreciated that their risk of HIV would be lower if they were to engage in sex with a HIV positive partner as it allowed them to make better informed decisions.

It would be useful if men were first asked about their risk perception before being risk assessed and if time was taken to understand the behaviours that led to perceived risk. It is clear from the interviews that individual and interpersonal factors are important drivers of risk perception. In clinical consultations, formally risk assessing MSM could be an asset as it will objectively calculate risk scores and promote risk awareness among MSM. From the interviews, there was no indication that HIV risk assessing would be unacceptable and men were willing to use services if their actual risk was high and they were in need of support. HIV risk assessing is likely to be acceptable because MSM are already routinely assessed when they attend GUM using behavioural questions (11). Implementation of risk assessing would formalise an existing system and could even improve current practice through standardisation and documentation.

Two recommendations are suggested based on the content of the interviews. Before the implementation of risk assessment tools for HIV, a clear set of prescribed pathways should be developed and available so that service providers know what to do with the results of risk assessing MSM. Secondly, risk assessing

and triaging should also incorporates an individual's willingness to change. Both service providers and users were unsure whether behaviours could be modified through risk assessing and triaged interventions unless the individual is willing to engage and be motivated. Interventions are unlikely to be successful if they are offered to men who will not fully benefit.

7.8.1 Implications for thesis

There is currently limited qualitative research conducted among service providers who have direct clinical contact with patients and who have a range of backgrounds. I believe this strengthens the applicability of the interview findings and by taking this opportunity I have shown that their opinions were positive in relation to using the behavioural data to develop and implement formalised risk triaging in clinical consultations. This is important as they would be impacted by any suggested changes to practice. The lack of significant objections from MSM to being risk assessed is further encouraging for this thesis and any future implementation of risk assessment tools.

These interviews were the first to look at risk perception in relation to a risk assessment tool in the UK. Interviews among MSM have particularly emphasised the importance of self-perception of risk, which has important implications for the delivery of a risk assessment tool. Clinical consultations should consider including a discussion on risk perception in discussions of risk and risk assessing as it may impact the success of uptake and outcomes of prevention services. In light of positive feedback from the interviews, the final step for this thesis will be to develop a risk assessment tool that could be implemented in clinics.

8 Clinical risk assessment tool

8.1 Introduction

I have demonstrated in Chapter 7 that a HIV risk assessment tool is acceptable to both service providers and users. Service users recognised its potential to aid clinical decision making and objectively stratify men into distinct risk groups. Risk assessment tools have been proposed for determining HIV testing screening thresholds among MSM (288, 289). Using the methodologies described in these and other risk tools developed for sexual health, in this final results chapter, I develop clinical risk assessments tools using clinical (GUMCAD) and behavioural (behavioural study) variables.

8.2 Aims and Objectives

Although the original aim was to develop a risk assessment tool that predicts for HIV infection, sufficient HIV endpoints were not available from the behavioural study. Therefore I modified the aim to develop a tool that is predictive of diagnosing “high risk” bacterial STIs (rectal chlamydia and gonorrhoea, syphilis, or LGV) and HIV as proof-of-concept. The results will demonstrate the methodology and steps undertaken to derive a risk assessment tool from available clinical and behavioural data.

The specific objectives included:

- To derive a diagnostic risk assessment model that uses clinical (GUMCAD) and behavioural indicators (behavioural study, see chapter 6)
- To performance test and validate the model

- To determine the impact of using multiple imputation (MI) on model performance
- To investigate the predictive ability of the derived model through HIV incidence analyses

8.3 Overview of methods and analyses

Logistic regression modelling was used to develop four risk prediction models and the outcome variable was an HIV or high risk bacterial STI diagnosis. The four models are:

1. GUMCAD only (complete case)
2. Full GUMCAD and behavioural variables (complete case)
3. Reduced GUMCAD and behavioural variables (complete case)
4. Multiple imputation (MI) with reduced GUMCAD and behavioural variables (full dataset)

After development, the models were tested through measures of discrimination (c statistic) and calibration (calibration plot, Hosmer-Lemeshow test). The sensitivity and specificity values at different thresholds were calculated in conjunction with the false positive rate to determine the optimal cut-off at which men would be referred to interventions and finally the models were internally validated using bootstrapping to calculate correct c-statistic and calibration slope values. Further details of the methods can be found in section 3.5 and appendix 7.

8.4 Model 1: Complete case using demographic and clinical data from GUMCAD

Model 1 only includes individuals who had complete information for all candidate predictors available in GUMCAD. There were 1,278 MSM who could be linked to GUMCAD and had a behavioural attendance (see Figure 6.1). Though only GUMCAD predictors were included in this model, I restricted the sample to those MSM who were included in the behavioural study to allow comparisons with the subsequent models in this chapter.

Of the 1,278 MSM with 111 events (8.7%), there were 1,205 (94%) who had complete demographic and clinical information and were included in this model with 104 outcomes (8.6%). Living in London was associated with significantly reduced likelihood of having an infection at baseline (Table 8.1); β coefficient was -1.41 and the p value <0.001. Men who did not attend in the year prior to the baseline visit were at greater odds to be diagnosed HIV or high risk bacterial STI (OR: 20.7, 95%CI 2.7-160.2) compared to men who did attend as were men with a previous syphilis diagnosis (OR: 9.0, 95%CI 1.4-57.3) and HIV test or STI screen (OR:16.7, 95%CI 2.2-128.5). The coefficient of the intercept was -4.32.

Table 8.1 Complete case using GUMCAD, Model 1 (n=1,205)

Variable		Odds Ratio	95%CI	β Coefficient	95%CI	P value
Ethnicity & birthplace	White UK-born	1		0		
	White European	0.90	[0.49,1.66]	-0.11	[-0.72,0.51]	0.74
	White non-European	0.90	[0.36,2.26]	-0.1	[-1.02,0.82]	0.83
	Non-white UK-born	0.29	[0.07,1.25]	-1.23	[-2.68,0.22]	0.10
	Non-white born abroad	1.17	[0.57,2.40]	0.16	[-0.57,0.88]	0.67
Age group	15-24	1		0		
	25-34	1.51	[0.88,2.60]	0.41	[-0.13,0.95]	0.13

	35-49	0.81	[0.43,1.55]	-0.2	[-0.85,0.44]	0.53
	50+	0.40	[0.11,1.41]	-0.91	[-2.17,0.35]	0.16
Living in London	No	1		0		
	Yes	0.24	[0.14,0.42]	-1.41	[-1.95,-0.87]	<0.001
Sexual orientation	Heterosexual	1		0		
	Homosexual	0.71	[0.35,1.43]	-0.34	[-1.05,0.36]	0.34
	Bisexual	0.37	[0.06,2.12]	-0.99	[-2.73,0.75]	0.27

Table 8.1 continued

Variable		Odds Ratio	95%CI	β Coefficient	95%CI	P value
Deprivation rank	Quintile 1 (highest)	1		0		
	2	0.96	[0.58,1.58]	-0.04	[-0.55,0.46]	0.87
	3	0.91	[0.52,1.60]	-0.09	[-0.66,0.47]	0.74
	4	0.36	[0.12,1.05]	-1.03	[-2.11,0.05]	0.06
	Quintile 5 (lowest)	0.22	[0.03,1.65]	-1.53	[-3.57,0.50]	0.14
Attendance in prior year	Attendance	1		0		
	No attendance	20.73	[2.68,160.23]	3.03	[0.99,5.08]	<0.001
Gonorrhoea in prior year	No	1		0		
	Yes	0.93	[0.34,2.50]	-0.08	[-1.07,0.92]	0.88
Syphilis in prior year	No	1		0		
	Yes	8.95	[1.40,57.32]	2.19	[0.33,4.05]	0.02
Rectal STI in the prior year	No	1		0		
	Yes	2.0	[0.67,5.95]	0.69	[-0.39,1.78]	0.21
HIV test/STI screen in the prior year	No	1		0		
	Yes	16.73	[2.18,128.50]	2.82	[0.78,4.86]	0.01

Based on the estimated coefficients from this logistic regression model, each individual's risk score can be calculated. The following example is used throughout to demonstrate how the score would be calculated. The probability of being diagnosed with HIV/high risk STI for a white European MSM aged 34 years, living in London in the 3rd quintile of deprivation, whose sexual orientation was homosexual, and who had not attended in the prior year would be 5.6%:

1. Log odds of HIV =

   *Intercept + coeff*white_European + coeff*aged_25-34 + coeff*living in London + coeff*living_3rdquintile + coeff*homosexual + coeff*not_attended*

   -4.32 + -0.11 + 0.41 + -1.41 + -0.34 + -0.09 + 3.03 = -2.83

2. Odds of outcome = $e^{(-2.83)}$ = 0.059
3. Probability of outcome = (0.059/1+0.059) x 100 = 5.6%

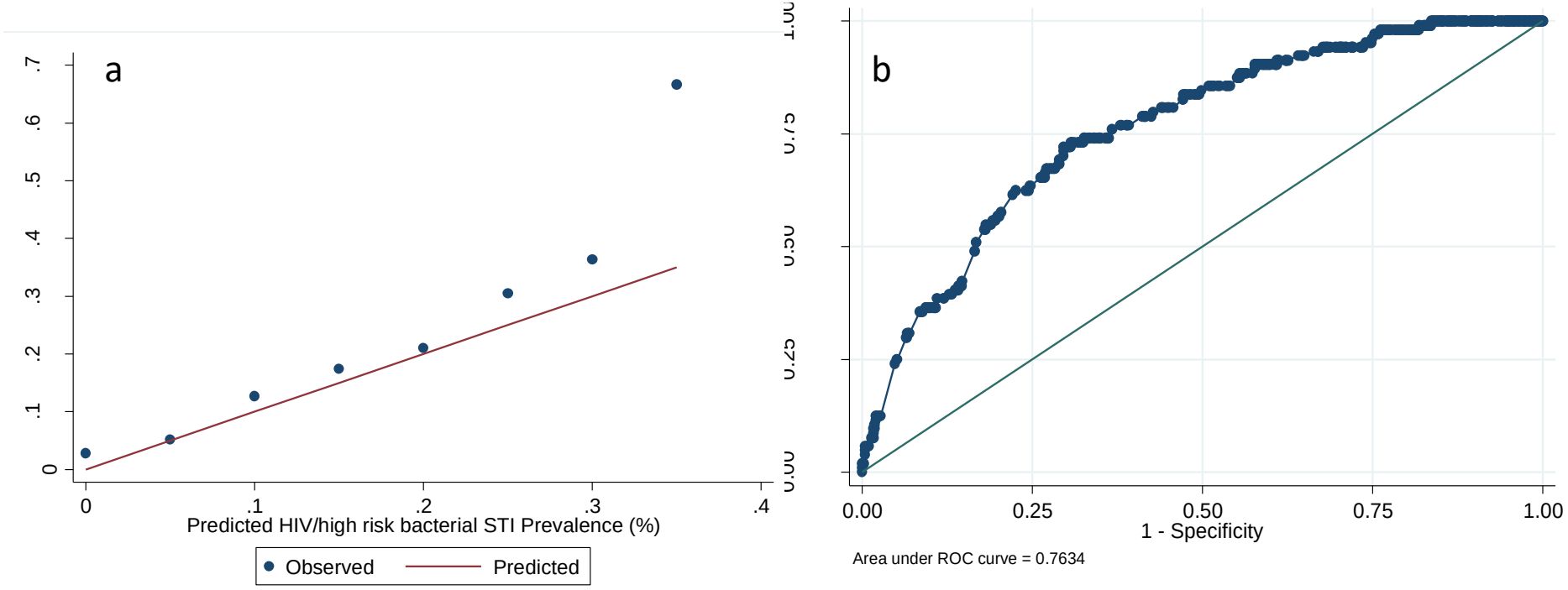
The events per variable (EPV) of this model was 5.5 (104 events/19 regression coefficients) (recommended value is 10). Thus there are too many predictors in this model and it is likely to be over-fitted, which means risk will probably be over-predicted for high risk patients and under-predicted in low risk patients.

8.4.1 Model Performance

The calibration plot, which examines the agreement between the observed prevalence of high risk bacterial STI/HIV and predicted outcome, showed good concordance, except at higher prevalence values (Figure 8.1a). For example, when the model predicted 10% probability of having the event for a patient, the observed frequency should be 10 out of 100 such patients and was observed as 12%. However at higher prevalence values the model under-predicted the outcome. Poor calibration at higher probabilities could be due to small numbers; only three MSM were included in the highest prevalence group and two had the outcome suggesting the observed value could have occurred by chance. The p-value of the Hosmer-Lemeshow goodness-of-fit test was 0.91 (8 degrees of freedom (df), chi squared: 3.41), further indicating the observed rates match the expected and that the model is well-calibrated.

The apparent c-statistic was calculated to measure the discriminatory ability of the model and was found to be 0.76 (95%CI 0.72-0.81) (Figure 8.1b). This indicates a 76% probability that a randomly selected patient with the outcome will have a higher predicted probability of having the outcome occur compared to a randomly selected patient without the outcome.

Figure 8.1 (a) Calibration plot of observed and predicted outcomes (b) Area under ROC curve, Model 1



8.4.2 Model Prediction & Clinical Utility

Each individual was assigned a probability of having an infection at baseline. The distribution of probabilities ranged from less than 1% to 55% (Figure 8.2) with three-quarters of the probabilities less than 15%. The median probability of being infected was 5.0% (IQR: 2-13%) and the mean was 8.2% (SD:7.9).

Figure 8.2 Distribution of probabilities of outcome, Model 1

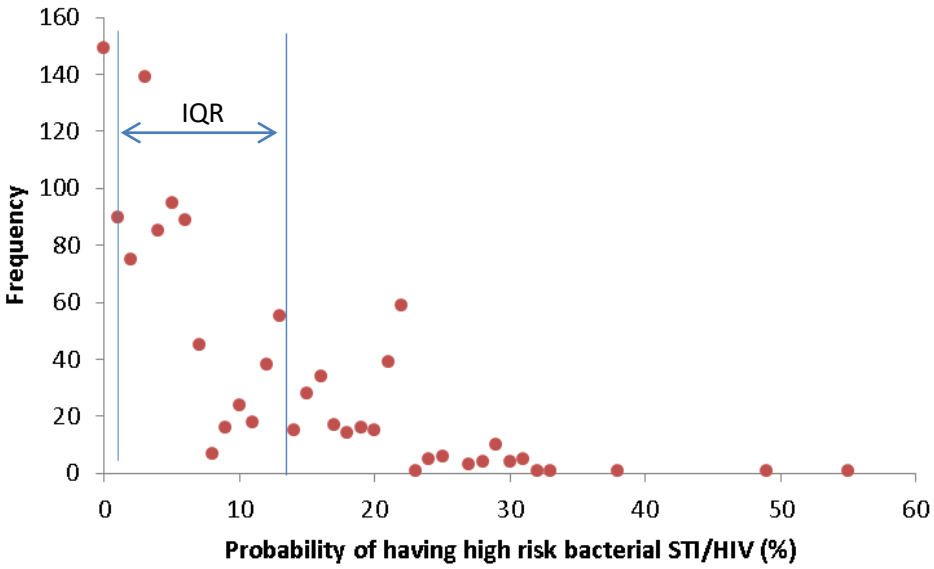


Table 8.2 documents the sensitivity, specificity, PPV and NPV values at different prediction thresholds. At a threshold of 4%, i.e. any MSM with a 4% or greater probability of being infected, sensitivity was high (90%), specificity was low (40%) and PPV was 13%. The best balance of sensitivity and specificity for identifying MSM who should be offered tailored interventions was between cut-offs of 8-10%. At 10% threshold, sensitivity and specificity would be 73% and 69% and 31% would be false positives, i.e. MSM who were incorrectly assessed as being positive. This is the proportion of men that would be referred to interventions. As the cut-off increased, the sensitivity dropped as did the false positive rate and the proportion of men who would be referred for interventions.

Table 8.2 Sensitivity, specificity, PPV and NPV at different risk prediction thresholds, Model 1

Cut-off (%)	Sensitivity (%)	Specificty (%)	PPV[1] (%)	NPV[2] (%)	False positive (%)
4	90	40	13	98	60
5	86	48	13	97	52
8	74	67	18	96	33
10	73	69	18	96	31
12	67	72	19	96	28

[1] Positive predictive value, [2] Negative predictive value

8.4.3 Model Validation

After bootstrapping the corrected c-statistic was 0.65. I also examined the calibration slope, which is another measure of agreement between observed and predicted risk of the outcome. In the development model, the slope value was 1 as would be expected but after internal validation it was 0.79. A value less than 1 indicates that some predictions are too extreme, which is consistent with over-fitting in the model development.

Given the drop in the c-statistic below what would be considered reasonable for clinical practice (0.70) after internal validation, I next determine the impact of adding behavioural data to the risk model.

8.5 Model 2: Complete case using demographic and clinical data from GUMCAD and behavioural data

There were 965 MSM with complete information in GUMCAD and the behavioural study. However, 84 MSM dropped from the model due to variables that predicted failure perfectly (where an independent variable perfectly predicts the outcome), leaving 881 MSM in model 2 and 63 events (7.2%). Specifically, there were no events among MSM without any partners and in MSM living in the

lowest quintile of deprivation and these categories dropped from the model. The variables rectal diagnosis and having a HIV test or STI screen in the previous year were excluded from the model due to collinearity. That is, both these variables were highly correlated with the other clinical history variables in the model.

In this model, a syphilis diagnosis and no attendance in the prior year, men reporting 2-4 and more than four numbers of sexual partners were at greater risk than men reporting one partner (Table 8.3). Additionally, compared to men reporting no partners with whom they had CRAI, those reporting 1 and 2-4 were at greater risk of having an infection (OR: 2.2 and 2.6, respectively).

Table 8.3 Complete case analysis of GUMCAD and behavioural variables, Model 2 (n=881)

Variable		Odds ratio	95%CI	β Coefficient	95%CI	P value
Ethnicity & birthplace	White UK-born	1		0		
	White European	0.91	[0.43,1.89]	-0.10	[-0.83,0.64]	0.79
	White non-European	0.36	[0.08,1.65]	-1.01	[-2.53,0.50]	0.19
	Non-white UK-born	0.20	[0.03,1.60]	-1.59	[-3.65,0.47]	0.13
	Non-white born abroad	0.97	[0.36,2.65]	-0.03	[-1.03,0.97]	0.96
Age group	15-24	1		0		
	25-34	2.50	[1.19,5.26]	0.92	[0.17,1.66]	0.02
	35-49	0.97	[0.39,2.37]	-0.04	[-0.93,0.86]	0.94
	50+	0.38	[0.05,3.16]	-0.97	[-3.10,1.15]	0.37
Living in London	No	1		0		
	Yes	0.24	[0.12,0.45]	-1.45	[-2.10,-0.79]	<0.001
Sexual orientation	Heterosexual	1		0		
	Homosexual	0.60	[0.24,1.47]	-0.51	[-1.41,0.39]	0.26
	Bisexual	Predict failure perfectly				

Table 8.3 continued

Variable		Odds ratio	95%CI	β Coeffi cient	95%CI	P value
Deprivation rank	Quintile 1 (highest)	1		0		
	2	1.12	[0.58,2.14]	0.11	[-0.54,0.76]	0.74
	3	1.21	[0.57,2.57]	0.19	[-0.56,0.94]	0.62
	4	0.37	[0.08,1.71]	-0.99	[-2.51,0.54]	0.20
	Quintile 5 (lowest)	Predict failure perfectly				
Attendance in prior year	Attendance	1		0		
	No attendance	2.70	0 [1.35,5.42]	0.99	[0.30,1.69]	0.01
Gonorrhoea in prior year	No	1		0		
	Yes	0.24	[0.03,1.91]	-1.45	[-3.54,0.65]	0.18
Syphilis in prior year	No	1		0		
	Yes	13.49	[1.31,138.49]	2.60	[0.27,4.93]	0.03
Total number of partners	0	Predict failure perfectly				
	1	1		0		
	2-4	2.17	[1.00,4.73]	0.78	[-0.00,1.55]	0.05
	>4	2.62	[1.11,6.18]	0.96	[0.10,1.82]	0.03
No of CRAI partners	0	1		0		
	1	2.24	[1.12,4.51]	0.81	[0.11,1.51]	0.02
	2-4	2.59	[0.95,7.06]	0.95	[-0.05,1.95]	0.06
	>4	2.27	[0.23,22.07]	0.82	[-1.45,3.09]	0.48
No of CIAI partners	0	1		0		
	1	1.38	[0.70,2.72]	0.32	[-0.36,1.00]	0.35
	2-4	0.59	[0.19,1.85]	-0.54	[-1.69,0.62]	0.36
	>4	0.57	[0.06,5.05]	-0.57	[-2.76,1.62]	0.61

The probability of being diagnosed with HIV/high risk STI for a white European MSM aged 34 years, living in London in the 3rd quintile of deprivation, whose sexual orientation was homosexual, who had not attended in the prior year, had one partner with whom practiced CRAI and CIAI and 3 total partners would be 13%:

1. Log odds of HIV =

   -3.48 + -0.10 + 0.92 + -1.45 + -0.19 + -0.51 + 0.99 + 0.81 + 0.32 + 0.78 =-1.91

   2. Odds of outcome = $e^{(-1.91)}$ = 0.14

   3. Probability of outcome = (0.148/1.148) x 100 = 13%

Due to the small number of events, the occurrence of perfect prediction and collinearity in this model, I used Firth's bias reduction method. The details of the methodology are described in 3.5.2.6. In this model, 965 MSM with 63 events (6.5%) were included. Inclusion of finite estimates where partner number is '0', removed the association between partner numbers and the outcome (Table 8.4). Collinearity was no longer a problem and the variables rectal STI and HIV test/STI screen in the last year were included in this model. The probability of the outcome was 14%.

Table 8.4 Application of Firth's reduction bias to Model 2, (n=965)

Variable		Odds ratio	95%CI	β Coefficient	95%CI	P value
Ethnicity & birthplace	White UK-born	1		0		
	White European	0.92	[0.45,1.87]	-0.08	[-0.79,0.63]	0.82
	White non-European	0.45	[0.11,1.73]	-0.81	[-2.16,0.55]	0.24
	Non-white UK-born	0.30	[0.06,1.67]	-1.19	[-2.89,0.51]	0.17
	Non-white born abroad	1.03	[0.40,2.66]	0.03	[-0.93,0.98]	0.96
Age group	15-24	1		0		
	25-34	2.33	[1.14,4.75]	0.84	[0.13,1.56]	0.02
	35-49	0.96	[0.40,2.26]	-0.05	[-0.91,0.82]	0.92
	50+	0.53	[0.09,3.16]	-0.63	[-2.41,1.15]	0.49
Living in London	No	1		0		
	Yes	0.26	[0.14,0.48]	-1.36	[-2.00,-0.73]	<0.001

Table 8.4 continued

Variable		Odds ratio	95%CI	β Coefficient	95%CI	P value
Sexual orientation	Heterosexual	1		0		
	Homosexual	0.60	[0.25,1.41]	-0.51	[-1.37,0.35]	0.24
	Bisexual	0.18	[0.01,3.38]	-1.72	[-4.65,1.22]	0.25
Deprivation rank	Quintile 1 (highest)	1		0		
	2	1.10	[0.59,2.07]	0.10	[-0.53,0.73]	0.76
	3	1.20	[0.58,2.49]	0.19	[-0.54,0.91]	0.62
	4	0.46	[0.12,1.80]	-0.78	[-2.15,0.59]	0.26
	Quintile 5 (lowest)	0.12	[0.01,2.20]	-2.12	[-5.03,0.79]	0.15
Attendance in prior year	Attendance	1		0		
	No attendance	2.53	[1.29,4.95]	0.93	[0.26,1.60]	0.007
Gonorrhoea in prior year	No	1		0		
	Yes	0.35	[0.06,1.98]	-1.06	[-2.79,0.68]	0.23
Rectal STI in prior year	No	1		0		
	Yes	0.22	[0.01,4.36]	-1.47	[-4.43,1.47]	0.33
HIV test/STI screen in prior year	No	1		0		
	Yes	8.77	[0.55,139.24]	2.17	[-0.59,4.94]	0.12
Syphilis in prior year	No	1		0		
	Yes	15.56	[2.24,108.20]	2.74	[0.80,4.68]	0.006
Total number of partners	0	1		0		
	1	3.91	[0.22,69.68]	1.36	[-1.52,4.24]	0.35
	2-4	8.08	[0.48,137.28]	2.09	[-0.74,4.92]	0.15
	>4	9.71	[0.56,168.46]	2.27	[-0.58,5.13]	0.12
No of CRAI partners	0	1		0		
	1	2.17	[1.11,4.28]	0.78	[0.10,1.45]	0.02
	2-4	2.54	[0.97,6.62]	0.93	[-0.30,1.89]	0.06
	>4	2.80	[0.41,19.17]	1.03	[-0.89,2.95]	0.29
No of CIAI partners	0	1		0		
	1	1.38	[0.71,2.67]	0.32	[-0.34,0.98]	0.34
	2-4	0.64	[0.22,1.91]	-0.44	[-1.53,0.65]	0.43
	>4	0.80	[0.13,5.04]	-0.22	[-2.05,1.62]	0.82

Although Firth's bias reduction regression solves perfect prediction and collinearity, the EPV is 2.3 (63/28), which very strongly suggests there are too many parameters in this model and over-fitting is very likely. For this reason, I did not develop the model further, or validate it. Instead I looked to whether this model could be improved by being reduced. The final model included predictors that were statistically associated with the outcome (from this study or literature) and/or which were clinically meaningful. These final predictors were: numbers of sexual partners (from the literature), numbers of partners with whom had CRAI (literature and Chapter 5), syphilis in the last year (literature and Chapter 5), gonorrhoea in the last year (literature and Chapter 5), attendance in the last year (Chapter 8), age group (Chapter 8) and residence (inside/outside London) (Chapter 5).

8.6 Model 3: Reduced complete case using demographic and clinical data from GUMCAD and behavioural data

In the model from complete case analysis, there were 1,066 individuals with complete information on the seven covariates and 85 events (8.0%) (Table 8.5). As Firth's logistic regression improved Model 2, it was also employed in this model. In this model, no attendance at the GUM clinic in the prior year (OR: 2.4), syphilis in the prior year (OR: 7.1) and one partner with whom the individual practiced CRAI were associated with the outcome (OR: 1.8)

Table 8.5 Reduced complete case using GUMCAD and behavioural data and Firth's bias reduction, Model 3 (n=1,066)

Variable		Odds ratio	95%CI	β Coefficient	95%CI	P value
Age group	15-24	1		0		
	25-34	1.51	[0.85,2.67]	0.41	[-0.16,0.98]	0.16
	35-49	0.93	[0.48,1.85]	-0.07	[-0.76,0.61]	0.83
	50+	0.29	[0.05,1.59]	-1.23	[-2.93,0.46]	0.16
Living in London	No	1		0		
	Yes	0.20	[0.11,0.34]	-1.62	[-2.17,-1.07]	<0.001
Attendance in prior year	Attendance	1		0		
	No attendance	2.42	[1.39,4.21]	0.88	[0.33,1.44]	0.002
Gonorrhoea in prior year	No	1		0		
	Yes	1.01	[0.37,2.78]	0.01	[-0.99,1.02]	0.98
Syphilis in prior year	No	1		0		
	Yes	7.13	[1.53,33.24]	1.96	[0.43,3.50]	0.01
Total number of partners	0	1		0	0	
	1	2.82	[0.49,16.20]	1.04	[-0.71,2.78]	0.25
	2-4	3.28	[0.58,18.37]	1.19	[-0.53,2.91]	0.18
	>4	4.05	[0.69,23.80]	1.40	[-0.37,3.17]	0.12
No of CRAI partners	0	1		0		
	1	1.75	[1.04,2.95]	0.56	[0.04,1.08]	0.03
	2-4	1.65	[0.74,3.64]	0.50	[-0.30,1.29]	0.22
	>4	1.70	[0.39,7.37]	0.53	[-0.94,2.00]	0.48

8.6.1 Probability of being diagnosed

The probability of being diagnosed with HIV/high risk STI for a MSM aged 34 years, living in London, who had not attended in the prior year, had one partner with whom practiced CRAI and 3 total partners would be 8%:

1. Log odds of HIV =

   -3.89 + 0.41 + -1.62 + 0.88 + 0.56 + 1.19 = -2.47

2. Odds of outcome = $e^{(-2.47)}$ = 0.085

3. Probability of outcome = (0.085/1.085) x 100 = 8%

8.6.2 Points scoring

I also used points based scoring using a method described by Menza *et al* (Appendix 8) where weights are applied to calculate an overall score (Table 8.6). This model may be more appropriate in settings where an electronic automated system is not available to calculate the probability of being infected and where a paper system is operated.

Table 8.6 Points score weighting using method described by Menza et al

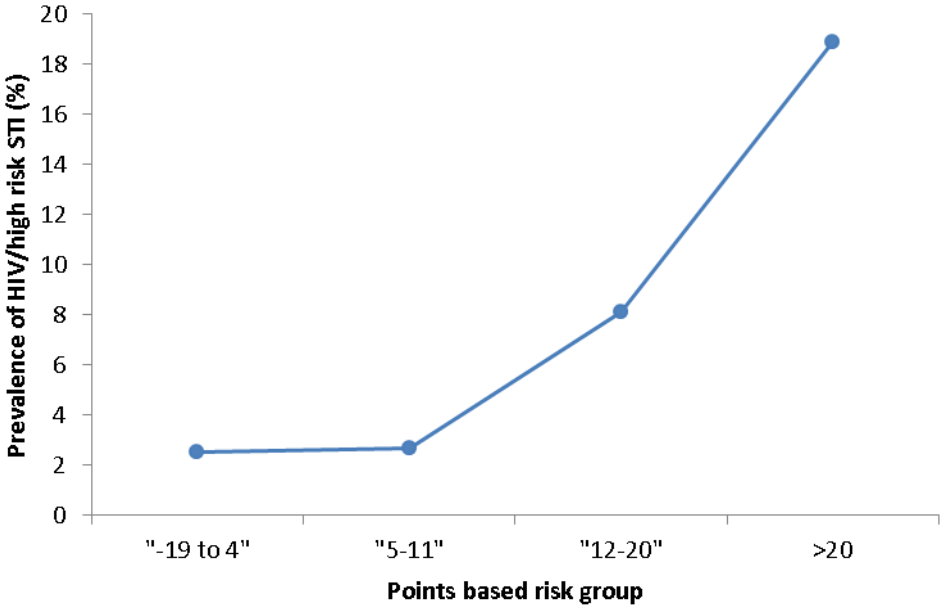
Variable		β coefficient	β *10	Weight
Age group	15-24	0	0	0
	25-34	0.41	4.1	4
	35-49	-0.07	-0.7	1
	50+	-1.23	-12.3	-12
Living in London	No	0	0	0
	Yes	-1.62	-16.2	-16
Attendance in prior year	Attendance	0	0	0
	No attendance	0.88	8.8	9
Gonorrhoea in prior year	No	0	0	0
	Yes	0.01	0.1	0

Table 8.6 continued

Variable		β coefficient	β *10	Weight
Syphilis in prior year	No	0	0	0
	Yes	1.96	19.6	20
Total number of partners	0	0	0	0
	1	1.04	10.4	10
	2-4	1.19	11.9	12
	>4	1.40	14.0	14
No of CRAI partners	0	0	0	0
	1	0.56	5.6	6
	2-4	0.50	5.0	5
	>4	0.53	5.3	5

The number of points for a MSM aged 34 years, living in London, who had not attended in the prior year, three total partners and one partner with whom practiced CRAI would be 15 using this method. A risk score was assigned to each man and the number of outcomes by quartiles of risk score was plotted (Figure 8.3). The graph shows an increase in the prevalence of outcome by increasing risk group except at the two lower points based risk groups. As there was no difference in these two groups, they were combined.

Figure 8.3 Prevalence of HIV/high risk STIs using points scoring



These prevalence values were used to estimate an individual's probability of being infected at a GUM clinic attendance (Table 8.7). A risk score of 15 calculated for the individual with an 8% probability of the outcome would equate to an 8-19% probability of being infected with HIV/high risk STI at the visit. The three categories could be used to determine MSM at low, medium and high risk of HIV.

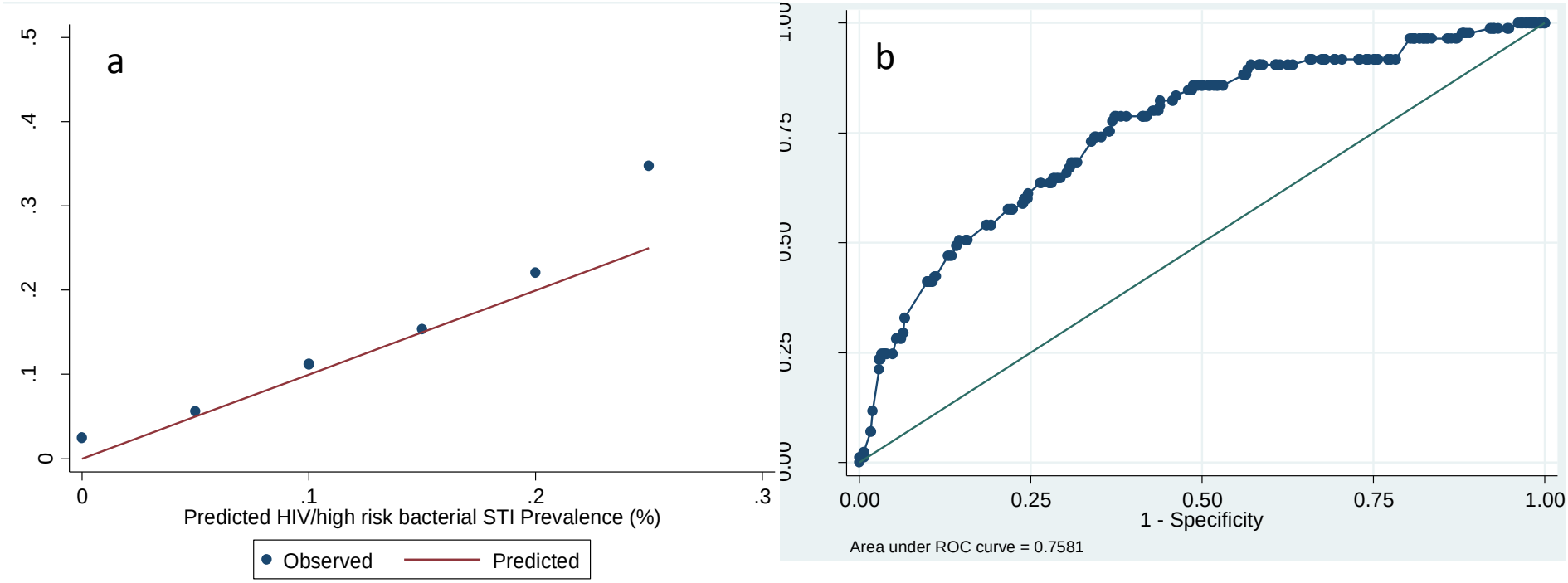
Table 8.7 Estimating an individual's probability of being infected using Menza *et al* scoring

Total Points	Estimated probability of being infected %
-19 to 11	<8
12 to 20	8-19
≥ 21	>19

8.6.3 Model Performance

The calibration plot indicates this model fits the data better than Model 1, even at higher prevalence values of high risk bacterial STI/HIV, though there was still discrepancies between the predicted and observed values (Figure 8.4a). This discordance was likely due to small numbers in the highest prevalence group as in Model 1 though the larger sample size at these values could also indicate the model does not predict well at higher prevalence. The Hosmer-Lemeshow goodness-of-fit test p value was 0.89 and the apparent c-statistic was 0.76 (95%CI 0.70-0.81) (Figure 8.4b). This indicates a 76% probability that a patient with the outcome had a higher predicted probability of having the outcome than a patient without the outcome, for a random pair of patients with and without the outcome.

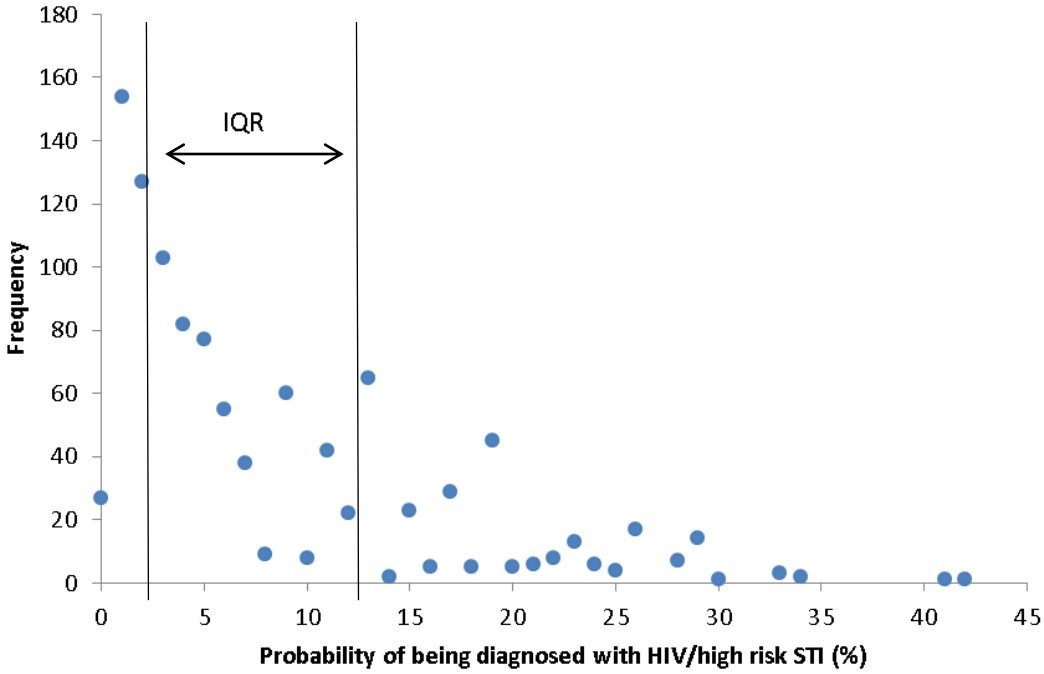
Figure 8.4 (a) Calibration plot of observed and predicted outcomes (b) Area under ROC curve, Model 3



8.6.4 Model Prediction & Clinical Utility

As with the other models, each individual was assigned a probability of having an infection at baseline. The distribution of probabilities ranged from less than 1% to 42% (Figure 8.5). The median probability of being infected was 5% (IQR: 2-12%) and the mean was 7.9% (SD:7.5).

Figure 8.5 Distribution of probabilities of outcome, Model 3



At a threshold of 4%, sensitivity would be 91% and 59% would be referred for an intervention (all those that are false positives) (Table 8.8). Conversely as the threshold increased to 10%, sensitivity and specificity would be 65% and 72%, respectively, and 28% of the population would be referred for an intervention.

Table 8.8 Sensitivity, specificity, PPV and NPV at different risk prediction thresholds, Model 3

Cut-off (%)	Sensitivity (%)	Specificty (%)	PPV[1] (%)	NPV[2] (%)	False positive (%)
4	91	41	12	98	59
5	86	49	13	98	51
8	74	65	16	97	35
10	65	72	17	96	28
12	59	76	18	96	24

[1] Positive predictive value, [2] Negative predictive value

8.6.5 Model Validation

In this model, there were 13 estimated regression coefficients and 85 events, an EPV of 6.5 indicating this model, like the previous ones, is likely to be over-fitted and the performance statistics over-optimistic. The optimism corrected c-statistic was 0.72 and the calibration slope was 0.73 indicating some predictions were too extreme.

8.7 Sensitivity analyses: Multiple imputation

8.7.1 Multiple imputation results

In order to develop a risk prediction model in the complete cohort, multiple imputation was performed and the same steps were repeated as for Model 3 to develop and test a model based on the complete dataset. After excluding individuals with missing information on numbers of total partners (n=28), there were two variables from model 3 with incomplete information: living in London and number of CRAI partners. These variables were successfully imputed using ten rounds of multiple imputation (Table 8.9).

Table 8.9 Multiple imputation of missing values

Variable	Complete	Incomplete	Imputed	Total
Ethnicity & birthplace	1226	24	24	1,250
London resident	1218	32	32	1,250
Sexual orientation	1241	9	9	1,250
Deprivation	1217	31	31	1,250
CRAI partners	1093	157	157	1,250
CIAI partners	1054	196	195	1,250

I compared main descriptive statistics from the fifth and the last imputation to those from the observed data to verify imputation was reasonable especially for the behavioural data which had a greater amount of missing information and found the summary statistics of the imputed data were comparable. For example, the mean number of CRAI partners for the observed data was 0.49 (SD: 0.74), while for the fifth and tenth imputation it was 0.50 (SD: 0.76) and 0.52 (SD: 0.78), respectively. Similarly, the mean number of CIAI partners for observed data was 0.60 (SD: 0.84) compared to 0.62 (SD: 0.88) and 0.63 (SD: 0.90) for the fifth and tenth imputation, respectively. I also examined the distribution of other covariates and the outcome for those with CRAI partners. In the observed data, among MSM reporting CRAI with one partner, 77% of those with the outcome were white-UK born. This proportion was 77% and 80% for the fifth and tenth imputation. Having established imputation was successfully achieved; I next present the results of the derived model and its performance, where analyses were possible.

8.7.2 Derivation of MI model, Model 4

There were 1,250 MSM with 109 (8.7%) events in this model. Living in London was protective of being infected with HIV or another high risk STI (OR:0.2). Not attending a clinic in the previous year was associated with increased likelihood of the outcome (OR: 1.8) whereas a previous syphilis was only borderline significant (OR:5.1). The association between numbers of partners with whom

practiced CRAI and the event remained (OR for 1 partner vs none: 1.9) (Table 8.10).

Table 8.10 Multiple imputation of reduced model 3, Model 4 (n=1,250)

Variable		Odds ratio	95%CI	β Coefficient	95%CI	P value
Age group	15-24	1		0		
	25-34	1.73	[1.02,2.94]	0.55	[0.02,1.08]	0.04
	35-49	1.00	[0.53,1.88]	-0.03	[-0.64,0.63]	0.99
	50+	0.42	[0.12,1.46]	-0.87	[-2.12,0.38]	0.17
Living in London	No	1		0		
	Yes	0.18	[0.11,0.31]	-1.70	[-2.23,-1.17]	<0.001
Attendance in prior year	Attendance	1		0		
	No attendance	1.80	[1.12,2.90]	0.59	[0.11, 1.06]	0.02
Gonorrhoea in prior year	No	1		0		
	Yes	1.02	[0.44,2.38]	0.02	[-0.83,0.87]	0.96
Syphilis in prior year	No	1		0		
	Yes	5.08	[0.98,26.49]	1.63	[-0.02,3.28]	0.05
No of CRAI partners	0	1		0		
	1	1.87	[1.08,3.2]	0.62	[0.08,1.17]	0.03
	2-4	1.54	[0.71,3.36]	0.43	[-0.35,1.21]	0.27
	>4	1.84	[0.48,6.99]	0.61	[-0.73,1.94]	0.37
Total number of partners	0	1		0		
	1	4.00	[0.50,32.28]	1.37	[-0.70,3.47]	0.19
	2-4	4.84	[0.62,38.05]	1.58	[-0.48,3.64]	0.13
	>4	5.61	[0.70,44.93]	1.72	[-0.36,3.81]	0.11

The probability of being diagnosed with HIV/high risk STI for a MSM aged 34 years, living in London, who had not attended in the prior year and had one partner with whom practiced CRAI and three partners in total would be 6.4%:

1. Log odds of HIV =

   -4.19 + 0.55 + -1.70 +0.62 + 0.59 + 1.58 =-2.55

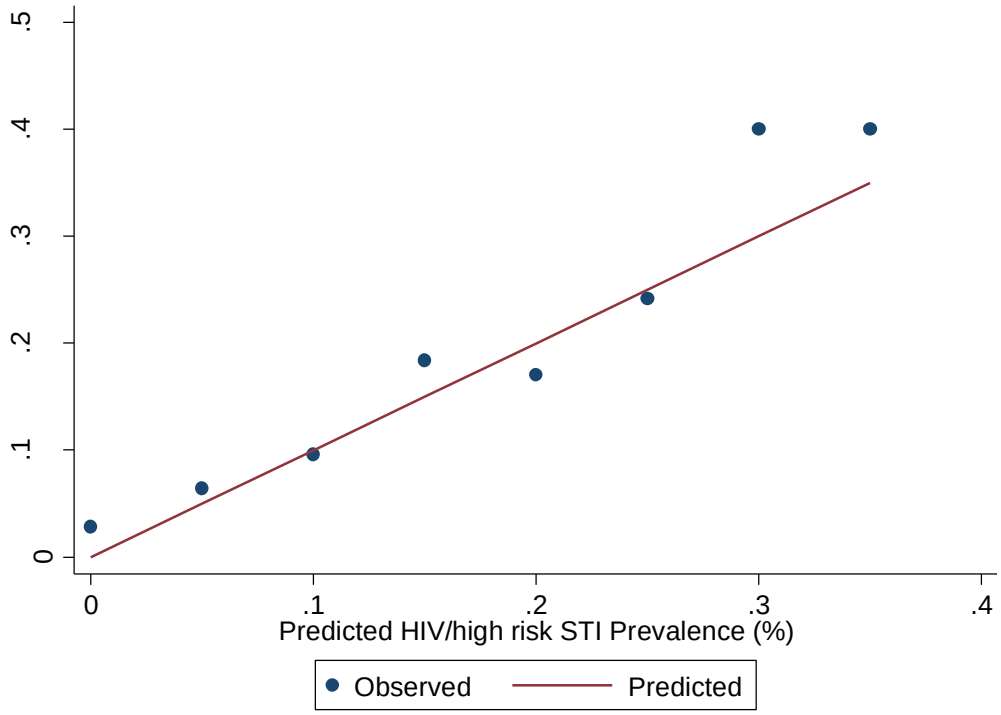
2. Odds of outcome = $e^{(-2.55)}$ = 0.069

3. Probability of outcome = (0.069/1.069) x 100 = 6.4%

8.7.3 Model Performance

The calibration plot demonstrated reasonable calibration at lower observed values; however at higher prevalence there was some discord between the predicted event and the observed prevalence of high risk bacterial STI/HIV where the model under-predicted risk (Figure 8.6).

Figure 8.6 Calibration plot of observed and predicted outcomes, Model 4



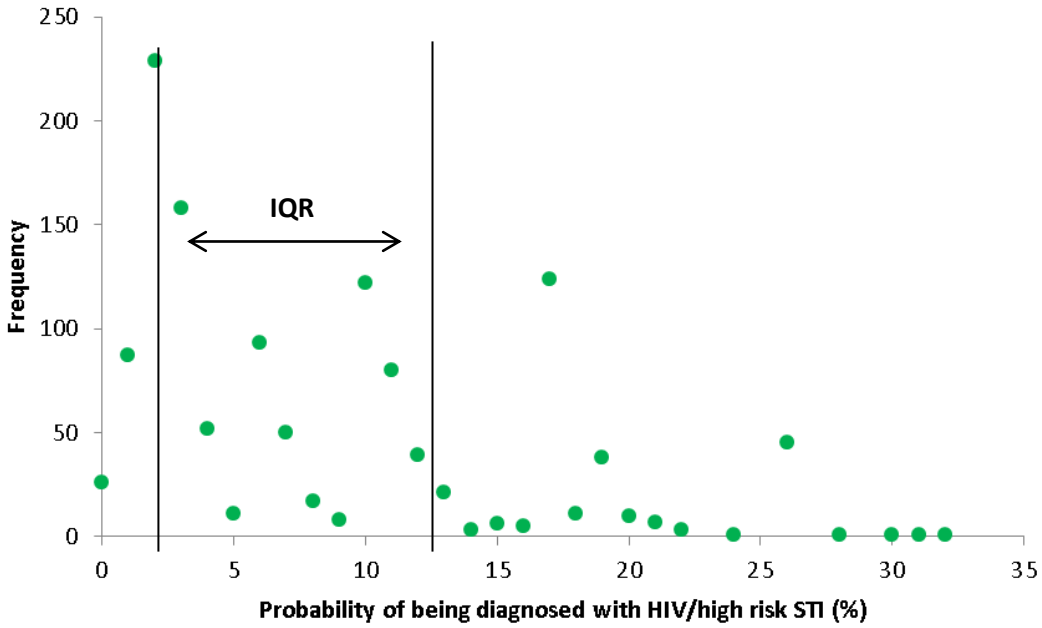
The discriminatory ability of the first imputation was 0.76 (95%CI 0.71-0.80).

8.7.4 Model Prediction & Clinical Utility

The probabilities ranged from less than 1% to 32% (Figure 8.7). The mean probability was 8.2% (SD:6.8) and the median was 6% (IQR: 2-12). More men

had higher probabilities of outcome, for example, 10% of men had a 10% probability of the outcome and another 10% had a probability of 17%.

Figure 8.7 Distribution of probabilities of outcome, Model 4



At a threshold of 4%, 60% of men would be referred for an intervention and sensitivity would be 90% (Table 8.11). The false positive rate and hence the proportion that would be referred drops by 26% when the cut-off was raised to 10% and sensitivity decreased to 72%.

Table 8.11 Sensitivity, specificity, PPV and NPV at different probability cut-offs, Model 4

Cut-off (%)	Sensitivity (%)	Specificty (%)	PPV[1] (%)	NPV[2] (%)	False positive (%)
4	90	40	13	98	60
5	85	49	14	97	51
8	76	62	16	96	38
10	72	66	17	96	34
12	66	70	18	96	30

[1] Positive predictive value, [2] Negative predictive value

8.7.5 Validation

I used the first imputed dataset for internal validation and after bootstrapping, the corrected c-statistic was 0.72. The calibration slope was 0.79, suggesting less over-fitting than Model 3.

8.8 Subsequent HIV seroconversion or diagnosis of a high risk STI

Finally, I determined how well Model 3, which was developed as a diagnostic risk tool, might perform as a prognostic marker of future risk by measuring subsequent infections of incident HIV and other high risk STIs. The 1,066 MSM were followed from baseline (i.e. the attendance at which the questionnaire was completed) until their last attendance occurring before 31st December 2016 or until they were diagnosed with HIV or a high risk bacterial STI, whichever came first.

In total, 650 (61%) re-attended the clinic at least once during this time period with 1,344 person-years (py) of follow-up. There were 89 diagnoses of incident HIV and other high risk STIs, which equated to an incidence of 6.6/100 py (95%CI 5.4-8.2).

Men with an 8% estimated probability of being infected at baseline (i.e. the group with the lowest probability) were the group with the lowest subsequent incidence (4.6/100 py) (Table 8.12). With increasing baseline probability, subsequent incidence also non-significantly increased so that men who were assigned a probability of >19% at baseline of being infected were also the group among whom incidence was highest (13.7/100 py).

Table 8.12 Subsequent diagnoses of incident HIV and high risk STIs by estimated probability at baseline

Total risk score	Estimated probability of being infected at baseline %	Number of MSM (%)	New diagnoses, n (%)	Incidence/100 py (95%CI)
-19 to 11	<8	397 (61)	42 (47)	4.6 (3.4-6.2)
12 to 20	8-19	156 (24)	24 (27)	8.9 (6.0-13.3)
≥ 21	>19	97 (15)	23 (26)	13.7 (9.1-20.7)
		650 (100)	**98 (100)**	**6.6 (5.4-8.2)**

8.9 Key Findings

This is the first HIV/STI risk assessment tool that has specifically been developed for MSM attending GUM clinics in the UK context. I collected primary data to inform the development of this tool and despite the limitations in data quality discussed earlier, I have shown through a prospective cohort study that baseline risk can be used to predict future risk. There are other HIV risk tools developed in other settings (section 8.12.3); however this tool is unique to the GUM setting and specifically targeted to HIV negative MSM who may (or may not) be in relationships. The tool is focussed on the individual and it primarily aims to identify risk and enable triaging of those most in need of interventions, which has not been developed for MSM previously.

The different model statistics and indicators are summarised in Table 8.13. The number of MSM and outcomes included in model development differed between models. All models had EPV values below 10 and were therefore likely to be over-fitted. The MI model achieved the highest EPV (8.3) and model 2 had the lowest (2.3). The probability of outcome for the used example ranged from 5.6% to 14%; the lowest outcome probability was from Model 1 (only using GUMCAD) and highest from Model 2 (GUMCAD and behaviours). Probabilities of outcome calculated from the reduced models (Models 3 and 4) were closer to Model 1.

Models 1, 3 and 4 performed similarly. The calibration plots were visibly similar and the c-statistic was between 0.75-0.76. However, after internal validation, though the calibration slope was comparable across models, the c-statistic dropped below 0.7 in Model 1. Further Model 1 included a large number of variables, which as discussed, reduced the EPV to a greater extent than in the other two models. The MI model has similar performance statistics to Model 3 though the probability of outcome was closer to Model 1. This suggests Model 3 may overestimate outcome probabilities. Though Model 4 may be a less biased model, Model 3 did produce measures of effects that were comparable to the MI model and as it was not based on any statistical assumptions, it was the final model. The area under the curve was 0.72 after internal validation, which is considered acceptable for clinical practice and there was no difference between the expected and observed values indicating no evidence of poor fit.

The best identified cut-off for Model 3 was ≥8%. At this cut-off, sensitivity was 74% and the false positive rate was 35%, which means a third of men would be referred to HIV prevention services at this threshold. Model 3 (as the other models) has been developed as a diagnostic risk scoring system; an assessment

of its predictive ability in a prospective cohort analysis highlighted the model also determined future risk well: incidence increased with increasing estimated probability of being infected at baseline from 4.6/100 py among men with a <8% probability to 13.7/100 py among men with a ≥19% probability. Therefore men who had a low risk of being infected at baseline were also less likely to subsequently acquire an infection. It should be noted that the confidence intervals of the increasing incidence point estimates do overlap.

Table 8.13 Summary statistics for Models 1-4

Model	N	No. of outcomes	EPV*	Probability of outcome** (%)	Hosmer-Lemeshow	C-statistic (95%CI)	Validated calibration slope	Validated c-statistic	Prediction threshold (%)	Sensitivity (%)	% referral
1 Complete case GUMCAD	1,205	104	5.5	5.6	0.91	0.76 (0.72-0.81)	0.79	0.65	8	74	33
2 Complete case GUMCAD & behaviours	965	63	2.3	14	-	-	-	-	-	-	-
3 Reduced model of model 2	*1,066*	*85*	*6.5*	*8.0*	*0.89*	*0.76 (0.70-0.81)*	*0.73*	*0.72*	*8*	*74*	*35*
4 MI reduced model	1,250	109	8.4	6.4	0.38	0.76 0.71-0.80	0.79	0.72	8	78	38

*Event per variable
**Probability of being diagnosed with HIV/high risk STI for a MSM aged 34 years, living in London, who had not attended in the prior year and had one partner with whom practiced CRAI and three partners in total

8.10 Strengths and Limitations

One of the strengths of this piece of work is that it demonstrates the added value of behavioural data when compared to risk prediction models composed of demographic and clinical variables by improving the discriminatory ability of the model It also comprehensively examines each step of the model derivation process for a number of options to determine the most appropriate clinical decision model. Validation is often overlooked during model derivation despite being an important step. In this analysis, I internally validate the models to determine whether results can be repeated with confidence. A further strength of this piece of work is that the cohort of men completing the questionnaire at baseline was followed prospectively to determine their clinical outcomes and to determine the predictive ability of Model 3.

There are limitations to the analyses performed. Firstly, as previously stated, I supplemented the HIV infections diagnosed in the population with other STI endpoints to allow stable models to be developed. Due to this composite outcome, the relationship reported between the predictors in the models and the outcome may differ than if only HIV were to be included. Having a previous STI is likely to be a predictive of a subsequent STI, for example, a previous gonorrhoea could increase the likelihood of having another gonorrhoea infection (that is, repeat gonorrhoea infections) rather than HIV infection. However earlier results show rectal infections are predictors of HIV so it is reasonable to include these infections in the outcomes. It should be noted that the incidence of HIV and high risk bacterial STI is higher than for HIV alone suggesting these additional infections overestimate as a proxy measure of HIV incidence. This will be because not all high risk bacterial STIs will lead to HIV infection. As a result of

using this composite outcome variable, these models are presented as a proof-of-concept to illustrate the steps that would be undertaken and the model predictors that should be considered when developing a model.

As discussed in Chapter 6, MSM in this cohort are likely to be a higher risk population for HIV. If the prevalence of outcome is higher for those among whom the model was developed compared to the population among whom the tool will be implemented the model is likely to over-predict risk in the implementation cohort. For this reason, external validation is essential before implementation to test for this. The model can be recalibrated and the intercept term amended to match the new prevalence. In this case, the intercept would shift down by a constant.

There are limitations inherently associated with some of the statistical measures used in this chapter. The Hosmer-Lemeshow test individuals are grouped according to their predicted probabilities. The test is sensitive to the number of groups used, with 10 being the default and the option used in these models and by others (270). Changing the grouping did not have a significant impact on the results and interpretation (for example, reducing the number of groups to five in the MI model changed the p value from 0.37 to 0.56). Further, a large p-value does not mean the model fits well; the result would suggest there is a lack of evidence against the null hypothesis but not necessarily evidence in favour of the alternative hypothesis. The sample sizes in these models were not large, and it is possible a high p-value could simply be a consequence of the test having less power to detect misspecification, rather than being indicative of good fit. Further, the calibration plot and Hosmer-Lemeshow test are, strictly speaking, measures of goodness-of-fit rather than true measures of calibration when measured in the

development dataset. An external dataset would be required to definitively calculate these measures.

The availability of an external dataset would facilitate external validation, which is the best form of validation. It is essential to support the generalisability of the prediction model because when externally validated the patients included will differ to the development model patients. However, external validation was not possible because the behavioural study was not repeated at another time point, different geographic location or in a different setting. Thus the model could only be internally validated.

The multiple imputation model is presented as a sensitivity analysis because though it performed comparably to Model 3, it is based on a number of key assumptions and if these assumptions are violated, we cannot be sure the results are valid. One of the key assumptions made to conduct MI is that the data are MAR and while the results of Chapter 6 indicate this could be the case, there is also the possibility of some data being MNAR e.g. higher risk MSM may not have responded to questions on numbers of CRAI partners. In this case MI may not be able to produce unbiased estimates for the missing values. Another limitation of MI is that the model usefulness parameters (e.g. sensitivity) and internal validation were based on a single imputation because of the lack of established statistical methods. I did however re-run the analyses on the fifth imputation and found comparable results (c-statistic: 0.75, 95%CI 0.70-0.80, sensitivity: 79%, validated c-statistic: 0.73, validated calibration slope: 0.78).

8.11 Reflections

It was clear by the end of recruitment, the behavioural study was underpowered. This had important repercussions for the HIV risk acquisition analysis using sexual behaviour data (where a multivariable analysis was not possible) (Chapter 6) and the development of the HIV risk assessment tool. I included high risk STIs in the outcome to have sufficient power, which resulted in the development of a tool for HIV and high risk STIs. The variables included in the tool may therefore not be specific markers for subsequent HIV risk and this is likely to impact the validation of the tool. A longer follow-up period was not possible given that the cohort was already followed to the end of December 2016. More HIV endpoints could have been achieved with a larger sample size from recruitment of more clinics. The study may have benefited from the inclusion of clinics not usually included in research/surveillance activities. Though a large number of clinics may be required (as they would probably see fewer MSM and HIV seroconversions), they may face fewer barriers (e.g. competition with other studies) and be more likely to be able to recruit a greater proportion of their MSM population.

8.12 Discussion

8.12.1 Attributes of the model

Two conceptually different risk tools can be traditionally developed: a diagnostic tool to predict likelihood of currently being infected and a prognostic tool to predict future likelihood of infection. In England, all MSM not known to be HIV positive at a GUM attendance are already routinely offered a HIV test so a diagnostic risk prediction tool would serve no purpose in this situation. A prognostic tool could, however, determine future risk for those who test negative through risk stratification. In this thesis, methodologically, a diagnostic risk

prediction tool was developed to identify the likelihood of being infected with HIV (or a high risk bacterial STI) given a set of characteristics. It was envisaged that the results of the diagnostic risk prediction could be used to infer future risk.

The principle would be that current probability of being infected with HIV would be a marker of future risk, so that men with probabilities above a pre-determined threshold who remain HIV negative after testing for HIV at the attendance would be assumed to also be at high risk of acquiring HIV in the future and would be the men who are offered intensified prevention. This assumption was tested in this thesis and importantly, the diagnostic tool did determine future risk using a prospective cohort. The prospective analysis is a strong method to determine if the risk tool can correctly identify men at future risk. The results imply current risk can be used to predict subsequent risk and that the model is appropriate for approximating future risk and for triaging HIV prevention services.

In some situations it is more important for the model to be better calibrated than more discriminatory. For example, for cancer prognosis after a cancer diagnosis, a well-calibrated model would reliably and correctly estimate the average risk of the group and the concordance between the observed and predicted risk would be good. In contrast, discrimination may be more important for diagnostic settings where the purpose is to identify people with and without the outcome. Ideal discriminatory values would be closer to 1 (perfect discrimination) so that people with the disease always have a higher predicted risk than those without.

Both parameters are important for the HIV risk assessment tool developed here. Its predictive role requires that both measures perform well because the tool should stratify individuals correctly into categories (well calibrated) and classify

more into the highest and lowest categories as long as the classifications are accurate. The final reduced model achieved reasonable discrimination at 0.72 after internal validation and was relatively well-fitted. Despite performing well, the EPV was below the recommended value of 10, which is related to the sample size and number of events. Due to the low EPV, the model may be over-fitted so that the probability of the outcome in low risk individuals will typically be underestimated while among high risk individuals it will be overestimated. The model may, therefore, not perform as well in other samples of MSM. Further, a calibration slope value of less than 1 is consistent with over-fitting.

Measures of sensitivity and specificity can be used to assess clinical utility. The optimal model referral threshold depends on the purpose of the tool. A risk assessment tool for HIV would not want to miss any HIV infections and therefore high sensitivity is a key attribute so that all those who are infected with HIV are diagnosed. Another attribute in this risk tool is the false positive rate. The tool is for men who do not have HIV (i.e. they test negative) but who are assigned a high probability of being infected with HIV by the risk tool. These are ideally the men who would be referred onto prevention interventions. Though the false positive rate is important, the specificity is also a consideration because low specificity would result in large numbers of false positive men that would be referred. To achieve the desired balance between sensitivity and specificity values that would identify the men who would most benefit results in an optimal threshold of approximately 8%. Therefore, anybody who remains HIV negative and whose probability is above 8% should be referred onto prevention services, which approximates to a third of the men in the sample. At lower thresholds though sensitivity will be higher, more of the men classed as false positive are likely to be low risk and there is a greater chance of referring these men to

services they may not require. At higher thresholds one can be more confident that men categorised as false positive are likely to be at risk.

In practice, model attributes are unlikely to be the only factors that determine the final threshold. For example, cost-effectiveness would assess whether the use of a clinical decision making tool improves calculating the outcomes sufficiently to justify the additional costs of referrals. Available resources and the feasibility of offering over a third of men intensified prevention may in reality be important limitations at the clinic level. A practical risk score cut-off would be one that results in a number of patients that the resources of the clinic can accommodate. Therefore in reality, two thresholds that split the high risk group into two (such as demonstrated and suggested by the points scoring methodology) may be more appropriate. This will ensure a smaller proportion of MSM would require intensified services (e.g. those with a probability of being infected above 19%) and men at increased risk but not at highest risk (between 8-19%) would receive services considered above standard care such as risk reduction. Possible risk based interventions are discussed in section 9.3.4.

If the risk tool and probability scoring cannot be incorporated into electronic systems, points scoring is an alternative method used to achieve the same results. Both methods were explored and both were comparable though, as anticipated, probability scoring was more accurate. The points score system is, however, simple to understand, the included variables are easy to complete by clinical staff and the information can be completed on a paper form and a score quickly computed using simple mathematical addition. It is no more complicated than other established risk scores such as the Framingham risk score (290).

8.12.2 Model Selection

The MI model produced similar results to Model 3; as well as comparable measures of model fit and ROC curves the odds ratio estimates between groups were similar in the two models. Therefore the regression coefficients, which are key parameters in these analyses, were not dissimilar. Since the results of the two models are similar, the missing data from the behavioural study have been recovered through MI and the complete case analysis approach adopted in Model 3 was appropriate. Further evidence of this comes from prognostic predictive ability of Model 3. The prospective incidence analysis was based on a cohort among whom the outcome had not occurred at the time the behavioural data were collected and consequently the missing data could not be related to the subsequent clinical outcomes. For this reason I chose Model 3 as the final model. It is simpler and it does not make any assumptions like the MI model. Given these conclusions, Model 3 attributes should hold true when applied to clinical practice (assuming there would be no missing data when used clinically and the model performs well externally).

Seven variables were included in Model 3. These variables were selected based on their association with the outcome from the literature review, earlier results of the thesis and on clinical relevance. Two of these variables were clinical history markers and were included because though their PAR is not necessarily high, addressing acquisition of STIs could be important at the individual level. The behavioural variables are known to be associated with HIV infection. Age was included because the data suggest (though not significant) that the probability of being infected declines with increasing age. Unexpectedly residence in London was protective as other data suggest that HIV prevalence and risk is higher among MSM living in London (12, 130, 254). Thought it is not possible to

determine whether this is real or an artefact of the data, I would err on the side of an artefact of the data as the results were unexpected. Adjustment with other factors makes no difference to the protective effect of London. From unpublished analyses I conducted on the cohort, there was no evidence that men in London were more likely to attend for routine screens than men outside London who might attend only with symptoms, which may have explained the results. In fact, MSM from London are more likely to report HIV testing in general but less likely to test in response to perceived risk events (253). Despite this result, residence was included because it is likely to be important in any future model that is implemented. If as the results of Chapter 6 indicate residence in London is a risk factor for HIV, the model will not perform as well during external validation but there is a real need to externally validate the model to determine if risk is lower in London residents, which may certainly be the case now given the recent decline observed in HIV diagnoses among MSM in London. The two behavioural variables included in the models are likely to be collected through future surveillance and these results provide evidence that their inclusion provides some better discrimination of higher risk MSM than models without sexual behavioural data.

8.12.3 Other HIV risk assessment tools

HIV risk prediction has been developed and utilised to target testing for acute HIV infection in the general population. These models reported c-statistics ranging between 0.86-0.89 and sensitivities above 90% (289, 291). Developing a tool to estimate the prevalence of undiagnosed HIV infection among general population also achieved high performance with a calibration slope value of 0.95 and c-statistic of 0.85 (288). Among MSM populations, there are tools to

determine the best cut-off for targeted acute testing (269) and to predict incident risk of HIV infection (146, 268, 292) (Table 8.14).

Three studies specifically looked at developing models to predict for HIV risk among MSM (Table 8.14). The first by Menza *et al* reported HIV incidence to be 2.3% over a four year period among a repeat testing sample of MSM. The model was well-calibrated with modest discrimination (c-statistic: 0.66) (146). In the second study, in a cohort of MSM participating in HIV prevention trials, the HIRI score was developed with a similar risk score sheet as by Menza *et al* (268). The tool reported reasonable discrimination and at the chosen cut-off of 10%, sensitivity was 81%. The calibration of the model was not reported. In the final study, a risk score model was developed that was predictive of acute early HIV infections (292). After validation, the c-statistic was 0.70, and sensitivity was above 60%. Importantly, all three studies externally validated the score in another cohort of MSM and two of them (Smith *et al* and Menza *et al*) recommended the score for adoption in clinical settings while the third recommended more external validation.

The number and type of predictors included in the final models varied (Table 8.14). All studies developed full and simple models that showed the simple models were easier to adopt in practice and also performed as well as the full models. All studies included sexual behaviours; CRAI was specified in two of the studies while Menza *et al* used CAI with serodiscordant partners. Numbers of male partners was also included in some format in all studies. Drug use, history of STIs and age group were other predictors. All of these variables, except drug use, were included in the model developed in this thesis. The inclusion of fewer

behavioural variables in the thesis model may be particularly advantageous in clinical settings where detailed risk history is not routinely collected.

These studies aimed to be as generalisable as possible by only including variables that could be broadly applicable to other MSM populations because simple models are better at generalising than more complex models that have been finely tuned to the dataset being used to create the model. In the tool developed in the thesis partner numbers and age, which were not significant in multivariable analyses were included as they are known to be associated with the outcome. The overall aim is to facilitate predictions to generalise to new subjects by ensuring minimal overfitting over the data and this is facilitated by using a reduced model that only incorporated variables considered associated with HIV as exemplified in this thesis. Nevertheless, even the final model is likely to be overfitted due to the relatively low EPV value.

Although not discussed by any of the other studies; in the simplest sense the risk assessment process and being given a risk score could be used to improve self-perception of HIV risk. MSM may underestimate their HIV risk as indicated by the results of the semi-structured interviews presented earlier. A probability scoring indicating high risk may be discordant with how men perceive themselves and their risk and it could be a necessary first step to highlighting actual risk and discussing risk behaviours.

Table 8.14 Comparison of risk assessment tools predictive for HIV infection among MSM

	HIV risk assessment tool (thesis)	SDET* (Hoenigl *et al*)	HIRI**-MSM (Smith *et al*)	Seattle risk score (Menza *et al*)
Setting	England	San Diego, US	US	Seattle, US
Predictors	-CRAI partner numbers -Partner numbers -Gonorrhoea -Syphilis -Age group -Residence	-CRAI with HIV-infected partner -CRAI and ≥5 male partners -≥10 male partners -Bacterial STI	-CRAI -Partner numbers -Number of positive partners -CIAI with HIV infected partner -Amphetamines -Inhaled nitrates -Age group	-CAI with serodiscordant partner -≥10 male partners -Bacterial STI -Methamphetamine or inhaled nitrates
Calibration	0.73	0.703 (Hosmer-Lemeshow)	Not reported	1.01, 95%CI 0.97-1.05 (slope)
Discrimination (c-statistic)	0.76 (95%CI 0.7-0.81)	0.70, 95%CI 0.63-0.78	0.74	0.66, 95%CI 0.61-0.71
Proposed cut-off (%)	≥8	≥5	≥10	≥1
Sensitivity (%)	74 (derivation cohort)	60% (validation cohort)	81 (validation cohort)	86 (validation cohort)

*San Diego Early Test **HIV Incidence Risk Index

8.12.4 Methodological refinements

There are some changes that could be applied to improve the overall methods used to develop the risk prediction model. One proposed improvement is the use of penalised regression, which potentially limits over-fitting (293). Over-fitting was an issue for all models and was due to the large number of parameters in relation to the number of outcomes. Penalised regression is a recommended statistical technique in the case of few events. The methods apply a shrinkage factor to the regression coefficients, which results in more reliable coefficients and in turn more reliable predictions for patients.

Although the use of c-statistic is an established method to measure discrimination and compare between models, it may not be the most appropriate in the case of rare events. When the area under the curve performs well, the addition of extra risk factors may have a negligible impact on the c-statistic. This may be because the risk factor is irrelevant but could also be due to the insensitivity of the model. In the case of rare events, a very small part of the ROC curve is practically relevant as most risk probabilities will be low (at high sensitivities and low specificities); therefore an alternative approach to measuring discrimination could focus on performance at specific thresholds. At proposed thresholds correct classification of patients is essential because being assigned a probability of 19% or 21% when the threshold is 20% has referral implications if the patient was misclassified. A more recent methodology is reclassification (294), which is the extent to which one model is superior to another in correctly categorising with respect to pre-specified thresholds.

8.12.5 Implications for thesis

This is the first HIV/STI risk assessment tool that has been developed for MSM attending GUM clinics in England. This Chapter has shown that the behavioural and clinical/demographical data can be used to develop a risk assessment tool. The addition of behavioural data delivered a more discriminatory tool that could be used to enhance HIV prevention. Vitally, the tool was predictive of future risk as exemplified by prospective follow-up of the cohort. There were a number of challenges during development and evaluation, which will require refinement and validation of the tool is essential before it can be recommended for clinical practice. However, the first steps have been taken through this thesis and the remaining steps can be undertaken beyond the thesis.

9 Discussion

In this final chapter, I summarise the key findings of the thesis in the context of work done by other investigators and in the evolving sexual health services landscape. I also discuss the public health and policy implications of this research, the limitations of the research as a whole and suggest future research given the key questions that arise from this thesis.

9.1 Key findings

Throughout this thesis the question of whether behavioural data can improve HIV prevention service delivery to HIV negative MSM attending GUM clinics has been addressed using a mixed-methods approach. I undertook a literature review (Chapter 4) to help shape the methodology used to calculate HIV incidence among MSM attending GUM clinics in England (Chapter 5). This analysis determined current incidence in this cohort and highlighted the limitations of available clinical and demographic data as risk factors of HIV acquisition. Behavioural data were collected from MSM attending five GUM clinics to document sexual behaviours and better describe risk associated with HIV infection (Chapter 6). Interviews were undertaken with clinical staff at GUM clinics to explore the utility of behavioural data and with MSM to understand their views on being formally risk assessed (Chapter 7). A clinical decision making tool for predicting HIV infection was developed and validated (Chapter 8). The key findings are summarised in the next section.

9.1.1 HIV incidence

In Chapter 5 an analysis of HIV negative MSM attending GUM clinics in England in 2012 found that HIV incidence was 2.0/100 person-years in this cohort. This compares to estimates of 0.3%-0.9% in the general MSM population in England and Wales (5-7) and is comparable to other estimates among clinic attending MSM in the US (2.4/100 py, (136), Spain (2.4/100 py, (295)) and Portugal (2.8/100 py, (296)). The analysis identified distinct risk strata of MSM; incidence was significantly higher among MSM diagnosed with a rectal STI in the prior year (5.4/100 person-years) (130). Therefore though MSM who attend GUM clinics are a high risk population (when compared to all MSM), I demonstrated that even among clinic attendees, risk was not uniform, and being able to identify subgroups of MSM at higher (or highest) risk of infection has implications for both public health and clinical practice. It could be considered the first step towards better triaging of services.

9.1.2 Risk stratification of HIV negative MSM

I demonstrated in Chapter 5 that risk of HIV varied considerably in sub-groups of MSM attending GUM clinics. The strongest clinical predictors of HIV acquisition were a diagnosis of gonorrhoea and of syphilis in the previous year, which increased the risk of incident HIV in the following year two- and four-fold, respectively (130). However, the low prevalence of STIs in the population resulted in small population attributable risks thus suggesting the prevention of STIs, though important at an individual level, will have a limited impact on population HIV transmission. This has similarly been reported by others (124). Comparatively, the unadjusted PAR for CRAI with at least two partners, which was associated with HIV infection, was considerably higher at 32% (Chapter 6).

This finding highlights the importance of sexual behaviours to facilitate better risk stratification of MSM.

9.1.3 Utility of behavioural data

Service providers identified the systematic collection and recording of behavioural data as key in the life cycle of service provision as the data could help identify local needs, shape the service and inform service evaluation (Chapter 7). A national standardised behavioural questionnaire would also ensure a uniform and impartial approach to clinical history taking within and between clinics. Further, the data can be used in a clinical decision making tool (e.g. HIV risk assessment tool) to help determine appropriate HIV prevention services the individual could benefit from.

Standardised behavioural data collection from HIV negative MSM is feasible. There was no evidence to suggest that MSM found it unacceptable to complete a standardised set of sexual behavioural questions and this was as expected as MSM already provide sexual behavioural data during GUM consultations. However, collection of this data in a paper format at every GUM attendance is not feasible in the long-term; it is especially not a sustainable method in clinics with high throughputs of MSM as demonstrated by the low recruitment rates (Chapter 6). An electronic format that facilitates collection at every attendance or periodic cross-sectional paper data collection could be alternative suggestions.

9.1.4 HIV risk assessment to risk stratify MSM

I formalised risk stratification of MSM by developing a HIV risk assessment tool for MSM that was composed of seven key predictors. Two of these were behavioural variables (numbers of CRAI partners and total number of partners).

The risk tool performed well (validated c-statistic: 0.72, Hosmer-Lemeshow p value: 0.89) indicating the model could identify men with the outcome. The probability threshold at which MSM would be referred to interventions was ≥8% so that any MSM whose probability of the outcome is above 7% should be referred onto triaged HIV prevention services. The main limitation, however, was the insufficient HIV endpoints that prevented a HIV specific risk assessment tool from being developed. Therefore the tool demonstrates a proof-of-concept that risk assessing with clinical and behavioural data would be a good means by which to target HIV prevention services.

9.1.5 Triaged HIV prevention services

Chapter 7 discusses the acceptability of formal risk assessing to service providers and users. Service providers saw the benefit of using behavioural and clinical data to risk assess MSM as it facilitated standardised decision making in terms of services offered (Chapter 7). HIV negative MSM expressed mostly positive views on being risk assessed; the outcome could confirm what they already know, it could act as a 'wake-up call' that makes them realise they are at higher risk than they believed and the tool could also facilitate greater discussion around behaviours and engagement in risky behaviours. However, the concept of tiered services was met with some resistance as men were used to having access to all available services (Chapter 7). Despite high awareness of HIV, perception of HIV risk was generally low among the interviewed MSM, which has similarly been reported by others (272, 273). In the interviews, risk perception was potentially associated with utilisation of triaged services; for example, men who had greater perception of their own risk used HIV testing services frequently (Chapter 7). The link between risk perception and HIV testing has been previously reported for MSM (35, 280). Formal risk assessments will therefore

be an important mechanism by which actual versus perceived risk can be determined with the attendant benefits of enhanced prevention being targeted to those at greatest need.

9.2 Limitations

Ideally, the research would have measured sexual behaviours over a longer time period to allow more nuanced sexual behavioural and HIV outcome analyses. For example, sexual behaviours in the recent months prior to HIV acquisition could be investigated and could potentially be more informative than examining the association of behaviours at one time point and subsequent infection. Further, the study would also have been conducted in a larger cohort as this would have increased the number of HIV outcomes. Both of these limitations could be addressed by GUMCADv3 and the AURAH2 (Attitudes to and understanding of risk of acquisition of HIV over time) study (297). GUMCADv3 will capture information from all HIV negative MSM at every GUM attendance in England (an open cohort) while AURAH2 is currently recruiting a cohort of MSM from three GUM clinics to complete online questionnaires every four months on behaviours including sexual behaviours, drug use and PrEP use during three years of follow-up (closed cohort). In both these examples, behaviours will be examined over a longer period, which, in the case of GUMCADv3 can then be linked to a larger number of HIV infections.

Second, the thesis uses the term MSM, which is traditionally used in public health as a catch-all category of gay/bisexual and other men who have sex with men. However, incidence analysis and recruitment into the behavioural study was based on self-reported gender (male/female) and sexual orientation (as this is how it is recorded in national surveillance) and these categories do not

necessarily reflect actual behaviours and do not include gender identity. As a result not all MSM will be captured in the analyses presented here. MSM who do not identify themselves as gay or bisexual but who do have sex with men will have been excluded such as men who identify as heterosexual or straight or as queer, which does not imply any particular behaviour. Recognising distinct identities and the diversity is important for HIV prevention. HIV prevalence has been reported at 28% among male-to-female transgender women in the US with 27-48% reporting engagement in high risk behaviours (298). The sexual behaviours captured in this thesis will therefore omit those of transgender MSM and others who did not self-report as homosexual/bisexual men.

Finally, the thesis focussed on the role of sexual behaviours in HIV infection and prevention and by doing so I did not extensively examine drug use among HIV negative MSM attending GUM clinics and its association with HIV. The behavioural questionnaire collected reasons for non-condom use with 4% of men reporting being high on drugs as one of the reasons why a condom was not used at last CRAI. 'Chemsex' (sex under the influence of psychoactive drugs (typically crystal methamphetamine, mephedrone and gammahydroxybutyric acid/gamma-butyrolactone)) has recently become more widely captured in surveillance and studies: 12% (299) and 23% (258) of MSM attending GUM reported chemsex in the last three months and 4% of MSM in the UK although with higher rates in cities such as Manchester, Brighton (16% each) and London (13%) and among MSM living with HIV (13%) (300). Significant associations with chemsex and condomless sex have been reported (258). Qualitative research also highlighted that condomless sex can be a feature of chemsex among HIV negative MSM (301). The evidence clearly indicates that monitoring chemsex is important to understand sexual behaviours, though less is known of its association with HIV

infection. One study found MSM with STIs were significantly more likely to report chemsex than MSM without STIs (302).

Recreational drugs such as amphetamines and nitrate inhalant use are associated with HIV infection (146, 173, 174, 177, 219). The inclusion of recreational drug and sexualised drug use as independent risk factors could have potentially produced a more holistic risk assessment tool that accounted for the main predictors of HIV infection as has been done in other tools (146, 268). It may, however, not improve the predictive ability of the current model. Overfitting can occur when there are too many parameters relative to the sample size included in model development and when it occurs the model describes random error or the background noise rather than the actual relationship between parameters and the outcome. In this case the simple model, which would be the current model, may be preferred although the final decision will also depend on the importance of the identified variable for predicting HIV infection.

Regardless of the risk tool, drug use should be monitored to understand the prevalence of this behaviour, inform the risk of HIV infection and to ensure onward referral to appropriate services. This should be possible through GUMCADv3 and the behaviour could be incorporated into the tool at a later date should it be necessary.

9.3 Thesis reflections

I felt there were often challenges in successfully meeting the requirements of the thesis and conducting my job at PHE. For example, though I would have preferred to conduct the behavioural study as research, this was not possible as PHE envisaged the study to lead to wider enhanced surveillance of sexual

behaviours among MSM. Further, as already discussed, I had to conduct the behavioural study before I could undertake my cognitive interviews. Had I been a full-time research student these issues would not have arisen and I could have better led my own research.

There were other factors that also played a role in how the research was carried out and reported. As I conducted my PhD part-time, I was only able to dedicate 2.5 days per week to it. This was of particular significance during the running of the behavioural study. I was not able to visit clinics regularly and be on site, particularly at the London clinics. I think my presence would have identified issues in the recruitment process earlier and been a constant reminder to staff of the study. It would have been useful to negotiate a period of a few months where I was full-time or almost full-time PhD as this would have benefitted my work. Of equal significance were my two maternity leaves that occurred during the thesis. In response, my methods and timelines had to remain adaptive. I had to ensure the semi-structured interviews with MSM were conducted before I went on maternity leave. However, though my timelines changed, Brighton conducted their interviews later and the analyses were also conducted at different periods. The consequence of this was delays in communicating the findings of the interviews. The greatest impact of my breaks was on writing up publications as they occurred soon after I submitted manuscripts and I was unable to address comments in time. This lengthened the process of publication, particularly for the behavioural study work.

9.4 Policy and practice implications

The findings from this thesis highlight the need for further research to fully realise the potential of behavioural data to aid HIV prevention in GUM clinics. I next describe the implications of the research and discuss potential areas of future research.

9.4.1 Surveillance data

9.4.1.1 Incidence

HIV incidence estimates from this thesis when examined with other estimates available from the last one to two decades (26, 157) suggest incidence among MSM attending GUM has remained stable. Incidence calculated for 2014 provides further evidence of no reduction in or control of HIV transmission (unpublished data). The stable number of annual new HIV infections is also in line with estimates from the general MSM population (7).

Over the same time period new HIV diagnoses and HIV testing has increased (9, 21, 253). The increase in testing will have contributed to the observed increase in diagnoses among MSM although it is unlikely to entirely account for it. Once diagnosed, linkage to HIV care is excellent with high ART coverage and viral suppression (18). Despite high ART coverage, HIV transmission is ongoing as demonstrated by this research and others and with only 36% diagnosed in the same year as acquiring the infection (303), transmission is probably due to men who are unaware of their infection. Increased HIV testing should ultimately reduce HIV transmission though to reduce incidence to levels seen among heterosexuals in the UK, annual testing might have to increase over three-fold compared to current levels (303).

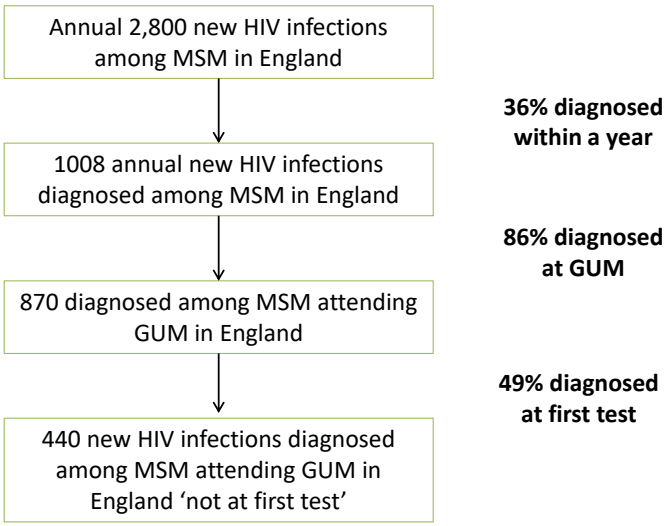
As discussed in Chapter 2, GUM clinics observed a significant drop in new HIV diagnoses in 2016. Increased HIV testing among new and repeat testers in recent years and adoption of treatment as prevention are considered to be the major contributors to this drop (22). Others have also found that increased testing and rapid treatment ('test and treat') have had significant impact on new diagnoses (304, 305) and HIV transmission (306). A drop has been particularly seen in London, where a large number of HIV diagnoses are made, and HIV incidence estimates are likely to have also reduced among repeat testing MSM at GUM clinics in 2016, which advocates for routine measuring of annual HIV incidence in this population (Box 9-2).

Though HIV testing may have impacted HIV incidence, changes in reported sexual behaviours are likely to also have an impact. Condomless sex has increased among MSM (20) and MSM in the behavioural study certainly reported high levels of CAI and CRAI (Chapter 6). Going forward, monitoring changes in behaviours in this GUM population will greatly improve our understanding of how they impact incidence as modelling data found increases in unsafe sexual behaviour can offset the benefit of starting ART after diagnosis on incidence (307, 308).

In total, 2,800 annual new HIV infections were reported among MSM in England from modelling data (7) which is considerably more than the number identified in incidence analyses (Chapter 5, n=324). This is due to a combination of reasons as depicted in the flowchart below (Figure 9.1). I assumed 36% of new HIV infections will be diagnosed within a year of acquisition which is obtained from a recent modelling study (303). Of these, 86% are diagnosed in GUM (28) giving 870 diagnoses of new infections in GUM. This is lower than the 1,710 new

infections that would be identified if the 2.0/100 py incidence estimate (chapter 5) is applied to all HIV negative MSM (85,500). Unpublished analyses using surveillance data indicate that half of men are diagnosed with HIV at their first HIV test which means these men cannot be included in incidence analyses, which rely on repeat testing. As a result, only approximately 440 (51% of new infections diagnosed in GUM) could be identified using repeat testing and of these the majority were included in incidence analyses.

Figure 9.1 Number of new HIV infections among MSM in England



The exclusion of half the incident cases diagnosed in GUM may have resulted in an overestimation of HIV incidence reported in this thesis; incidence would be 1.0% (870/85,500) among all HIV negative MSM which is in accordance with estimates of incidence among MSM attending GUM using recent serological testing (309) and similar to estimates obtained in sensitivity analyses in chapter 5. The missed infections were likely to be among infrequent testers. Analyses in chapter 5 suggested repeat testers are a higher risk population for HIV than MSM who do not repeat test because they attended the clinic more frequently

and more were diagnosed with an acute STI in the prior year. Others have also reported repeat testers to be a higher risk population risk than single testers (253, 310). The qualitative interviews (Chapter 7) further indicated MSM who acknowledged their risk and engaged in risk behaviours (e.g. casual sex, sex with large numbers of partners) tested regularly. However, MSM do underestimate their risk for HIV including those who infrequently attended GUM and tested for HIV. Although HIV incidence did not significantly differ by strata of previous HIV testing history (Chapter 5), incidence was lowest among those who had never attended before (0.5/100 py) and highest among regular testers (tested in last year, 2.3/100 py). A greater proportion of non-repeat testers had never attended before suggesting incidence may be lower in the overall non-repeat testing population compared to repeat testers.

Overestimation of incidence may also impact risk factor and PAR analyses, which are currently restricted to a small sub-population and could be strengthened by being conducted in a larger cohort of MSM. PAR is dependent on population prevalence and should prevalence differ in the entire population, PAR could be over- or underestimated. For example, the proportion diagnosed with an acute STI in the prior year was lower among non-repeat testers, which would lower the prevalence in the overall population and reduce the PAR associated with an acute STI. A further implication relates to monitoring sexual behaviours over time of individuals not captured in current analyses and which are important to inform HIV prevention.

9.4.1.2 Repeat HIV testing

Although 84% of HIV negative MSM tested for HIV at a GUM clinic in 2012, a significantly smaller proportion repeat tested within a year (31%) with only a

moderate increase observed for 2014 (35%) (unpublished surveillance data). Though a small number of GUM clinics have improved testing and repeat testing in recent years, overall, repeat testing has not significantly improved in the country despite recommendations from national HIV testing guidelines to test MSM annually and more frequently where indicated (47). In order to capture half of the new infections that are currently missing from analyses and for HIV estimates to be generalisable to the wider MSM population attending GUM, repeat testing needs to significantly improve and the date of last HIV negative test (regardless of where the test was taken) should routinely be collected. Public health benefits from increasing repeat testing will be the reduction in the interval between infection and diagnosis and therefore a reduction in transmission opportunities before diagnosis.

Increases in testing and repeat testing could be achieved through normalising testing and facilitating easy access to tests in GUM. The qualitative interviews indicated that MSM who regularly tested (e.g. annually or more frequently) for HIV may be men who perceived themselves at risk of HIV whereas those who perceived their risk as low did not see the need to regularly test. The interviews (Chapter 7) and others have found that perceived risk does not always reflect actual risk (273, 274). MSM should attend annually for HIV testing and this should be considered normal practice. Regular repeated HIV testing was not normal practice among the sample of MSM who were interviewed. Easier access to testing is demonstrated by Dean St Express (http://express.dean.st/) where individuals without symptoms self-take samples for STIs tests and point of care tests are used for HIV with results mostly available within 6 hours via text message. Guy's and St Thomas' GUM clinics offer asymptomatic patients living

in the borough the option of obtaining STI (including HIV) testing kits online (https://www.sh24.org.uk/).

The need to improve HIV testing coverage and reduce undiagnosed HIV has led to the development of guidance advocating for expanded HIV testing beyond sexual health services (47, 311) and more recently to guidelines that recommend considering HIV self-sampling, particularly for hard-to-reach populations (312) and self-testing (47, 313). While these innovations improve accessibility they could have significant implications on our ability to measure and monitor HIV incidence because a greater number of tests will be performed outside GUM. Early evidence shows that self-testing could be more frequently adopted by less frequent testers and by MSM who feel they are likely to test negative (314). Should reporting of negative tests to national GUM surveillance drop, self-reported date of last HIV negative test collected at each GUM attendance may become increasingly important for incidence analyses.

9.4.1.3 Sexual behaviours

Sexual behaviours have significant impact on sexual health and are major determinants of HIV and STI transmission and acquisition. High-risk behaviours were not uncommon among the cohort of MSM recruited in the behavioural study (Chapter 6). These behaviours included reporting CAI in the last three months and particularly CRAI. Over a third (35%) of HIV infections could be accounted for by engagement in CRAI with discordant partners. Therefore, assuming there are 870 diagnosed new HIV infections, up to 320 HIV infections could be prevented if this sexual behaviour could be removed from the population.

The service provider interviews highlighted that although sexual history taking was routine clinical practice, the quality of collected data varied within and between clinics, as reported previously (11) and these data were not fully utilised; they were only used to document sexual history at the visit. Standardising data collection is an important step in improving sexual history recording; it will facilitate better usage of behavioural data for needs evaluations and service planning and provision.

These findings highlight the importance of understanding sexual behaviour patterns and identifying high risk behaviours associated with HIV infection. While others have used ecological approaches to measuring and evaluating changes in behaviours and HIV incidence over time (181), the behavioural data have provided insights at the individual level into a GUM attending population of MSM in England and shown how sexual behaviours can contribute to HIV infection and prevention. A similar reporting mechanism in the Netherlands reported STI trends over time and the associated sexual behaviours to give more insights into a GUM attending population (315). Surveillance data showed that increasing partner numbers and no condom use with a steady partner were associated with having an STI among MSM. In Australia, sentinel surveillance data identified sexual behaviours such as six or more partners and inconsistent condom use as risk factors for HIV among MSM attending primary care clinics for HIV testing (92). All of these data have been used to inform testing practices and HIV/STI prevention needs in the respective populations.

The behavioural data have informed the development and piloting of GUMCADv3. GUMCADv3 will facilitate electronic collection of behavioural data and the questions included in the behavioural study informed the questions in

GUMCADv3. Though the mechanism of sexual behavioural data collection will change from self-completed to clinican-led, analyses from the behavioural study found no differences in responses from attendees where the questionnaire was completed with the clinician compared to clinics where it was self-completed (Chapter 5). Though the median number of sexual partners reported by men at Manchester (clinician-led) was lower than the other clinics, the proportion reporting CAI or CRAI in the last three months was not. This may partly be because men who attend GUM are accustomed to talking about sexual behaviour and questions that might otherwise be considered sensitive may not be in these situations. In fact, evidence suggests sexual behaviour item non-response is generally low in surveys (62, 316) and is more affected by the mode of question delivery than setting (62, 317). The cognitive interviews further attest that men would provide the same responses to staff as they do in the questionnaire.

9.4.2 Risk stratification to inform policy and programmes

The findings have emphasised that MSM attending GUM clinics are not a homogenous population rather they are a group among whom heterogeneity in HIV risk is significant. The concept of risk stratification of MSM, which has been central to this thesis, can make important contributions to policy and programme development as it allows services in clinical settings to be targeted to certain sub-groups of MSM.

9.4.2.1 PrEP

One such area of contribution is to the service delivery of PrEP. International clinical trials have demonstrated the efficacy of PrEP to prevent HIV infection among MSM (10, 318), while the effectiveness using a real-world setting has

been demonstrated in England (52). NHS England and PHE together announced in December 2016 they will be making £10 million available to PHE to enrol 10,000 participants into a clinical trial of service delivery over three years (100). The PreP-Impact trial will aim to address the outstanding questions about need, uptake, adherence and duration of use of PrEP and it is anticipated the majority of those recruited will be MSM.

As not all MSM can be offered PrEP, risk stratification becomes vital to determine those that would most benefit from the drug. I conducted analyses looking at HIV incidence in sub-populations of MSM attending GUM to identify those at higher HIV risk and help inform the decision of MSM who should be given PrEP. Some of these results have been already discussed earlier in the thesis; HIV incidence was significantly higher among MSM who had a bacterial STI in the prior year or at the current attendance (3.3/100 py, 95%CI 2.7-4.0) (unpublished data) than all repeat testers (2.0/100 py, 95%CI 1.8-2.2). The eligibility criteria that were finalised for PrEP through the trial are described in Box 9-1 and identify a sub-population of MSM who are at higher risk of HIV than all MSM attending GUM. A recent bacterial STI (excluding pharyngeal only infections) was considered to be a proxy for MSM engaging in CAI.

Box 9-1 Inclusion criteria for MSM into the PrEP trial

Inclusion criteria for MSM:

1. A negative HIV test in the prior year and on day of starting PrEP
2. CAI in the previous three months
3. Likely to engage in CAI in next three months

Data from the behavioural study show that 51% of GUM attending MSM engaged in CAI in the last three months (Chapter 6). This is higher than the proportion with a bacterial STI in the prior year/at current attendance (33%) and is likely due to

some overestimation of CAI among MSM (higher risk MSM recruited in the behavioural study) and the fact that not all condomless sex acts result in transmission of a STI. With the availability of behavioural data, we can calculate the number of HIV negative MSM who met the criteria (in 2012): assuming that 31% repeat test for HIV (criteria 1) and 51% engage in CAI (criteria 2) and assuming the same proportion are likely to engage in CAI in the future (criteria 3), there could be as many as 13,000 HIV negative MSM attending GUM who are eligible for the PrEP Impact trial. Considering only 10,000 participants can be enrolled in the upcoming trial, additional criteria may be required to identify those at greatest need and where additional risk stratification based on other behaviours may be of value.

One of the key areas of research in any future PrEP trial or programme of delivery will be PrEP's impact on engagement in risky behaviours and whether the protection afforded by PrEP results in greater practice of risky behaviours and more STIs, which could offset the benefits of PrEP. The current evidence is mixed with some finding a reduction in condom use and an increase in STIs (50) and others no change (52, 53). Risk stratification of MSM taking PrEP could be useful for assessing risk compensation where increases in the proportion of men stratified as high risk over time would indicate greater engagement in risk behaviours. The risk tool would particularly be well-placed to measure and quantify any changes in behaviour and HIV risk over time.

9.4.2.2 Dean St Prime

The risk factors analyses identified rectal infections as highly associated with HIV infection and the behavioural study highlighted the role CRAI played in HIV acquisition. The findings of these results have been presented at numerous

collaborators meetings and have provided important insights into behaviours and clinical risk factors for clinical staff. The risk factor analyses have been a key impetus for Dean St GUM clinic to develop and implement a new online prevention programme called 'Dean St Prime' (www.prime.dean.st) in 2015 (personal communication, A McOwan). HIV negative MSM who had a previous diagnosis of syphilis, rectal gonorrhoea or chlamydia or reported CRAI with more than one person in the last three months are being invited to join the programme. Five programmes are offered to men: i) abstinence, ii) monogamous relationship, iii) condoms and PEP (if required), iv) PrEP and v) managing condomless sex through frequent HIV testing. The advantage of the programme is that it is managed by the individual online. Though only initiated in one clinic, the programme demonstrates the utility of identifying groups at increased risk of HIV infection and how services can be designed and individually tailored to allow men to take control of their sexual health. In 2015, Dean St accounted for 39% of MSM attending GUM clinics in London and 20% in England and for 42% of new HIV diagnoses among MSM in London and 20% in the UK (unpublished 2015 PHE surveillance data). Further decreases in HIV diagnoses than those already observed could be expected at Dean St with this programme and in conjunction with the other HIV prevention activities already in place at the clinic.

I have collaborated with Dean St to evaluate the early stages of the programme. As of September 2016, over 600 MSM have been recruited to the programme and appeared in national surveillance. In 527 years of person time there have been no HIV seroconversions. Among men who had GUMCAD records prior to and after recruitment, the proportion diagnosed with an STI declined from 33% (3 months prior to recruitment) to 15% (within 3 months of recruitment) (unpublished data). These early data already tentatively suggest that by allowing men to take

control of their sexual health and by providing support, Prime is having an impact on STI rates and potentially on HIV seroconversions. This would conform to current models of behaviour such as theory of planned behaviour (319) or COM-B (320) in which self-efficacy is a key component to sustainable behaviour change. Self-efficacy is a measure of how confident an individual feels in being able to successfully undertake a specific behaviour.

Dean St Prime is an excellent example of how behavioural data can lead to understanding the local population and to developing tailored programmes. There are other clinics which have a high throughput of MSM and these clinics could also benefit from prevention models as employed by Dean St. These clinics include Mortimer Market (11% of MSM in London) and St Thomas's (6%) in London and Manchester Royal Infirmary (5% of MSM outside London) and Royal Sussex (6%) outside London. These are all (except St Thomas's) clinics that participated in the behavioural study and the study results have already highlighted that these men are potentially high risk sub-populations who could benefit from such programmes.

9.4.3 HIV risk assessment

To my knowledge, HIV risk prediction models for MSM have, to date, not been investigated or used in GUM settings in England. SANTE have developed a risk assessment tool for STIs among all MSM and young people attending GUM using similar concepts (321). This thesis is the first to examine HIV risk prediction for MSM in GUM clinics in England and its development was undertaken with the aim of demonstrating what such a tool would look like and the development steps involved. The advantage of a HIV risk tool is that it is standardised and objective

so it can potentially guide clinical decision making in an unbiased way in GUM settings.

HIV risk assessment tools that predict HIV infection for MSM have been developed in the US by numerous investigators (146, 268, 292). The HIRI-MSM risk index has been employed by the CDC to aid triaging of HIV prevention services including PrEP. Men reporting a score above nine are recommended for evaluation for PrEP. The utility of the tool at identifying men who would benefit from PrEP has, however, as yet not been evaluated. Research by Wilton *et al* among MSM in Toronto found a large proportion of MSM potentially met the score criteria but very few were willing to use PrEP and/or perceived themselves at risk (322). This implies that though a tool may identify individuals who would benefit from PrEP or other prevention services, a score is unlikely to be sufficient in itself to ensure high uptake. I found similar themes from my interviews with MSM and service providers. Despite high awareness of HIV, self-perception of HIV risk was generally low among the interviewed MSM, even among men who reported inconsistent condom use or causal sex. Men based their risk on their normal and usual behaviours rather than high risk events that were infrequent. Self-perception could impact service utilisation because men who did not perceive themselves at risk also did not test frequently. As already discussed, risk assessing may be the first step in establishing actual risk and from the interviews it was clear men were willing to accept the results of the risk score even if the score was at odds with what they believed their risk to be. Service providers voiced concerns that engagement and willingness to change behaviours were probably more important than simply being risk assessed and given a score indicative of high risk. A more holistic risk assessing approach which includes these additional components should be considered to optimise

the utility of the risk assessment process and ensure prevention services are offered to those who are most likely to benefit.

Changes to the threshold may also be warranted as discussed by Wilton *et al*. Although the tool developed from my research suggests an optimal cut-off of 8-10%, a higher probability threshold may be preferred if it can be established that higher probabilities are associated with self-perception of risk. If men who are identified as high risk are also men who perceive themselves to be at risk, this could maximise service utilisation. On the other hand, raising the threshold of referral any further would considerably impact tool sensitivity and limit the public health impact of intensified HIV prevention services on reducing HIV transmission if the number of people who receive these services is reduced. For example, increasing the threshold from 8% to 12% would reduce the proportion of MSM testing HIV negative and referred from 35% to 24%. The ideal threshold will depend on available resources, required sensitivity and optimal uptake.

As a number of HIV risk assessment tools have been developed among specific MSM cohorts (e.g. Seattle MSM) and applied to MSM from other geographical or recruitment settings it could be argued that another HIV risk assessment tool did not need to be developed. However, the predictive ability of a risk prediction tool depends on the prevalence of the outcome. The long-established Framingham risk score, which has become an accepted method for primary prevention of cardiovascular disease was shown to over-predict mortality in the British population and this difference was mostly attributed to underlying differences in risk between the British and US populations among whom the score was derived (323). Similarly, a single HIV risk assessment tool is unlikely to be appropriate for all situations. HIV prevalence differs between US and British MSM

populations (15% in 2012, (324) vs 5% in 2008, (3), respectively). The lower prevalence of HIV among English MSM implies that a tool developed on a US MSM population would probably over-predict risk in an English population.

Another factor that could affect the predictive ability is the prevalence of risk factors; differences in sexual behaviours and the mechanism of action between the behaviour and outcome could affect the magnitude of association especially if background prevalence of outcome differs. Though CRAI prevalence was comparable between MSM recruited in my research (36%) and those included in the HIRI risk index (32%, (268)), the mechanisms of action between CRAI and HIV could differ. For example, CRAI might be associated with long term relationships in some populations whereas in others it may be associated with drug use. Condomless sex has been associated with chemsex among HIV negative MSM in England (301). Though not included in the final model, Menza *et al* included ethnicity as a risk factor in the full model due to the higher prevalence of HIV among non-white populations including black American MSM, which cannot be explained by differences in sexual behaviours (237). Others in the US have also identified higher incidence among non-white MSM (325).There is no evidence of such disparities in incidence among MSM in the UK and ethnicity was not included in the final model. The US risk tools used different behavioural risk predictors and though this may only reflect differences in available data it may also reflect differences in behaviours between populations. The HIRI index included CIAI with a HIV infected partner, which was not associated with HIV outcomes in this research and with limited evidence from the literature review (Chapter 4). Other indicators are likely to be associated with HIV infection (e.g. CRAI with serodiscordant partners) but they are unlikely to be adopted in GUM settings in England because a balance has to be reached

between indicators that are essential for risk assessment and the extent of data in the tool that is above what is collected in routine practice.

Differences in prevalence, behaviours and other factors such as sexual networks between sub-groups of MSM in England will also have similar effects on the predictive ability of the tool. The risk tool was developed among MSM attending five of the GUM clinics with the highest MSM throughput and due to the low recruitment rate the tool was developed in a subset who may be a higher risk population than those that were not recruited. It is thus conceivable that the tool was developed in a high risk cohort that is not representative of MSM attending GUM, especially of MSM attending GUM in more rural areas where background prevalence may be lower. In these instances, the tool will likely overestimate risk leading to poor sensitivity. Further implications of overestimating risk include smaller benefits of interventions than anticipated and an undermining of an individual's ability to make informed decisions around their HIV risk. If the tool is dependent on background prevalence, a single nationally derived and implemented tool may not feasibly function as prevalence is likely to differ locally. This challenge could effectively be tackled during external validation as the model can be re-calibrated to account for differing prevalence.

Little is known about the generalisability of HIV risk assessment tools to other samples, thus underlining the need for extensive external validation in different settings and compositions of the MSM population, as has been undertaken for the Framingham risk score to ensure optimal performance in the target population. Risk prediction models are often derived from large epidemiological cohorts to improve the generalisability of the outcomes and should be externally validated before incorporation into clinical use. This is one outstanding area of

work for the risk assessment tool developed through this research and while it may be beneficial to repeat the development and validation of the tool in a larger cohort with additional non-sexual behavioural data (i.e. drug use), it would also be of value to determine how well the tool in its current form performs in a different cohort and test its clinical utility. If it performs well and is found to be clinically useful, the tool could be implemented soon after with relative ease whereas any further research to improve the tool would take time.

There are three types of external validation: testing in more recent samples of HIV negative MSM (temporal validation), in samples recruited in other clinics (geographic validation) or in completely different settings (strong external validation) (145). Temporal validation may be feasible for this risk assessment tool; Dean St GUM clinic have expressed an interest in validating the risk assessment tool in their Chemsex clinics where staff can find it difficult to discuss sexual risk and raise the topic of HIV testing (personal communication, A McOwan). The risk prediction model could be a means to broach these topics and facilitate HIV testing and STI screening for high risk bacterial STIs and HIV. It should, however, be noted the model may not perform as well in this population as among HIV negative MSM attending GUM as they are attending for drug use support. Their characteristics and HIV risks may differ to MSM attending GUM for sexual health services (258).

Additionally, given the substantial decline in new HIV diagnoses among MSM, validation in a single clinic is unlikely to generate sufficient HIV endpoints to conclusively determine the validity of the model. The overlap between the questionnaire and the behavioural enhancement of GUMCAD provides an opportunity to validate the tool in a large number of GUM clinics in England. A

prospective cohort study among HIV negative MSM could be considered whereby individuals are risk assessed with the risk tool developed in this thesis at baseline and given a risk score. The cohort would be followed over time to determine annual HIV incidence by risk score as has been demonstrated in this thesis (section 8.8). The size of the cohort and the length of follow-up will depend on the sample size calculation including the expected number of endpoints. Assuming incidence has dropped to 1/100 py, a sample of over 10,000 MSM would be required to ensure sufficient HIV endpoints, which is possible given earlier analyses in this thesis, which included a cohort over 26,000 MSM. At the end of the study, model calibration and discrimination would be determined in this validation cohort to assess tool validity. This would be considered as temporal and geographic validation and would be most appropriate given the tool has been developed for a GUM attending population.

A further consideration for this risk assessment tool is its applicability among MSM populations attending non-GUM sexual health settings, which may become increasingly important for HIV prevention. This would equate to external validation in a different setting and a strong form of validation. A substantial proportion of attendees to other sexual health settings (e.g. enhanced GP practices, sexual and reproductive health services and young people's services) are MSM. MSM attending these non-specialist services were more likely to be younger, be diagnosed with chlamydia and gonorrhoea (326). However, thes men were less likely to be diagnosed with HIV or syphilis. The numbers attending non-GUM are still relatively small but increasing demand may shift care to these sites and warrant further research into the benefits of a tool to triage HIV prevention services and the potential for HIV prevention in these settings.

It is anticipated that an externally validated HIV risk assessment tool could have considerable benefits to optimising the offer and delivery of HIV prevention services. The tool would stratify men according to their risk and this stratification would result in tiered prevention services being offered. This may be particularly pertinent in GUM where MSM may be relatively easily identified as being at low or high risk of HIV but those men who are in-between the two groups are identified with less ease. Three tiered stratification as proposed in this research may be greatly beneficial in formally identifying this 'middle' group of MSM.

9.4.4 HIV prevention services

Currently, the offer of prevention services is not standardised and MSM may receive different services depending on where they go due to the differences in policies, commissioning and available resources between GUM clinics across England. An audit found that the policy in all clinics was to offer safer sex advice to MSM and the majority also offered at least one type of structured behavioural intervention (e.g. motivational interviewing, cognitive behavioural therapy, counselling) (11). In practice, less than a quarter of men were offered and accepted a structured behavioural one-to-one intervention, with similar proportions reported for MSM considered at higher risk.

It is likely that the disparity in offered services will continue in the current climate of austerity with recent budget cuts that have seen a 3.5% drop in spending in GUM (327). Sexual health services, as other public health infrastructures, are increasingly expected to deliver services with diminishing resources. The funding drop has occurred over a period when GUM service demand has increased; the number of GUM attendances increased by nearly a third between 2011 and 2015

and the number of diagnoses also increased (21). The financial pressures exerted by the budget cuts could reasonably lead to reductions in service provision including health advice and prevention services. This will clearly impact the HIV prevention services that GUM clinics offer and the services MSM might expect to receive.

In a situation of scant resources and continuing demand, the adoption of service delivery methods that continue to provide comprehensive services within the available resources becomes essential. The use of a tool to triage services is an excellent example of how service delivery can be adapted to not only better identify target populations but also adapt what services are offered. Although adopting a tool may not entirely eliminate disparities in service provision (as services offered will depend on what services are commissioned), it will help standardise and streamline what should be made available based on calculated risk. As identified in the MSM interviews, men were not wholly supportive of the idea that services should be offered based on need rather than demand.

Demand is defined as what men ask for and expect to receive and can be thought of as rational demand (demand that corresponds to need) and irrational demand (demand that does not correspond to need) (328) whereas need is the ability to benefit from 'health care', and depends on morbidity of the outcome and the effectiveness of intervention (329). Interventions may become more effective when they are targeted to meet need.

Currently there is widespread evidence of health inequities in provision of care; inverse care law suggests that those who most need health care are least likely to receive it whereas those in least need use services more (56). These

inequalities arise due to differences in access to services, quality of services and due to external factors such as socio-economic status, wealth and lifestyle. For example, the middle class population through better education, articulacy and self-confidence may be better at persuading GPs of their need for services than patients from deprived areas (330). Sexual health inequalities exist among MSM by ethnicity (236, 331, 332) with evidence suggesting ethnic minority MSM express more concerns about using sexual health services than white British MSM (333). Differences are also apparent in service utilisation by education where MSM with higher education test more frequently (314).

Clinical decision making tools could make an important contribution to tackling these inequalities, provided they include the important predictors of the outcome (e.g. social deprivation, (334)), by freeing the decision on what services are merited for each individual from bias. The benefits of the tool are however premised on the assumption that those in most need access services, which, as already suggested, may not be the case. Improving awareness and providing culturally appropriate HIV prevention services will be important to challenge unmet need and as one man stated in the MSM interviews, it will take a mind shift in thinking about service provision before these changes could and would be accepted by men.

Interventions that should be recommended based on risk have not yet been identified but are required to facilitate the offer of better HIV prevention. One of the recommendations from the qualitative interviews with service users was to define a clear path of referrals once an individual is risk assessed (Chapter 7) and this is also one of the key recommendations of this thesis as a risk assessment tool can only be operationalised once it is clear what should be

done with the results (Box 9-2). Development of these pathways is beyond the scope of this thesis but an important next step to realise risk prediction in clinical practice.

There are a number of biomedical, behavioural and structural prevention interventions available for MSM attending GUM services. Behavioural interventions such as safer sex advice and motivational interviewing (117, 118) have some evidence of effectiveness at changing behaviours and a recent review suggests interventions should be delivered face to face and immediately after a HIV negative test result (115). Biomedical services including condom use and prescription of PEP are available at all clinics. PrEP is not currently available on the NHS but anecdotally men are accessing the drug online and the trial will begin recruiting soon. Structural interventions that can facilitate easier access to services such as HIV testing, condoms and PEP provision are also important (e.g. available appointments, ease of check in, rapid testing, dedicated clinics). I have proposed a set of interventions based on current testing guidelines and safer sex advice (Table 9.1) although more research and mapping of services is required to determine the final referral pathways.

Table 9.1 Possible HIV prevention interventions based on level of calculated risk

Level of risk	Interventions
Low	• Annual HIV/STI testing • Condom provision
Medium	• 6-monthly HIV/STI testing • Condom provision • Risk reduction (e.g. safer sex advice, counselling)
High	• 3-monthly to monthly HIV/STI testing • Condom provision • Intensive counselling, motivational interviewing • PrEP

HIV testing is recommended for all MSM although the frequency of testing could be tailored to the level of risk where a high risk individual is recommended to test every three months. High risk MSM may be offered a greater package of intensified behavioural (e.g. one-to-one structured interventions) and biomedical interventions whereas MSM at medium risk may only be offered basic risk reduction. A greater frequency of repeat testing is essential to reducing the time between diagnosis and infection. In light of the reductions in public health spending it may be unlikely for such comprehensive HIV prevention to be available to MSM and a simplified version of these pathways may only be feasible. For example, all HIV negative MSM could be recommended the basic interventions (HIV testing and condom provision) and higher risk individuals who are above the cut-off threshold identified from the assessment tool could also be referred for risk reduction with a health advisor.

While increased frequency is recommended for different risk strata of MSM, if self-testing and –sampling strategies are adopted to achieve these frequencies, they could have significant implications for HIV risk assessing and prevention in GUM clinics (and this is certainly the model adopted for asymptomatic patients at Guy's and St Thomas' GUM clinics). Both self-testing and –sampling potentially remove the need for MSM to attend sexual health services, especially if test results are negative. If men preferentially begin testing using online kits, fewer of them could attend GUM and these testing visits which are currently used as opportunities to discuss risk behaviours and triage men to HIV prevention services, could be lost. In these situations, a HIV self-risk assessment could be proposed as an additional component when receiving the negative test result. Men could be encouraged to make use of an online risk assessment tool that uses the same concept to calculate personalised risk and

identify the next steps for the individual. A few online HIV risk calculators are available that assess your likelihood of being at risk of HIV (http://www.scienceoflife.com/HealthCalculators/hiv.aspx, http://www.tht.org.uk/our-charity/Get-help-now/Have-you-taken-a-risk). Online assessments may also benefit MSM who are less likely to attend GUM clinics.

Conversely, kits may primarily be used by MSM who otherwise would not engage with services due to the confidentiality they provide and men who do use them may not use them as their primary testing method (109). Should this be the case, there would be little impact on GUM attendances and opportunities to risk assess men and triage services. Monitoring the potential impact of self-testing/sampling on HIV prevention will be important as these strategies become more widely used.

Finally, these proposed HIV prevention services do not give due consideration to the wider determinants of health that MSM face during different life stages. Sexual health is closely linked to mental health and wellbeing as well as substance use and evidence shows MSM report poorer mental and sexual health outcomes than heterosexual men (15). Anxiety is higher for those who self-reported as gay and bisexual in the UK and general well-being lower (335) and MSM are more likely to feel anxious or be depressed compared to other men(15), which is particularly apparent among adolescents (336). Depression is associated with greater use of drugs and alcohol (337), and greater engagement in unsafe sexual behaviours (338). Substance use is also more common among MSM than heterosexual men (15), can be related to low self-esteem and self-confidence (339) and can result in greater engagement in unsafe sex (especially among those using drugs before or during sex) (301). MSM are at increased risk

of experiencing sexual and domestic violence (340) with childhood rates of abuse reported as high as 46%. Men experiencing childhood abuse are more likely to engage in high risk behaviours, substance use and suffer from depression (341).

The interrelatedness of these health domains argues for the need for a more holistic service delivery approach that includes a detailed assessment of the wider health and well-being needs of MSM and the development of integrated HIV prevention services that also aim to address mental health and substance use comorbidities. GUM clinics are well-placed to conduct assessments and offer or refer MSM for more holistic care if required.

Box 9-2 Key recommendations arising from this thesis

Key recommendations:

1. Build annual HIV incidence estimates among MSM into routine surveillance outputs
2. Collect two key sexual behavioural variables for behavioural research: numbers of partners and numbers of partners with whom practice CRAI
3. External validation of the HIV risk assessment tool in another cohort of MSM
4. Use risk assessing to improve risk awareness and perception and to triage HIV negative MSM onto targeted HIV prevention services
5. Develop a set of predetermined intervention pathways after risk assessment

9.5 Concluding statement

This thesis aimed to document available measures of HIV incidence and risk factors for infection and to determine whether sexual behaviour data could better HIV prevention. It provides evidence for high incidence among MSM attending GUM clinics and with the collected behavioural data shows the contribution of risky sexual behaviours in HIV acquisition. A substantial number of HIV infections

could be prevented by addressing risk behaviours such as CRAI (up to 320 infections in a year) through targeted prevention interventions. With the large numbers of HIV negative MSM attending GUM, a HIV risk assessment tool that incorporates clinical and behaviour variables should be used to objectively assess an individual's level of risk and direct the offer of resource intensive behavioural interventions to a smaller number of MSM identified as at high risk and in need of these services. The use of such a tool was acceptable to service providers and users and the only remaining step is external validation of the tool before it could be incorporated into clinical practice. There are major advantages to introducing a HIV risk assessment tool; it can facilitate objective and equitable distribution of limited resources and improvement of the effectiveness of HIV prevention services whilst addressing health inequalities in a heterogeneous MSM population attending GUM clinics in England.

10 References

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Appendix 1 PRISMA checklist and summary table for papers included in HIV incidence review

Relevant to Chapter 4

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	116
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Not relevant
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	117
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	117
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	119-120
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	119-120
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	118-119
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	120

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	120
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	120
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	121
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	120-121
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	122-123
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 1 & 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Discussion of identified biases
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	130,134, 135
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not

			applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	136
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	143
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	140
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding

Table 10.1: Summary table of HIV incidence estimates

Author, year	Country setting	Period	Study type	Study setting	Study Population	Number of MSM	HIV incidence	Confidence interval	Quality score
Murphy G et al, 2004 (AIDS)	National, England, Wales & Northern Ireland, Europe	1995-2001	Cross-sectional surveys	STI clinic	MSM providing blood specimen for syphilis also used for testing	1,645	2.40%		++
Elford J et al, 2001	London, England, Europe	1997-1998	Retrospective cohort study	STI clinic	Previous test at least 3 months before current test, date and number of tests available	275	1.8/100 py	0.9-3.2	++
Dougan S et al, 2007	National, England, Wales & Northern Ireland, Europe	1997-2004	Cross-sectional surveys	STI clinic	MSM providing blood specimen for syphilis also used for testing	Not reported	1997: 2.4% 2004: 3.0%	1997: 1.5-4.0 2004: 1.9-4.6	++
Murphy G et al, 2001	National, England, Wales & Northern Ireland, Europe	1998	Cross-sectional surveys	STI clinic	MSM providing blood specimen for syphilis also used for testing	6,202	3.30%	2.1-5.3	++
Murphy G et al, 2004	National, England, Wales & Northern Ireland, Europe	2000-2002	Cross-sectional surveys	STI clinic	MSM providing blood specimen for syphilis also used for testing	Not reported	2000/01: 2.5% 2002: 3.5%		++
Harte D et al, 2011	London, England, Europe	2008-2009	Prospective cohort study	STI clinic	HIV negative at baseline and tested at 3 months, diagnosed with CT, GC, syphilis or LGV at baseline	144	8.3/100 py	0.0-17.7	+++
Presanis AM et al, 2011	National, England & Wales, Europe	2002-2007	Modelling	General MSM population	15-44 years	Not reported	0.90%	0.5-1.3	++
Le Vu S et al, 2010	National, France, Europe	2003-2008	Modelling	General MSM population	New diagnoses tested for recent infection, 18-69 years	2008: 329,950	1,006/100,000 population	857-1,155	+++

Le Vu S et al, 2012	Paris, France, Europe	2009	Cross-sectional surveys	Commercial venues	MSM providing blood specimen for testing, 18+ years, sex with a man in past 12 months	886	3.80%	1.5-6.2	++
Giuliani M et al, 2005	Rome, Italy, Europe	1984-2003	Retrospective cohort study	STI clinic	HIV negative at baseline with a subsequent test using database	976	2.7/100 py	2.5-3.5	+++
van der Bij AK et al, 2005	Amsterdam, Netherlands, Europe	1984-2002	Prospective cohort study	Municipal health service, venues	HIV negative at baseline and tested every 6 months, <31 years, at least one male partner in past year	863	1984: 6.7/100 py 1988: 1.3/100 py 1995: 1.1/100 py 2002: 1.3/100 py		+++
Dukers NH et al, 2007	Amsterdam, Rotterdam, Netherlands, Europe	1984-2005	Prospective cohort and cross-sectional surveys	STI clinic, ACS cohort: gay venues and chain referral. ROHOCO: gay venues in Rotterdam	MSM providing blood specimen for testing (STI clinic), HIV negative at baseline and tested every 6 months (ACS, ROHOCO), at least one male partner in last year	STI:3,733 ACS:1498 ROHOCO:265	1999-2005: STI: 3.8 ACS: 1.2/100 py ROHOCO: 1.5/100 py		+++
Jansen IA et al, 2011	Amsterdam, Netherlands, Europe	1984-2009	Prospective cohort study	STI clinic, meeting places	HIV negative at baseline and tested every 3-6 months	1,642	1.9/100 py		+++
Dukers NH et al, 2002	Amsterdam, Netherlands, Europe	1991-2001	Cross-sectional surveys	STI clinic	MSM attending for a possible new STI providing blood specimen for testing, written consent	3,090	3.2/100 py	1.8-4.6	+++
van der Snoek EM et al, 2006	Rotterdam, Netherlands, Europe	1999-2000	Prospective cohort study	STI clinic, community venues	HIV negative at baseline and tested every 6 months, one male partner in last 12 months	190	3.20%		++

Heuker J et al, 2012	Amsterdam, Netherlands, Europe	2000-2009	Prospective cohort study	STI clinic	PEP users: HIV negative at baseline and tested 3-6 months after PEP prescription. ACS: HIV negative at baseline and tested every 6 months to one year	PEP: 355 ACS: 782	PEP: 6.4/100 py ACS: 1.6/100 py	PEP: 3.1-11.6 ACS: 1.3-2.1	+++
Amundsen EJ et al, 2000	Denmark, Norway and Sweden, Europe	1977-1995	Modelling	General MSM population	All ages	Not reported	Denmark 1990-95: 44/6 months Norway 1992-95: 19/6 months Sweden 1993-95: 37/6 months	Denmark: 35-55 Norway: 12-32 Sweden: 22-63	+
McDonald SA et al, 2012	National, Scotland, Europe	1980-2009	Retrospective cohort study	VCT sites	HIV negative at baseline with a subsequent test using database	8,667	15.3/1,000 py	13.8-17.0	+++
del Romero J et al, 2001	Madrid, Spain, Europe	1988-2000	Prospective cohort study	STI clinic	HIV negative at baseline with a subsequent test >90 days and <5 years, no history of IDU	2,670	1988: 4.7/100py 1995: 1.1/100 py 2000: 2.2/100 py		+
Hurtado I et al, 2007	Valencia, Spain, Europe	1988-2003	Prospective cohort study	VCT site	HIV negative at baseline with a subsequent test	2,761	1988: 8.3/100 py 1998: 0.5/100 py 2003: 3.3/100 py		++
Nascimento CM et al, 2004	Catalonia, Spain, Europe	1995-2001	Prospective cohort study	Anonymous VCT site	HIV negative at baseline with subsequent test within 5 years	678	1.9/100 py	1.2-2.9	++
Calzavara L et al, 2002	Ontario, Canada, North America	1992-2000	Retrospective cohort study	All voluntary diagnostic tests	HIV negative at baseline with subsequent test	Not reported	1992: 1.2/100 py 1996: 0.8/100 py 2000: 1.2/100 py	1992: 0.6-1.8 1996: 0.1-0.4 2000: 0.8-1.5	++

Hogg RS et al, 2001	Vancouver, Canada, North America	1995-2000	Prospective cohort study	Community, clinics, doctors	HIV negative at baseline and tested annually, 15-30 years	668	1.4/100 py	0.8-1.9	++
Weber AE et al, 2003	Vancouver, Canada, North America	1995-2000	Prospective cohort study	Community, clinics, doctors	HIV negative at baseline and tested at one year, 16-30 years	674	1.9/100 py	1.3-2.5	+++
Remis RS et al, 2002	Montreal, Canada, North America	1996-2000	Prospective cohort study	Not reported	HIV negative at baseline and tested every 6 months	1,244	0.6/100 py	0.3-0.8	++
Lavoie E et al, 2008	Montreal, Canada, North America	1996-2003	Prospective cohort study	Community, clinics, doctors	HIV negative at baseline and tested every 6 months, 16+ years	1,846	0.6/100 py	0.4-0.8	+++
Lampinen TM et al, 2005	Vancouver, Canada, North America	1997-2003	Prospective cohort study	Not reported	HIV negative at baseline with at least one test in 1998-99, 2000-01, 2002-03, 18-35 years	247	0.9/100 py	0.4-1.4	++
Yang Q et al, 2010	National, Canada, North America	2008	Modelling	General MSM population	All ages	Not reported	1,452		++
Schwarcz S et al, 2001	San Francisco, United States, North America	1989-1998	Cross-sectional surveys	STI clinic	MSM providing blood specimen for syphilis also used for testing	5,302	6.60%		+++
Weinstock H et al, 2002	National, United States, North America	1991-1997	Cross-sectional surveys	STI clinic	MSM providing blood specimen for syphilis also used for testing	7,186	7.10%	4.8-10.3	+++
Kellogg TA et al, 2001	San Francisco, United States, North America	1993-1999	Retrospective cohort study	VCT site	HIV negative at baseline with subsequent test >90 days later	495	MSM+IDU: 3.8/100 py MSM:2.0/100 py	MSM+IDU: 2.7-5.1 MSM:1.0-3.6	+++
MacKellar DA et al, 2002	National, United States, North America	1994-1998	Cross-sectional surveys	Community venues	Self-reported previous tester (frequent:3+ tests) or never tester, 15-22 years	3,430	7% (repeat) 4% (first time)		+++

Buchbinder SP et al, 2005	National, United States, North America	1995-1997	Prospective cohort study	Prior cohort studies, STI clinics, bars, outreach and referral	HIV negative at baseline and tested every 6 months, anal sex in last 12 months	3,257	1.6/100 py	1.2-2.0	++
Sifakis F et al, 2007	Baltimore, United States, North America	1996-2000	Cross-sectional surveys	Public venues	Providing blood specimen for testing.15-22 years between 1996-1998 and 23-29 years between 1998-2000	843	4.2%/yr	1.2-10.5	++
Kellogg TA et al, 2005	San Francisco, United States, North America	1996-2002	Retrospective cohort study, cross-sectional	Anonymous VCT site	Self-reported (SR) previous testers with subsequent test, HIV negative at baseline with subsequent test (UTC) and MSM providing blood specimen for testing	SR:11,546 UTC: 908 STARHS: 15,232	SR:1.6/100 py UTC:1.4/100 py STARHS: 2.0%	SR: 1.5-1.9 UTC: 0.9-2.1 STARHS: 1.4-2.8	+++
Xia Q et al, 2011	California, United States, North America	1997-2007	Retrospective cohort study	VCT sites	HIV negative at baseline with a subsequent test, 18-64 years, history of sex with a man in past 2 years or since most recent HIV test	171,664	1997: 2.0/100 py 2003: 2.4/100 py 2006: 1.9/100 py	1997:1.8-2.2 2003: 2.2-2.6 2006: 1.7-2.0	+++
Truong HM et al, 2006	San Francisco, United States, North America	1998-2004	Cross-sectional surveys	STI clinic, testing sites	MSM providing blood specimen for testing	29,410	STI: 1998: 4.6%, 2004: 3.6% HIV testing: 1998: 1.1%, 2004: 3.2%		+
Scheer S et al, 2008	San Francisco, United States, North America	1998-2007	Cross-sectional surveys	STI clinic, HIV testing sites	MSM providing blood specimen for testing	Not reported	STI clinic: 2.7-4.9% HIV testing sites: 1.7-4.1%		++

Koblin BA et al, 2006	6 cities, United States, North America	1999-2003	RCT	STI clinics, bars, outreach, referral, internet, media	HIV negative at baseline and tested every 6 months, 16+ years, anal intercourse in past year	4,295	2.1/100 py	1.9-2.4	+++
Choi KH et al, 2004	San Francisco, United States, North America	2000-2001	Cross-sectional surveys	Venue based	Asian and Pacific Islander MSM providing blood specimen for testing, 18-29 years	483	1.80%	0.3-6.5	+++
Truong HM et al, 2009	San Francisco, United States, North America	2000-03 VCT 2000-04 STI clinic	Retrospective cohort, cross sectional survey	VCT sites and STI clinic	MSM providing blood specimen for testing	VCT:5,828 STI clinic: 9,182	VCT: 1.8%-4.5%, STI clinics: 2.4-4.2%		++
Nash D et al, 2005	New York, United States, North America	2001	Cross-sectional surveys	VCT, laboratory testing recruitment	New diagnoses tested for recent infection, MSM with previous HIV tests	4,750	2.50%	2.1-2.8	+++
Buchacz K et al, 2005	San Francisco, United States, North America	2001-2002	Cross-sectional surveys	Anonymous VCT site	MSM providing blood specimen for testing	2,991	2.50%	1.5-3.5	++
Menza TW et al, 2009	Seattle , United States, North America	2001-2008	Retrospective cohort study	STI clinic	HIV negative at baseline with a subsequent test, sex with another man in past year	1,903	2.6/100 py	2.1-3.1	++
Buchacz K et al, 2008	3 cities, United States, North America	2004-2005	Cross-sectional surveys	STI clinic	MSM with primary and secondary syphilis and providing blood specimen for testing	365	12%	4.5-19.0	+++
CDC et al, 2008	National, United States, North America	2006	RITA for incidence	General MSM population	New diagnoses tested for recent infection, 13+ years	Not reported	28,720	26,580-30,860	++

Hall HI et al, 2008	National, United States, North America	2006	RITA for incidence	General MSM population	New diagnoses tested for recent infection, 13+ years	Not reported	28,700	24,300-33,100	++
Lieb S et al, 2010	Florida, United States, North America	2006	RITA for incidence	General MSM population	New diagnoses tested for recent infection, 18+ years, lifetime history of any male-male sex contact	501,412	656/100,000 population		++
Prejean J et al, 2011	16 states and 2 cities, United States, North America	2006-2009	RITA for incidence	General MSM population	New diagnoses in States with at least 15% completeness of recent testing, 13+ years	Not reported	2006: 27,000 2009: 29,300	2006: 23-31,000 2009: 25-33,200	+++
Vignoles M et al, 2006	Buenos Aires, Argentina, South America	2001-2001	Cross-sectional surveys	NGO	MSM providing blood specimen for testing, 18+ years	694	6.70%	3.7-9.7	++
Segura M et al, 2007	Buenos Aires, Argentina, South America	2003	Prospective cohort study	NGO, gay venues and streets.	HIV negative at baseline and tested every 6 months, 18+ years, sexual relations with men in last 6 months, no IDU in last 12 months	327	3.9/100 py	2.0-6.7	++
Pando MA et al, 2011	Buenos Aires, Argentina, South America	2006-2008	Cross-sectional surveys	NGOs and hospital	Providing blood specimen for recent testing, 18+ years, written consent, had sex with a man in past 6 months	1,518 (156 newly diagnosed)	6.30%	4.4-8.3	++
Sutmoller F et al, 2002	Rio de Janeiro, Brazil, South America	1994-1998	Prospective cohort study	NGO, snowball, referrals, media	HIV negative at baseline with subsequent test, 18-50 years	385	3.3/ 100 py	1.9-4.7	++

Schechter M et al, 2004	Rio de Janeiro, Brazil, South America	1998-2001	Prospective cohort study	Participants of a previous HIV incidence study	HIV negative at baseline with a subsequent test, 18-35 years, sexual activity in last 6mths, willingness to use PEP	200	2.9/100 py	1.4-5.1	++
de Castro CA et al, 2010	Rio de Janeiro, Brazil, South America	2004-2005	Cross-sectional surveys	VCT sites	MSM providing blood specimen for recent testing	99	12.00%	6.1-17.8	++
Sanchez J et al, 2009	Lima, Peru, South America	1998-2000	Prospective cohort study	HIV/STI clinics	HIV negative at baseline and tested every 6 months, 18+ years, and any of following: STI at screening/last 6mths, CSW, CAI, >6 partners in 6mths, HIV infected partner	1,056	3.5/100 py	2.3-4.7	+
Wand H et al, 2010	National, Australia	1981-2006	Modelling	General MSM population	New diagnoses, recent infections and AIDS diagnoses among MSM, all ages	Not reported	1990-1999: 3,972 2000-2006: 4,731		++
McDonald A et al, 2001	National, Australia	1993-1999	Retrospective cohort study	STI clinic	Last negative test in prior year	5,346	2.10%		++
Poynten IM et al, 2010	Sydney, Australia	2001-2007	Prospective cohort study	Community	HIV negative at baseline and tested at one year	1,427	0.8/100 py	0.6-1.0	++
Pierce AB et al, 2011	Melbourne, Australia	2001-2008	Retrospective cohort study	Metropolitan hospital	HIV negative at baseline and presenting for NPEP	1,404	1.3/100 py	0.1-1.7	+++
Guy RJ et al, 2011	Victoria, Australia	2006-2009	Retrospective cohort study	MSM attending one of 3 GP sites	HIV negative at baseline with subsequent test	7,857	1.2/100 py	0.96-1.6	+++
Li SW et al, 2008	Beijing, China, Asia	2005-2006	Cross-sectional surveys	Community	MSM providing blood specimen for testing, 18+ years	1,067	2005: 2.9% 2006: 3.6%	2005: 0.8-5.0 2006: 1.3-5.9	++

Li D et al, 2010	Beijing, China, Asia	2006-2007	Prospective cohort study	Website, peers	HIV negative at baseline and tested every 6 months, 18+ years, sex with a male in past 3 months	507	2.6/100 py	1.1-4.1	++
Xu JJ et al, 2010	Shenyang, China, Asia	2006-2007	Prospective cohort study	NGO	HIV negative at baseline and tested at one year, 18+ years, at least 1 male partner in past 12months, written consent	218	5.4/100 py	2.0-11.3	++
Li HM et al, 2011	Five cities, China, Asia	2006-2008	Prospective cohort and cross-sectional surveys	Community	Meta-analysis of HIV incidence	122-1,044	3.5% (cohort) 6.7% (cross-sectional)	1.7-5.3 (cohort) 4.8-8.6 (cross-sectional)	+++
Zhang M et al, 2011	Shenyang, China, Asia	2007-2009	Prospective cohort study	Community	HIV negative at baseline and tested after one year, 18+ years, receptive/insertive intercourse with a man in the past 6 months	1,282	5.6/100 py		++
Yang H et al, 2010	Nanjing, China, Asia	2008	Prospective cohort study	Community venues, internet	HIV negative at baseline and tested at 6 months, 18+ years, anal or oral sex with a man in the past 12 months	286	5.1/100 py	1.3-8.9	+
Yan H et al, 2012	Nanjing, China, Asia	2008-2010	Prospective cohort study	Community	HIV negative at baseline and tested every 6 months, 18+ years, anal/oral intercourse with a man in the past 12 months	579	3.4/100 py	2.1-5.0	+++
Hao C et al, 2011	Nanjing, China, Asia	Not reported	Prospective cohort study	Community	HIV negative at baseline and tested at 6 months, 18+ years, anal/oral intercourse with a man in the past 12 months	250	4.2/100 py	0.5-7.8	++

Ko NY et al, 2011	Taipei, Taichung, Kaohsiung, Taiwan, Asia	2004-2008	Cross-sectional surveys	Gay bathhouses	MSM providing blood specimen for testing	1,432 (103 newly diagnosed)	2004: 7.8% 2007: 15%		++
van Griensven F et al, 2010	Bangkok, Thailand, Asia	2003, 2005, 2007	Cross-sectional surveys	Community venues	Thai MSM providing blood specimen for testing, 15-22 years, reporting anal/oral sex with a man in past 6 months	2003: 1,121 2005: 399 2007: 400	2003: 4.1%, 2005:6.4%, 2007:7.7%		++
Chariyalertsak S et al, 2011	Chiang Mai, Thailand, Asia	2008-2009	Prospective cohort study	VCT and STI clinic	HIV negative at baseline and tested every 3-6 months, 18+ years, with >1 VCT episode, written consent	81	8.2/100 py	3.7-18.3	+
Stall R et al, 2009	United States, Canada, Western Europe, Australia and New Zealand	1995-2005	Retrospective cohort study, STARHS assay, nucleic acid amplification screening	Community, STI clinic, HIV test sites	Weighted incidence estimates of different populations	Not reported	2.5%/year	2.3-2.6	++

Appendix 2 Summary table for papers included in risk factor review

Relevant to Chapter 4

Table 10.2 Summary table of risk factors for HIV acquisition

Authors, year	Country setting	Period	Study type	Study setting	Study population	Measure	Adjusted risk factors (95%CI)	Quality score
Barnabas RV et al, 2011	International	2004-2007	RCT	HIV vaccine trial	High-risk volunteers	HR	Placebo, 6 months prior to enrolment: HSV-2: 3.3 (1.6-6.9) Age <30: 2.7 (0.5-2.0) Vaccine and placebo 6 months prior: CIAI: 1.9 (1.2-3.1) CRAI: 1.8 (1.1-3.0) 6 months prior to infection: speed use: 3.2 (1.8-5.8)	+
Buchacz K et al, 2005	San Francisco, United States, North America	2001-2002	Cross-sectional surveys	Anonymous VCT	MSM providing blood specimen for recent testing	OR	Amphetamine use: 2.4 (0.9-6.3)	++
Buchbinder SP et al, 2005*	National, United States, North America	1995-1997	Prospective cohort study	Prior cohort studies, STI clinics, bars, outreach and referral	HIV negative at baseline and tested every 6 months, anal sex in last 12 months	OR	Nitrate inhalant use: 2.2 (1.4-3.7) CRAI with unknown status: 2.7 (1.6-4.8) CRAI with positive: 3.4 (1.6-7.2) Oral sex with ejaculation: 3.8 (1.5-9.4)	++
Carey JW et al, 2009	Chicago and Los Angeles, United States, North America	2003-2005	Matched retrospective case control study	HIV testing sites, STI clinics, hospitals, community, prison	Evidence of recent seroconversion (cases) or HIV negative (controls), 18+ years, ever having sex with another male,	OR	Household income: 2.1 (1.1-3.9) CAI with HIV positive: 3.0 (1.1-7.9)	+++
Elford J et al, 2001	London, England, Europe	1997-1998	Retrospective cohort study	STI clinic	Previous HIV test at least 3 months before current, date and number of tests available	IR	3 or more previous tests: 3.3 (1.1-10.5) Test in previous year vs. more than 12 months: 3.4 (1.0-11.2)	++

Freeman EE et al, 2006	International	up to 2004	Cohort study and nested case-control	Meta-analysis of HSV-2	HIV and HSV-2 status measures for all participants	RR	Prevalent HSV-2: 1.7 (1.2-2.4)	+++
Guy RJ et al, 2011*	Victoria, Australia	2006-2009	Retrospective cohort study	MSM attending one of 3 GP sites	HIV negative at baseline with subsequent test	HR	Previous syphilis: 2.5 (1.1-5.7) >6 anal partners: 3.3 (1.8-6.3) HIV positive partner: 3.4 (1.1-10.6) Inconsistent condom use with casual partner: 4.4 (1.7-11.5)	+++
Jansen IA et al, 2011	Amsterdam, Netherlands, Europe	1984-2009	Prospective cohort study	STI clinic, meeting places	HIV negative at baseline and tested every 3-6 months	IRR	Lower educational status: 2.0 (1.2-3.2) >5 partners: 2.5 (1.6-4.1) CRAI: 4.1 (2.4-7.0) History of gonorrhoea: 5.8 (2.5-13.7)	+++
Jin F et al, 2009	Sydney, Australia	2001-2007	Prospective cohort study	Community settings	HIV negative at baseline and tested every year, sex with another man in past 5 years	HR	CAI with negative: 2.2 (0.9-5.4) CAI with unknown: 4.4 (1.8-11.2) CAI with positive: 16.1 (6.4-40.5) Any CRAI: 4.8 (2.11-10.7) CAI with negative regular: 3.2 (1.0-10.0) (all vs no CAI)	+++
Koblin BA et al, 2006*	6 cities, United States, North America	1999-2003	RCT	STI clinics, bars, outreach and referral, internet, media	HIV negative at baseline and tested every 6 months, 16+ years, anal intercourse in past year	HR	Black ethnicity: 1.99 (1.3-3.1) 4-9 male partners: 1.6 (1.1-2.4) 10+ partners: 1.8 (1.2-2.7) CRAI with positive: 3.4 (2.3-5.1) CRAI with unknown: 2.9 (2.1-3.8) CRAI with negative: 1.9 (1.4-2.7) CIAI with positive: 1.6 (1.1-2.4) CIAI with negative: 0.5 (0.4-0.7) Amphetamine: 1.96 (1.4-2.7) Moderate alcohol: 1.97 (1.3-3.0) Heavy alcohol: 1.6 (1.1-2.3) Gonorrhoea: 2.5 (1.5-4.2)	+++

Lavoie E et al, 2008	Montreal, Canada, North America	1996-2003	Prospective cohort study	Community, clinics, doctors	HIV negative at baseline and tested every 6 months, 16+ years	HR	Increased number of partners (50+): 5.1 (1.78-15.5) AI with positive: 3.4 (1.1-11.1) CIAI/CRAI: 8.3 (2.3-30.1) CIAI: 4.7 (1.1-20.3) CRAI: 12.0 (3.1-47.1) Needle sharing with positive: 10.1 (1.3-79.2)	+++
Li D et al, 2010	Beijing, China, Asia	2006-2007	Prospective cohort study	Website, peers	HIV negative at baseline and tested every 6 months, 18+ years, sex with a male in past 3 months	HR	No perceived risk of HIV: 6.0 (1.6-22.7) Syphilis infection: 3.6 (1.1-11.6)	++
Li HM et al, 2011	5 cities, China, Asia	2006-2008	Prospective cohort and cross-sectional surveys	Community	Meta-analysis of HIV incidence	RR	Baseline syphilis: 3.3 (2.0-5.6) Multiple sex partnership: 2.8 (1.6-5.0) CRAI:3.9 (1.4-10.5)	+++
Macdonald N et al, 2008	3 cities, England, Europe	2002-2004	Prospective case control study	STI clinics	HIV positive test and negative in previous 2 years (cases) or HIV negative (controls), 16+ years	OR	CIAI with >1 partner 2.7 (1.3-5.5) Nitrate inhalants: 2.4 (1.1-5.2) CRAI with not negative partners: 4.1 (1.8-9.3)	++
Menza TW et al, 2009	Seattle, United States, North America	2001-2008	Retrospective cohort study	STI clinic	HIV negative at baseline with a subsequent test, sex with another man in past year	HR	Diagnosis/history of bacterial STI: 1.7 Meth/inhaled nitrates prior 6 months: 3.0 <40 years: 1.9	++
Prestage G et al, 2009	Sydney, Australia	2001-2007	Prospective cohort study	Community	HIV negative at baseline and tested every year, sex in last 5 years	HR	OEM: 1.9 (1.5-2.5) Amyl: 1.3 (1.1-1.7)	++

Read TR et al, 2007	Victoria, Australia	2001-2002	Case-control study	GPs and HIV registry	New HIV diagnosis with evidence of recent infection (cases) or HIV negative test (controls)	OR	CRAI with casual: 57.2 (6.7-489) CIAI with >1 casual: 19.2 (2.2-168.9) >14 casual partners at sex venues: 3.2 (1.1-9.1) >60g alcohol at one sitting weekly: 3.6 (1.1-11.4)	++
Renzi C et al, 2003	6 cities, United States, North America	1993-1997	Prospective case control study	Community, clinics, referrals	HIV negative at baseline, positive during study (cases) or men who remained negative (controls), anal sex in last year	OR	Prior HSV-2: 1.8 (1.1-2.9) >12 partners in last year: 2.9 (1.4-6.3) Lack of health insurance: 2.3 (1.4-3.8)	+++
Sanchez J et al, 2009	Lima, Peru, South America	1998-2000	Prospective cohort study	HIV/STI clinics	HIV negative at baseline and tested every 6 months, 18+ years, and any of following: STI at screening/last 6mths, CSW, CAI, >6 partners in 6mths, HIV infected partner	OR	Recently acquired syphilis/HSV-2: 5.9 (1.5-22.7)	+
Segura M et al, 2007	Buenos Aires, Argentina, South America	2003	Prospective cohort study	NGO, gay venues and streets	HIV negative at baseline and tested every 6 months, 18+ years, sexual relations with men in last 6 months, no IDU in last 12 months	HR	≥10 sexual contact in last 6 months: 3.3 (1.0-10.4)	++
Thiede H et al, 2009	Seattle, United States, North America	2002-2005	Prospective case control study	STI clinics, HIV clinics, community	HIV positive recruited within 3 months with recent seroconversion (cases) or HIV negative (controls), 18+ years, sex with men in last 6 months	OR	Original meeting location internet: 6.7 (1.6-27.7), bar: 8.2 (1.5-45.7), bathhouse: 11.5 (1.7-77.2) CAI with HIV positive: 6.8 (1.3-35.1) CAI with unknown: 3.4 (1.0-11.6) CAI with casual negative: 4.3 (1.3-13.9) Meth use during CAI: 9.1 (1.5-55.0)	+

Truong HM et al, 2009	San Francisco, United States, North America	2000-03 VCT 2000-04 STI clinic	Retrospective cohort, cross sectional survey	VCT sites and STI clinic	MSM providing blood specimen for recent testing	OR	STARHS: CRAI: 2.7 HIV positive partner: 2.0 >10 partners: 1.5 Asian: 1.7 Amphetamine use: 1.8 Retesting: CRAI: 2.4 HIV positive partner: 1.4 Latino: 1.9 African American:2.2 IDU: 1.9 Amphetamine use: 2.1	++
van der Bij AK et al, 2005	Amsterdam, Netherlands, Europe	1984-2002	Prospective cohort study	Municipal health service, venues	HIV negative at baseline and tested every 6 months, <31 years, at least one male partner in past year	RR	CAI with casual partners: 2.7 (1.1-6.5)	+++
Weber AE et al, 2001	Vancouver, Montreal, Canada, North America	1995-2000	Prospective cohort study	Community, clinics, doctors	HIV negative at baseline and tested at one year, 16-30 years	OR	Ever sex trade: 3.1 (1.4-6.7) CRAI: 2.3 (1.0-5.3)	+++
Weber AE et al, 2003	Vancouver, Canada, North America	1995-2000	Prospective cohort study	Community, clinics, doctors	HIV negative at baseline and tested at one year, 16-30 years	RR	Ever in prison: 6.0 (2.5-14.5) CRAI with positive partner: 6.5 (2.1-19.9) CRAI with casual partner: 4.9 (2.3-10.3) History of being in psychiatric ward: 3.8 (1.5-9.9)	+++
Xu JJ et al, 2010	Shenyang, China, Asia	2006-2007	Prospective cohort study	NGO	HIV negative at baseline and tested at one year, 18+ years, at least 1 male partner in past 12 months, written consent	OR	Syphilis infection: 11.4 (1.2-104.7) >5 partners in past 12 months: 6.5 (1.1-39.8)	++

Yang H et al, 2010	Nanjing, China, Asia	2008	Prospective cohort study	Community settings	HIV negative at baseline and tested at 6 months, 18+ years, anal or oral sex with a man in the past 12 months	RR	Men from saunas: 2.4, Syphilis at baseline: 2.8, CAI ≥1 regular partner in last 6 months: 2.2 Casual sex: 2.2 Multiple partners: 2.5	+

*study also included data on population attributable risk

Appendix 3 Sexual behavioural questionnaire used in behavioural study

Relevant to Chapter 3 & 6

The following document is enclosed in this appendix:

1. Study questionnaire (with missing boxes) pages 1-2
2. Study questionnaire (corrected) page 1

Behavioural monitoring pilot among HIV negative men who have sex with men attending GUM clinics

Clinic:	Date of completion/visit: DD/MM/YYYY
Patient ID:	☐☐/☐☐/☐☐☐☐

If you are a man who has sexual intercourse with other men, please complete the following questions as accurately as possible.

The Health Protection Agency (HPA) is collecting this information to help improve services and make them more relevant. The HPA will match this data to your clinical records to get information about the tests you have and your diagnoses. The HPA will not know who you are, and the clinic will not give us your name or address.

You can choose to answer as many or as few questions as you like but we hope you will answer all the questions. You can place the form directly in a collection box after completion. If you choose not to participate, your care and treatment will not be affected in any way. We do, however, ask that you return your unfilled questionnaire.

If you would like more information, please ask for the patient information leaflet.

The following three questions relate to the last 3 months. Please give an estimate if you can't say exactly

1.	In the past 3 months how many men have you had sex with (anal or oral)? (If 0, go to Q4) ☐
	a. Of these, how many were partners you had never had sex with before? ☐
2.	In the last 3 months how many men have you had **receptive** (bottom, passive) anal sex without a condom?
	a. Of these, how many did you know were HIV positive? ☐
	b. Of these, how many had an unknown HIV status? ☐
3.	In the last 3 months how many men have you had **insertive** (tops, active) anal sex without a condom?
	a. Of these, how many did you know were HIV positive? ☐
	b. Of these, how many had an unknown HIV status? ☐

The following question relates to the last time you had unprotected anal intercourse.

4.	When did you last have **receptive** (bottom, passive) anal intercourse without a condom?				
In the last 4 weeks	☐	In the last 1-3 months	☐	In the last 3-12 months	☐
Between 1-2 years ago	☐	Over 2 years ago	☐	Never	☐

4a. What was this person's HIV status?	
Don't know ☐	Thought he was HIV positive and on HIV treatment ☐
Thought he was HIV negative ☐	Thought he was HIV positive and not on HIV treatment ☐
Thought he was HIV positive and did not consider whether he was on treatment ☐	

4b. On this occasion why was a condom not used? Please tick all that apply	
I wanted him to use one, but he didn't ☐	I was high on drugs ☐
Condoms weren't discussed ☐	I was under the influence of alcohol ☐
I don't like using condoms ☐	I wanted to feel closer to my partner ☐
Neither of us had any condoms ☐	I feel at low risk because I am taking PrEP ☐
We don't use condoms with each other, but we do with other partners ☐	I planned to get HIV drugs after sex (PEP) ☐
He was only dipping ☐	I am in a monogamous relationship ☐
Other (please specify): _____	

If you have never been to this clinic before please also complete questions 5-9

5. When did you last attend a sexual health (or GUM) clinic?

   In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never ☐

   Which clinic did you attend? _____

6. Have you had a sexually transmitted infection (STI) in the **last year**?

   Yes ☐ No ☐

   If Yes, which of the following STIs have you had in the past year: (tick all that apply)

   Gonorrhoea ☐ Syphilis ☐ Chlamydia ☐ LGV ☐ Other _____

7. When was your last HIV negative test?

   In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never ☐

8. Have you ever taken **post**-exposure HIV prophylaxis (PEP)? (i.e. HIV drugs **after** sex)

   Yes ☐ No ☐ If yes, when was the last time?

   In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never ☐

9. Have you ever taken **pre**-exposure HIV prophylaxis (PrEP)? (i.e. HIV drugs **before** sex)

   Yes ☐ No ☐ If yes, when was the last time?

   In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never ☐

THANK YOU!

Behavioural monitoring pilot among HIV negative men who have sex with men attending GUM clinics

Clinic:	Date of completion/visit: DD/MM/YYYY
Patient ID:	☐☐/☐☐/☐☐☐☐

If you are a man who has sexual intercourse with other men, please complete the following questions as accurately as possible.

The Health Protection Agency (HPA) is collecting this information to help improve services and make them more relevant. The HPA will match this data to your clinical records to get information about the tests you have and your diagnoses. The HPA will not know who you are, and the clinic will not give us your name or address.

You can choose to answer as many or as few questions as you like but we hope you will answer all the questions. You can place the form directly in a collection box after completion. If you choose not to participate, your care and treatment will not be affected in any way. We do, however, ask that you return your unfilled questionnaire.

If you would like more information, please ask for the patient information leaflet.

The following three questions relate to the last 3 months. Please give an estimate if you can't say exactly

1. In the past 3 months how many men have you had sex with (anal or oral)? (If 0, go to Q4)	☐
a. Of these, how many were partners you had never had sex with before?	☐
2. In the last 3 months how many men have you had **receptive** (bottom, passive) anal sex without a condom?	☐
a. Of these, how many did you <u>know</u> were HIV positive?	☐
b. Of these, how many had an unknown HIV status?	☐
3. In the last 3 months how many men have you had **insertive** (tops, active) anal sex without a condom?	☐
a. Of these, how many did you <u>know</u> were HIV positive?	☐
b. Of these, how many had an unknown HIV status?	☐

The following question relates to the last time you had unprotected anal intercourse.

4. When did you last have **receptive** (bottom, passive) anal intercourse without a condom?		
In the last 4 weeks ☐	In the last 1-3 months ☐	In the last 3-12 months ☐
Between 1-2 years ago ☐	Over 2 years ago ☐	Never ☐

Appendix 4 Paperwork used in cognitive interviews among MSM

Relevant to Chapter 3

The following documents are enclosed in this appendix:

1. Patient information leaflet
2. Consent form
3. Topic guide

Central and North West London NHS
NHS Foundation Trust
Camden Provider Services

Public Health England

Interviews to test a questionnaire exploring sexual behaviours of men who have sex with men attending sexual health clinics

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We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. If there is anything unclear please ask the researcher for further information.

What is the purpose of the study?

This study is part of a larger public health exercise to collect sexual behavioural information from people attending sexual health clinics. In this study, we would like to better understand how men who have sex with men interpret and answer questions relating to their recent sexual behaviour by conducting in-depth individual interviews. The interviews will be an opportunity to test a sexual behavioural questionnaire and explore whether questions are understood and answered as intended.

Why have you been invited?

All men who meet the following criteria are invited to participate in the study:

- identify themselves as men who have sex with men
- are HIV negative

Do I have to take part?

No. You can choose whether you would like to take part in this study. If you agree to participate, you will be asked to sign a consent form and you will be given a copy. Taking part in this study is entirely voluntary and you can withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What does participating involve?

- You will be asked to complete a short questionnaire about your recent sexual behaviour and participate in a one-to-one interview in a private room in the clinic, which will last approximately 1 hour.

- During this discussion, you will be asked about the responses you give in the short questionnaire. This will include you saying out loud what you are thinking and how you arrived at responses or explaining your understanding of some questions.
- You can decline to answer any part of the questionnaire or any of the interview questions.
- You won't be asked for your name or contact details and no identifiable information will be collected.
- The interviews will be recorded to ensure no information is lost and the recordings will be securely stored. All of this information will remain anonymous.

What are the possible benefits or disadvantages of taking part?

If you take part in this study, we will give you a £20 gift voucher as a thank-you for helping us. You will be contributing to a better understanding of sexual behaviour among men who have sex with men, who remain at greatest risk of HIV in the UK and your responses will help improve the questionnaire that we are testing. There are no anticipated disadvantages in participating. If you feel uncomfortable with any of the questions you can decline to answer or you can terminate the interview.

What happens to the information you give?

The information you give will be recorded and analysed to summarise the main issues and themes that arise from the interviews. The information will also be used to adapt and improve the questionnaire to ensure it is easy to understand and measures what is intended. All information will be kept secure and confidential and we will not be able to identify any individual.

Who is organising and funding the research?

The study is funded and has been organised by the Health Protection Agency, (part of Public Health England (PHE) from 1st April 2013). For more information about the PHE please visit www.phe.gov.uk.

Who reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee (REC) to protect the safety, rights, wellbeing and dignity of individuals. This study has been reviewed by a REC and given favourable opinion (REC number: 13/LO/0475).

What if there is a problem or I want more information?

If you have any questions or concerns about any aspect of this study, please contact Sarika Desai (HIVSTI@phe.gov.uk or 020 8327 7769) who will do her best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from NHS Camden and Islington.

Public Health England

Participant Consent Form

Centre: Mortimer Market
REC Number: 13/LO/0475

Title of Project: Qualitative research to test the feasibility and acceptability of implementing behavioural surveillance among HIV negative men who have sex with men attending genitourinary medicine clinics

Please indicate your consent to each of the following statements by writing your initials in the relevant boxes

1. I confirm that I have read and understand the information sheet (ref: 02.05.13 Info sheet v5) and agree to take part in the above study ☐
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
3. I understand that the study is anonymous and that no patient identifiable information will be collected. ☐
4. I understand that the interview will be audio recorded and give my consent for this to happen. ☐
5. I understand that participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
6. I agree to receive a £20 voucher for taking part in this study. ☐
7. I understand that what I say may be directly quoted in reports. ☐

Participant
Signed:_____ Date: _____

Researcher
Signed:_____ Date: _____
Name: _____

Behavioural monitoring pilot among HIV negative men who have sex with men attending GUM clinics

TOPIC GUIDE

Introduction

- Introduce self – name, organisation
- Explain nature and purpose of research
- Introduce tape recorder
- Stress confidentiality
- Duration of interview
- Set ground rules (phone on silent, explain what is required of participant)

The following three questions relate to the last 3 months. Please give an estimate if you can't say exactly.

1. In the past 3 months how many men have you had sex with (anal or oral)? ☐

   (If 0, go to Q4)

   - ***Count each time or estimate***
   - ***Certainty of estimates and reasons for estimating – time frame, partners***

   a. Of these, how many were partners you had never had sex with before? ☐

   - ***Interpretation of "never" and of "sex" – include oral and anal***
   - ***Consideration of other words such as "new"***

2. In the last 3 months how many men have you had **receptive** (bottom, passive) anal sex without a condom? ☐

   a. Of these, how many did you know were HIV positive?

   b. Of these, how many had an unknown HIV status? ☐

   - ***Language used***
   - ***Count each time or estimate***
   - ***Certainty of estimates and reasons for estimating – time frame, partners***
   - ***Ascertainment of partner status – he told you, with him when got results, regular partner etc***
   - ***Interpretation of "anal intercourse without a condom" – condom broke/slipped off, condom not used but partner didn't ejaculate, put on prior to ejaculation, other***

3. In the last 3 months how many men have you had **insertive** (tops, active) anal sex without a condom?

   a. Of these, how many did you know were HIV positive? ☐

   b. Of these, how many had an unknown HIV status? ☐

   - ***Count each time or estimate***
   - ***Certainty of estimates and reasons for estimating – time frame, partners***
   - ***Ascertainment of partner status – he told you, with him when got results,***

regular partner etc

- ***Interpretation of "anal intercourse without a condom" – condom broke/slipped off, condom not used but partner didn't ejaculate, put on prior to ejaculation, other***
- ***Allocation of both active and passive partners – active, passive, either, neither, other***
- ***Difficulty of knowing type of partner vs. overall numbers***

The following question relates to the last time you had unprotected anal intercourse.

4. When did you last have **receptive** (bottom, passive) anal intercourse without a condom?

☐ In the last 4 weeks ☐ In the last 1-3 months ☐ In the last 3-12 months

☐ Between 1-2 years ago ☐ Over 2 years ago ☐ Never

- ***Exact date known or estimate***
- ***Certainty of response category***
- ***Usefulness of the provided options – aid recall, other options***

a. What was this person's HIV status?

☐ Don't know ☐ I thought he was HIV positive and on HIV treatment

☐ I thought he was HIV negative ☐ I thought he was HIV positive and not on HIV treatment

☐ I thought he was HIV positive and did not consider whether he was on treatment

b. On this occasion why was a condom not used? Please tick all that apply:

☐ I wanted him to use one, but he didn't
☐ Condoms weren't discussed
☐ I don't like using condoms
☐ Neither of us had any condoms
☐ We don't use condoms with each other, but we do with other partners
☐ He was only dipping (anal sex without ejaculation)
☐ I was high on drugs
☐ I was under the influence of alcohol
☐ I wanted to feel closer to my partner
☐ I feel at low risk because I am taking PrEP
☐ I planned to get HIV drugs after sex (PEP)
☐ I am in a monogamous relationship
☐ Other (please specify): _____

- ***Appropriateness of question***
- ***Suitability of options: number/missing***

If you've never been to <u>this</u> clinic before please also complete questions 5-9:

5. When did you last attend a sexual health (or GUM) clinic?
   ☐ In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never
   Which clinic did you attend?

_____

6. Have you had a sexually transmitted infection (STI) in the **last year**?
   ☐ Yes ☐ No
   If Yes, which of the following STIs have you had in the past year: (tick all that apply)
   ☐ Gonorrhoea ☐ Syphilis ☐ Chlamydia ☐ Lymphogranuloma venereum ☐ Other_____

7. When was your last HIV negative test?
   ☐ In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never
   - ***Exact date known or estimate***
   - ***Certainty of response category***

8. Have you ever taken **post**-exposure HIV prophylaxis (PEP)? (i.e. HIV drugs **after** sex)
   ☐ Yes ☐ No

   If yes, when was the last time?
   ☐ In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never
   - ***Exact date known or estimate***
   - ***Certainty of response category***
   - ***Prior knowledge of PEP***

9. Have you ever taken **pre**-exposure HIV prophylaxis (PrEP)? (i.e. HIV drugs **before** sex)
   ☐ Yes ☐ No
   If yes, when was the last time?
   ☐ In the last year ☐ Between 1-5 years ago ☐ Over 5 years ago ☐ Never
   - ***Exact date known or estimate***
   - ***Certainty of response category***
   - ***Prior knowledge of PrEP and difference to PEP***

OVERALL QUESTIONNAIRE

1. Was the questionnaire (circle as appropriate)
   Too long about right too short

2. Was the language in the questionnaire (circle as appropriate)

Too medical about right too simple

3. Of all the questions in the questionnaire, are there any you would not answer again and why?

_____

_____

4. Did you find any of the questions intrusive?
   Yes No
   Please explain your answer

_____

_____

5. If you were asked to fill in this questionnaire every time you visited this clinic, how would this affect your attendance (if at all) or perception of the service? **(NEGATIVE vs. POSITIVE)**

_____

_____

6. If the questionnaire negatively impacts your attendance/perception, can you say what we could change in the questionnaire to encourage you to come back/to improve your perception?

_____

_____

7. How open do you think you were with your answers to the questions?

_____

_____

8. How would your answers differ if you were asked these questions by a clinician/health advisor?

_____

_____

9. Any other comments?

_____

_____

Appendix 5 Paperwork used in the study of sexual behaviours among MSM

Relevant to Chapter 3 & 6

The following document is enclosed in this appendix:

1. Patient information leaflet

Do you have 10 minutes to help improve HIV prevention services for gay men in the UK?

Sexual behaviours of gay men attending sexual health clinics

What is the purpose?
The Health Protection Agency (HPA) would like to gather information about the sexual behaviours of HIV negative gay men who attend sexual health clinics using a new questionnaire. The questionnaire is initially being tested at a small number of sexual health clinics, including this one.

Why is this important and why take part?
Gay men remain at greatest risk of HIV in the UK, and many men with HIV are diagnosed in a sexual health clinic. By taking part, you will be contributing to a better understanding of sexual behaviour among gay men. This information will be used to improve future HIV information and prevention services, making them more relevant and useful to gay men and helping to reduce the risk of HIV in the UK.

Who can take part?
All HIV negative gay men attending a sexual health clinic can take part.

What does participating involve?

- You will be asked to answer some questions about your recent sexual behaviour each time you visit a sexual health clinic for a new episode of care.
- It takes no more than 10 minutes to complete - you can answer as many or as few of the questions as you like, but we hope you will answer all of them.
- You won't be asked for your name or contact details and all information collected will be anonymous and confidential.

What happens to the information I give?
Information on diagnoses and service use routinely collected by the clinic is sent to the HPA. Using just your clinic number this data will be matched to your questionnaire. The HPA will not be able to identify any individual, and all information will be kept secure and confidential.

If you have any questions or would like more information please contact the Health Protection Agency:
HIVSTI@hpa.org.uk

Appendix 6 Paperwork used in the service provider and user semi-structured interviews

Relevant to Chapter 3 & 7

The following documents are enclosed in this appendix:

1. Topic guide to conduct semi-structured interviews among service providers
2. Topic guide conduct semi-structured interviews among HIV negative MSM service users
3. Information sheet for MSM
4. Consent form for MSM
5. Demographic profile form

Topic Guide for semi-structured interviews with clinical staff

1. Introduction.

- This study is about understanding GUM clinic staff's opinions on the utility and feasibility of implementing behavioural surveillance among HIV negative MSM

- This study will also help determine what factors contribute to the success of the pilot in individual clinics and what can be done better

- Brief outline of interview (results in report/publication)

Explain: Timing (anticipating 30 minutes)
Confidentiality
Tape recording – not compulsory, obtain verbal consent
Check if any questions before begin

2. Overall experience of the pilot

Were you aware of the behavioural surveillance pilot in your clinic?

- How did they find out about it and what did they understand by it (i.e. the reasons for collecting this information)

How do you think the behavioural surveillance pilot went in your clinic?

- Your experience of participating
- General clinic experience of participating

3. Positives and negatives of the pilot

Now I would like to ask you what you think went well and what didn't go so well during the pilot

- Staff engagement – interest in the study, differences by staff type, willingness to ask men to participate
- Impact on routine work – consultation times, use of routine sexual proforma, work burden
- Patient engagement –reactions/interest when asked to participate, understanding of questionnaire, questionnaire fatigue
- Questionnaire completion – response rates, well completed
- Collaboration with HPA – support, feedback, engagement

4. Improvements to behavioural surveillance

I would like to get your opinion on how we can improve the behavioural surveillance among negative MSM

- Improvement of questionnaire – wording and layout
- Better engagement of men in the study – who, how
- Time point during visit when questionnaire is completed

5. Feasibility of long-term behavioural surveillance

Finally, how feasible do you think it is to monitor behaviours among negative MSM?

- Pros and cons of long term implementation
- Self-completion vs. clinician-led - response rates, bias, work burden
- Longitudinal vs. cross-sectional surveys
- Reasons for not completing questionnaire – intrusive, overlap with clinic proforma, longitudinal nature, interest/engagement
- Different delivery models: EPR vs paper vs other
- Impact on monitoring if part of EPR

6. Utility of behavioural surveillance

I would like to get your opinion on how useful you think the behavioural questionnaire would be in your clinic

- Purpose of behavioural surveillance
- Usage of questionnaire for their clinic (local use of the data, if no use why not, do they already collect similar data, useful includes: comparison with other local sites, commissioning, other? What is useful)
- Usefulness of linkage of behavioural data and GUMCAD
- Usefulness of behavioural data for MSM risk profiling – for staff to triage services and for men to change behaviours

INTRODUCE the idea of a tool (used in the States and would it be useful for clinic)

- Usefulness of risk assessment tool – change behaviour or clinical practice
- Features of the tool that facilitate usage
- Current risk assessment tools being used in the clinic –which, why, what for, other tool requirements

Topic Guide for semi-structured interviews among MSM

1. **Introduction**
   a. Introduce self
   b. Explain study and objectives
   c. £20 voucher
   d. Written consent and demographic questionnaire
   e. Confidentiality
   f. Length of interview and tape recording

2. **Opening questions:**
   a. What brings you here today/what brought you to the clinic the day you were recruited?
      (prompt: routine or recent risky behaviour)
   b. During your recent visit, did you talk to anyone about your sexual health?
      (Prompt: such as talking to HA or talking about condom use)

3. **(Attitudes to Sexual risk perception) People have different understandings of their chances of getting an STI or HIV, I am going to ask you some questions to explore your understanding of your own chances of getting STI if that's ok with you…**
   a. How likely do you think you are of getting STI?
   b. Why do you think so?
      (prompt: partner numbers, number & type of relationships, frequency of STI screens, condoms, other preventative measures)
   c. Would you say your chance of getting HIV is different?
   d. Could you expand on that a bit more?
      (prompt: number and type of relationships, partner HIV status, adoption of seroadaptive strategies, drug use, MSM parties/venues other preventative measures e.g. frequency of HIV testing, condom use)
   e. Would you say your risk of getting HIV changes over time? (if yes) How? Why?
   f. Suppose you came in today and talked about your recent sexual behaviour. How would you feel if we used that information to tell you that your chances of getting HIV/STI are low or high (such as alcohol screening scores)?
   g. How would you feel if you were offered some kind of support to promote your sexual health that was based on the results of the calculation I just mentioned?

4. **(Behavioural interventions) Sometimes when you attend a sexual health clinic you may be offered an opportunity to talk about your sexual health…**
   a. Have you ever been given any sexual health information or received support for your sexual health, if needed?
      (prompt: such as brief chat with a clinical staff, or receiving a leaflet or given condom)
   b. (If yes), what were they?

c. Was there anything (you thought was) good or bad about them?
d. Do you think any worked for you?
e. I am now going to give you some examples of possible programmes that we might develop from our study. Could you tell me what you think about these (only ask about intervention formats and aspects of these interventions not yet mentioned)?
    a. Suppose a possible support you might get is a brief chat with a healthcare professional? How would you feel about that?
        i. How long? How often? Where? What format e.g. phone, person, and email? Who?
    b. Suppose (If necessary) A video on safer sex behaviours in the waiting room?
    c. Talking with other SU about sexual health and ways to promote SH?
    d. Online information such as online videos or quizzes or things on social media (facebook)?
    e. Information on a mobile phone (app/SMS)?

    (Prompt: Such as a sexual health app with similar information as the online materials I just mentioned)
f. Thank you. These were the examples I gave but would you like to add any other services or methods to provide information that the clinic could offer? (If they are not talking) What would you really like?
g. Based on the last visit to a/any clinic, what would have made your experience nicer?
h. Given all the things we've discussed, do you think you would you actually use any of these programmes if you were offered them?

5. To conclude

a. Is there anything else you think would be helpful?
b. Thanks and voucher
c. Re-iterate confidentiality

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PARTICIPANT INFORMATION SHEET

Feasibility of sexual risk reduction interventions at sexual health services
Service users Semi-structured Interview

This study has been reviewed by the Westminster National Research Ethics Service (NRES) Committee. Project ID: 15/LO/0690.

You are being invited to take part in a research study. It is up to you to decide to join the study. Before you decide, it is important that you understand why the research is being done and what it will involve. We will describe the study and go through this information sheet. One of the researchers will ask you if there is anything you do not understand. If you agree to take part, we will then ask you to sign a consent form. This should take about five minutes.

What is the purpose of the study?
The number of new sexually transmitted infections diagnosed in England is rising every year. There is evidence that health promotion delivered through the sexual health services can reduce sexual risk and improve sexual health. At the moment, different clinics across the country approach this issue in different ways. We are exploring who does what, if we could do more, and what service users' preferences would be. We are looking to find effective interventions that are acceptable to service users and providers and don't increase the waiting time for an appointment.

Why have I been invited?
You have been invited because you are somebody who has accessed sexual health services in England.

Do I have to take part?
You do not have to take part in the study. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive. If you withdraw, any information you have provided up to the point of withdrawal will still be used for the purposes of the study.

What will happen to me if I take part?
Taking part in the study involves a semi-structured interview about your opinions on sexual health services provision, and your views on possible activities to reduce sexual risk taking, exploring what you might find acceptable and desirable, to help us create a system that would suit people like you. The interview will last approximately 30 minutes and will be audio-recorded. No identifiable data or names will be recorded, however if you would like to review the transcript for accuracy you will be asked to provide contact details for us to send you a copy of the transcript – this is optional. You can leave the interview at any time should you wish to do so.

Will my taking part in the study be kept confidential?
All discussions during the in-depth interview will be treated as confidential by the interviewer. Names and identifiable information will never be used. The information you provide will be treated as strictly confidential and handled in accordance with the Data Protection Act 1998. The audio recording will be kept secure in a locked cabinet and destroyed immediately after the interview has been transcribed and analysed. No identifiable information will be kept with the recording or transcript. This interview forms part of a doctoral student study, and information gathered will appear in the student's thesis. Excerpts from the semi-structured interview may be taken word for word for reports and the thesis, but you will be referred to anonymously, e.g. Participant 3.

What are the disadvantages or risks of taking part?
There are no disadvantages of taking part in the study. Your confidentiality will be maintained at all times, and you are not obliged to answer a question if you do not want to.

Will the study benefit me?
You will be compensated with £20 as a token for your participation in this study. If appropriate, this £20 honorarium must be declared for tax and benefit purposes. Your input will help us to develop interventions that are most effective at reducing future transmissions of sexually transmitted infections, ensuring that we do so in a way that is acceptable and accessible to patients.

Who is organising and funding the research?
This project is being organised by University College London, in collaboration with Brighton and Sussex Medical School, and is funded by a grant from the National Institute for Health Research, Health Technology Assessment Programme

What do I do if I have any questions or complaints about the study?
If you are unhappy about any part of the study, please discuss your concerns with the research team using the contact details below. If you are still unhappy and wish to make a formal complaint you can contact the Patient Advice and Liaison Service (PALS): 02032145773; pals.cnwl@nhs.net.

Principal Investigator
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Study coordinator
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You will be given a copy of this information sheet and signed consent form for your records.
Thank you for your time.

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CONSENT FORM

Feasibility of sexual risk reduction interventions at sexual health services
Semi-structured Interview

This study has been reviewed by the Westminster National Research Ethics Service (NRES) Committee. Project ID: 15/LO/0690.

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 07/05/2015 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that my interview will be audio-recorded and I consent to the use of this material by the research team, possibly including verbatim quotes. ☐

4. I understand that information I provide for this study will be treated as strictly confidential and handled in accordance with the Data Protection Act 1998. I am assured that no personal identifying information will be kept which could link me to my responses. ☐

5. I understand that data collected during the study may be looked at by individuals from Public Health England, from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Santé: Feasibility of sexual risk reduction interventions at sexual health services

Patient Demographic Questionnaire:

Interview ID: _____

The basic demographic information below is for study monitoring purposes. All questions are optional. No identifiable information will be stored.

Age (in years):_____

Ethnicity (please tick/specify the ethnicity which describes you best):

White	British	
	Other	
Black	British	
	Other	
Asian:	British	
	Other	
Mixed		
Other (Specify):		

Sex:

Male	
Female	
Other (specify):	

Sexual orientation:

Heterosexual/Straight	
Gay/Lesbian	
Bisexual	
Other (Specify)	

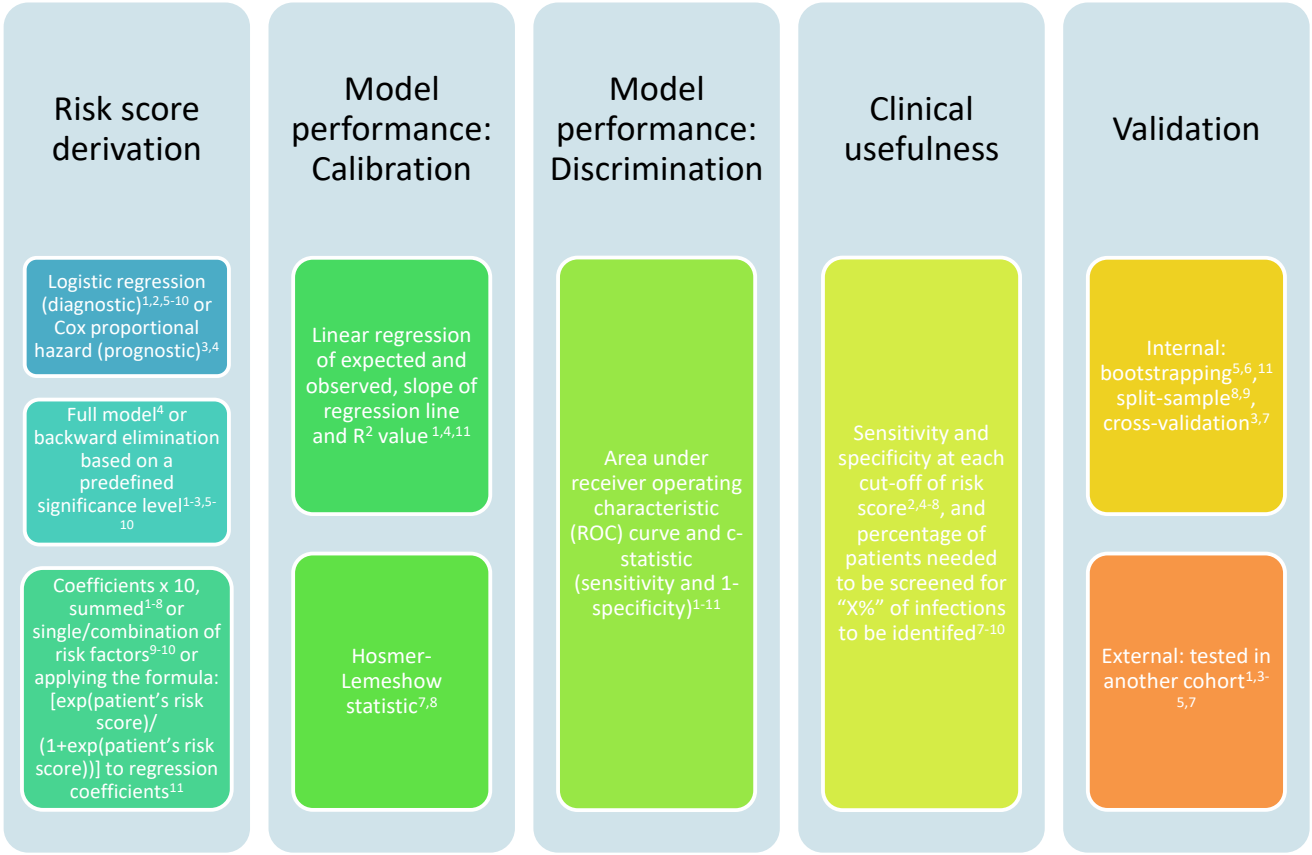
Appendix 7 Derivation and validation of risk prediction models: A review of the statistical steps

Relevant to 3 & 8

Based on research, I identified five important stages in the development and validation of risk prediction models. I included 13 articles that relate to the development of risk assessment tools to describe these five steps. Ten of these were papers specifically on HIV (n=7) and STIs (n=3). The remaining three papers gave an overview on risk prediction and the developmental steps (140;291;339). Of the seven HIV papers, three developed tools to identify acute HIV infection (269, 289, 291), two were prognostic tools to identify future risk of HIV among MSM (146, 268), one a tool to identify prevalent infection (288) and the final one a tool for HIV acquisition between serodiscordant couples (342).

The five standard statistical steps are summarised to give an overview of the development and validation of clinical risk prediction tools for HIV and STIs (Figure 10.1). The first step in the methodological framework is the derivation of a risk score. From the literature I identified two multivariable models to derive a risk assessment tool: logistic regression or cox proportional hazard. Logistic regression models were used by eight of the studies to develop diagnostic tools whereas cox proportional hazard models were employed for prognostic tools that determined future risk of HIV infection (146, 342). The methodologies used to arrive at the final model also differed between studies but broadly studies employed one of two methods: using a full model (146) or a predictor selection strategy (268-270, 288, 289, 291, 342-344). In the full model, all predictors included in the model remained in the final model whereas in the second method backward elimination was used to remove variables based on a predefined significance level.

Figure 10.1 Methodological steps used in risk prediction modelling



1. Haukoos JS **2**. Powers KA **3**. Kahle EM **4**. Menza TW **5**. Smith DK **6**. Al-Tayyib AA **7**. Falasinnu T **8**. Wand H **9**. Miller WC **10**. Facente SN **11**. Pavlou M

1-5 and 9-10 HIV related scores

Finally, once the models were run, the presentation of the risk score fell into three categories (Figure 10.1). A point-based scoring method was used where the β coefficients of the predictors in multivariable analyses were multiplied by five or ten, rounded to the nearest integer to allow easy addition and then summed to give an overall risk score for the individual. An example of this strategy is given in Figure 10.2, which has been taken from Menza *et al*. The table in this figure displays the results of the hazard model with the corresponding weights for each risk factor and the chart shows how the weights are then used to score individuals to predict their risk of HIV.

Figure 10.2 Multivariable prediction model and resulting scores

Variable	HR	*P*	β	β*10	Weight*
Full model					
Socio-demographic characteristics					
Nonwhite, non-API race/ethnicity	1.48	0.096	0.39	3.9	4
<40 yr of age	1.88	0.050	0.63	6.3	6
Sexually transmitted infection					
Diagnosis or history of bacterial sexually transmitted infection† at baseline	1.65	0.024	0.50	5.0	5
Substance use					
Methamphetamine or inhaled nitrites, prior 6 mo	3.00	<0.001	1.10	11.0	11
Sexual risk					
≥10 male sex partners, prior yr	1.47	0.096	0.39	3.9	4
Receptive nonconcordant unprotected anal sex, prior yr	1.09	0.711	0.09	0.9	1
Simple model					
Sexually transmitted infection					
Diagnosis or history of bacterial sexually transmitted infection† at baseline	1.57	0.039	0.45	4.5	4
Substance use					
Methamphetamine or inhaled nitrites, prior 6 mo	2.94	<0.001	1.07	10.7	11
Sexual risk					
≥10 male sex partners, prior yr	1.33	0.207	0.27	2.9	3
Nonconcordant unprotected anal sex, prior yr	1.16	0.536	0.14	1.4	1

*Weights are based on the coefficients (β) of the Cox proportional hazards regression. We calculated these weights by multiplying the model coefficient by 10 and rounding to the nearest whole integer. The weights rank the risk predictors in relative importance and dictate how one assigns integer point values for each risk predictor for a given individual. The assigned points are then summed to compute that individual's risk score.
†Gonorrhea, *Chlamydia*, early syphilis (primary, secondary, early latent).

Does your patient/client have gonorrhea, chlamydia, or syphilis, or does he have a history of these infections?	If yes, add 4 points If no, add 0 points	_____
Has your patient/client used methamphetamine or inhaled nitrites (poppers) in the prior 6 months?	If yes, add 11 points If no, add 0 points	_____
Does your patient/client report unprotected anal intercourse with a partner of positive or unknown HIV status in the prior year?	If yes, add 1 point If no, add 0 points	_____
Does your patient/client report 10 or more male sexual partners in the prior year?	If yes, add 3 points If no, add 0 points	_____
	Sum total number of points	_____ Total Points

Total Points	Estimated percentage of men with this score who will acquire HIV over 4 years
0	<5%
1-3	5%-9%
4-11	10%-14%
12+	>14%

How to use the chart

1. Calculate your patient's/client's risk score.
2. Match the risk score with the point range provided on the table to estimate 4-year HIV risk.
3. Follow up with testing recommendations, referrals to services, and prevention intervention according to risk.

An alternative strategy was to use either single or a combination of predictors that had not been weighted. For example, Miller *et al* identified five predictors for HIV infection and used the presence of any one of the five as the predictive criteria for screening for acute HIV infection. The final method used was based on the regression coefficients and was the most statistically accurate method (293). The probability of the outcome was assessed by taking the exponential of the log odds to derive odds for covariates. These odds were then used to calculate an individual's probability of being infected with HIV at the attendance. The calculations can be represented in three formulas:

1. *Log odds of HIV = regression equation [intercept + (variable value x coefficient) + all additional (variable values x coefficients)]*

2. *Odds of HIV = $e^{(patient's\ log\ odds\ value)}$*

3. *Probability of being infected with HIV = [Odds / (1 + Odds)] x 100*

Prior to running the model, some studies also considered and discussed certain aspects of data management. As is often the case datasets are not complete, and have missing values. There are numerous ways that missing data can be dealt with; the most popularly advocated is MI. When data are missing at random, MI can be an appropriate method to preserve the sample size and reduce the bias in outputs that can arise when conducting complete case analysis (i.e. excluding individuals with missing information). Briefly, MI is a technique in which missing values are replaced with simulated versions. Each of the simulated complete datasets is combined to produce estimates and confidence intervals that take the missing data into account. MI with 5 imputations using the Sequential Regression Imputation Method was described (270). Excluding individuals with missing demographic information where the level of missing data was low has also been reported (344). The issue of incomplete data was however not frequently mentioned in the examined literature.

A second consideration is dealing with continuous variables, for example, age. Two studies did not discuss continuous variables (146, 289), six either stated categorising continuous variables in the methods section or presented categorised results, and two studies used statistical methods to identify the best cut-offs to create categorised variables: fractional polynomials (288) and signal detection ROC analysis (342).

Once the model was derived, the next step was to assess the performance of the model through calibration and discrimination. Calibration tests the extent to which risk predicted by the model reflects the risk observed in the population. It was less well reported than other steps of the statistical process. The calibration of

the Denver HIV Risk score (DHRS), which was developed to help inform routine HIV screening in emergency departments in the US (288) was assessed by plotting the observed HIV prevalence against the predicted prevalence and calculating the slope of the line and the goodness of fit of the model using the R^2. A R^2 of 1 indicates perfect calibration. Other methods to assess calibration included goodness-of-fit tests such as the Hosmer-Lemeshow test (270, 344). The test assesses how well the model fits the data by dividing individuals into groups based on their predicted probabilities of having an infection and then calculating within each group the expected number and the number of positive and negative individuals. These figures are compared with the observed data and Pearson chi-squared statistic is used to test for differences. Significant p values (<0.05) would not suggest good calibration.

Discrimination determines how well a model can discriminate those with the outcome from those without the outcome. The discriminatory power of a model can be assessed by calculating the area under the curve (AUC) and providing the concordance (c) statistic, which was presented by all 10 studies. The area was between 0.7-0.8 for the majority of studies; a perfect model would have an area of 1 whereas a value of 0.5 suggests the model has no discriminatory power. Often, studies also plotted receiver operator characteristic curves of the sensitivity (true positive rate) against 1-specificity (false-positive rate) to visually present the relationship between the two at different cut-offs for the probability of an outcome (268, 270, 288).

Clinical usefulness is an important step during the development of a model and is dependent on both discrimination and calibration. A clinically useful model will allow better decisions to be made with the model than without. The role of a

number of the HIV and STI clinical prediction tools was to reduce the number of people tested for any given outcome (e.g. (269, 270, 291)). These selective screening decision making models were created to set a cut-off to determine the percentage of the population that would be needed to identify an acceptable proportion of cases. Falasinnu *et al* (270) identified that with a risk score of six or more, 68% of the population would need to be screened to identify 91% of chlamydia/gonorrhoea cases.

Once model performance has been established, it is then important to validate the model; internally and externally. Validation is required to correct for overfitting and optimism in model performance, which occurs because the model performs optimistically on the study sample from which it was developed compared with performance in a different set of individuals (345). Internal validity relates to the stability of the selected predictors and the quality of the predictions. The literature review highlighted three commonly used methods: bootstrapping, split-sample and cross-validation. Bootstrapping removes one patient from the sample, generates the tool using the remainder of the patients, and then tests it on the patient that was removed. The procedure is repeated in sequence for every patient being studied. Cross-validation partitions the dataset into sub-sets and the derivation occurs on one subset while validation is performed on the other subset. Multiple rounds of cross-validation are used with different partitions and the results are averaged. In both these methods samples are drawn with replacement from the development sample. During split sampling, a random sample of the population is used for the model development and the remaining is used for validation.

External validation determines the generalisability of the model in another related population and is a stronger test than internal validation. In the literature review, five studies undertook external validation and the types of validation included in these studies were: temporal where the model is tested on a more recent population (270), geographic where the model is tested in other hospitals/clinics (288, 342) or strong external where the model is tested in a fully different setting (146, 268, 342).

In summary, risk prediction modelling includes five steps that begin with model development and end with validation. These steps formed the framework for the development of a risk tool for HIV and high risk STIs.

Appendix 8 Item non-response analyses

Relevant to Chapter 6

The analysis indicates that missing data was related to country of birth and ethnicity, clinic of attendance and sexual behavioural variables (Table 10.3). Men who completed the question on numbers of CRAI partners also completed the same question for CIAI (94%) and men who did not complete CRAI partners also did not complete CIAI partners (87%). The majority of men who completed the question on CRAI/CIAI also completed the sub-questions on the HIV status of the partner.

Table 10.3 Comparison of MSM who completed the question on numbers of condomless anal intercourse partners with non-completers by demographic, clinical and behavioural variables

Characteristic	Condomless receptive anal intercourse			Condomless insertive anal intercourse		
	Completer (%)	Non-completer (%)	P value	Completer (%)	Non-completer (%)	P value
Age group			0.02			0.06
15-24	240 (22)	34 (20)		233 (22)	41 (19)	
25-34	483 (44)	63 (36)		461 (43)	85 (40)	
35-49	312 (28)	55 (32)		304 (29)	63 (30)	
50+	70 (6.3)	21 (12)		67 (6.2)	24 (11)	
Ethnicity and birthplace			0.574			0.150
White UK-born	609 (55)	108 (62)		580 (54)	137 (64)	
White European	208 (19)	25 (14)		203 (19)	30 (14)	
White non-European	95 (8.6)	15 (8.7)		96 (9.0)	14 (6.6)	
Non-white UK-born	68 (6.2)	9 (5.2)		65 (6.1)	12 (5.6)	
Non-white born abroad	104 (9.4)	13 (7.5)		99 (9.3)	18 (8.5)	
Other/Unknown	21 (1.9)	3 (1.7)		22 (2.1)	2 (0.9)	
Attendance at clinic			<0.001			<0.001
Outside London	465 (42)	133 (77)		435 (41)	163 (77)	
London	640 (58)	40 (23)		630 (59)	50 (23)	

Table 10.3 continued

Characteristic	Condomless receptive anal intercourse			Condomless insertive anal intercourse		
	Completer (%)	Non-completer (%)	P value	Completer (%)	Non-completer (%)	P value
Acute STI previous year			0.666			0.877
No	323 (29)	45 (26)		307 (29)	61 (29)	
Yes	182 (16)	31 (18)		175 (16)	38 (18)	
Did not attend	600 (54)	97 (56)		583 (55)	114 (54)	
Completed numbers of CIAI*/CRAI partners[$]**			<0.001			<0.001
No	62 (5.6)	151 (87)		22 (2.1)	151 (71)	
Yes	1,043 (94)	22 (13)		1,043 (98)	62 (29)	
Completed numbers of CRAI/CIAI* partners positive[§]**			<0.001			<0.001
No	46 (4.2)	56 (32)		58 (5.5)	74 (35)	
Yes	1,059 (96)	117 (68)		1,007 (95)	139 (65)	
Completed numbers of CRAI/CIAI* partners unknown[§]**			<0.001			<0.001
No	50 (4.5)	83 (47)		54 (5.1)	95 (45)	
Yes	1,065 (96)	93 (53)		1,011 (95)	118 (55)	
Partner numbers			<0.001			<0.001
0	39 (3.5)	0		39 (3.7)	0	
1	268 (24)	9 (5.2)		261 (25)	16 (7.5)	
2-4	463 (42)	52 (30)		435 (41)	80 (38)	
>4	323 (29)	96 (55)		319 (30)	100 (47)	
Unknown	12 (1.1)	16 (9.3)		11 (1.0)	17 (8.0)	
CIAI*/CRAI partners[$]**			<0.001			<0.001
0	620 (56)	9 (5.2)		680 (64)	28 (13)	
1	275 (25)	3 (1.7)		258 (24)	27 (13)	
2-4	109 (9.9)	4 (2.3)		82 (7.7)	5 (2.4)	
>4	39 (3.5)	6 (3.5)		23 (2.2)	2 (0.9)	
Unknown	62 (5.6)	151 (87)		22 (2.1)	151 (71)	
Total	**1,105 (100)**	**173 (100)**		**1,065 (100)**	**213 (100)**	

*condomless insertive anal intercourse (CIAI)
**condomless receptive anal intercourse (CRAI)

[$] Completion of CIAI and numbers of CIAI partners compared between MSM who completed the question on CRAI and those who did not. Completion of CRAI and numbers of CRAI partners compared between MSM who completed the question on CIAI and those who did not.
[§] Completion of CRAI partners of positive or unknown status compared between MSM who completed the question on CRAI and those who did not. Completion of CIAI partners of positive or unknown status compared between MSM who completed the question on CIAI and those who did not.

Where completed, numbers of partners men engaged in CIAI with and age were associated with numbers of CRAI partners (Table 10.4). With increasing numbers of CIAI partners men were also more likely to report more CRAI partners. This relationship was less evident at highest levels of partner numbers.

Table 10.4 Factors associated with numbers of CRAI partners

Characteristic	Relative risk ratio (95%CI)	P value
0 CRAI partners	**Base outcome**	
1 CRAI partner:		
Age	0.986 (0.969-1.002)	0.094
CIAI partners		
1	6.3 (4.5-8.8)	<0.001
2-4	2.3 (1.3-4.0)	0.004
>4	1.9 (0.7-5.5)	0.214
2-4 CRAI partners:		
Age	0.948 (0.918-0.979)	0.001
CIAI partners		
1	2.9 (1.4-5.8)	0.004
2-4	23.0 (12.4-42.8)	<0.001
>4	13.1 (4.5-38.5)	<0.001
>4 CRAI partners:		
Age	0.969 (0.923-1.018)	0.210
CIAI partners		
1	1.2 (0.2-5.7)	0.843
2-4	1.5 (0.2-12.8)	0.691
>4	73.0 (24.3-219.2)	<0.001

A similar association was also observed for numbers of CIAI partners (Table 10.5). However, a further two variables were also associated with CIAI partners. Broadly, men of non-white European ethnic groups were more likely to report CIAI partners. For example, non-white UK born men were more likely to report 2-4 (RRR: 3.2) and more than 4 (RRR: 4.3) partners than white UK born men.

Table 10.5 Factors associated with numbers of CIAI partners

Characteristic	Relative risk ratio (95%CI)	P value
0 CIAI partners outcome	**Base**	
1 CIAI partner:		
Age	0.984 (0.967-1.002)	0.094
Attendance London clinic	1.7 (1.2-2.4)	0.002
Ethnicity and birthplace		
White UK-born	1	
White European	0.7 (0.6-1.3)	0.528
White non-European	2.2 (1.3-3.7)	0.006
Non-white UK-born	1.5 (0.7-2.9)	0.278
Non-white born abroad	1.3 (0.7-2.2)	0.404
CRAI partners		
1	6.2 (4.4-8.8)	<0.001
2-4	2.7 (1.3-5.6)	0.009
>4	1.0 (0.2-5.1)	0.969
2-4 CIAI partner:		
Age	1.006 (0.980-1.032)	0.663
Attendance London clinic	1.7 (1.0-2.8)	0.042
Ethnicity and birthplace		
White UK-born	1	
White European	1.2 (0.6-2.2)	0.603
White non-European	1.8 (0.8-4.2)	0.153
Non-white UK-born	3.2 (1.4-7.3)	0.005
Non-white born abroad	2.3 (1.1-4.7)	0.020
CRAI partners		
1	2.4 (1.3-4.2)	0.003
2-4	22.0 (11.6-41.5)	<0.001
>4	1.5 (0.2-4.7)	0.723
>4 CIAI partner:		
Age	1.067 (1.027-1.108)	0.001
Attendance London clinic	1.9 (0.8-4.5)	0.149
Ethnicity and birthplace		
White UK-born	1	
White European	1.8	0.265
White non-European	1.3	0.769
Non-white UK-born	4.3	0.035
Non-white born abroad	2.6	0.143
CRAI partners		
1	2.1 (0.7-5.9)	0.181
2-4	10.9 (3.4-34.5)	<0.001
>4	77.2 (24.3-245.0)	<0.001

Appendix 9 Thesis outputs

Peer-reviewed publications

Desai S, Nardone A, Hughes G, Delpech V, Burns, F, Hart G, ON Gill. HIV incidence in an open national cohort of men who have sex with men attending sexually transmitted infection clinics in England. ***HIV medicine*** 2017 Jan; doi: 10.1111/hiv.12498

Articles submitted to peer-reviewed journals

Desai S, Burns F, Schembri G, Williams D, Sullivan A, McOwan A, Antonucci S, Mercey D, Hughes G, Hart G, Gill ON, Nardone A. Sexual behaviours and STI outcomes in a cohort of HIV negative MSM attending genitourinary medicine clinics in England. ***Int J STD AIDS, in press***

Desai S, King C, Roy A, Burns F, Nardone A, Gilson R, Shahmanesh M, Llewellyn C. What factors do HIV negative MSM consider when evaluating their HIV risk? A qualitative analysis. ***Sex Transm Infect***

Conference presentations

Desai S, Nardone A, Hughes G, Delpech V, Burns, F, Hart G, ON Gill. HIV incidence among MSM attending GUM clinics England, 2009. Oral Presentation. British Association for Sexual Health and HIV (BASHH). 2012. Brighton, UK

Desai S, Nardone A, Hughes G, Delpech V, Burns, F, Hart G, ON Gill. HIV incidence among MSM attending GUM clinics England, 2009. Oral Presentation. Health Protection Conference. 2012. Warwick, UK.

Desai S, Nardone A, Hughes G, Delpech V, Burns, F, Hart G, ON Gill. HIV seroconversion in an open national cohort of MSM attending STI clinics in England – Implications for prevention. Poster Presentation. Conference on Retroviruses and Opportunistic Infections (CROI). 2012. Seattle, US.

Desai S, Nardone A, Hughes G, Delpech V, Burns, F, Hart G, ON Gill. HIV incidence in the open cohort of 38,000 MSM attendees of Sexually Transmitted Infection clinics across England: 2008-2011. Conference on Retroviruses and Opportunistic Infections (CROI). Poster Presentation. 2013. Atlanta, US.

Desai S, Burns F, Hughes G, Hart G, Sullivan A, Schembri G, Williams D, Antonucci S, McCormack S, McOwan A, Mercey D, Gill ON, Nardone A. High rates of STIs and HIV among men who have sex with men reporting seroadaptive behaviours, England, 2012/13. 2014. Third Joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH), Liverpool, UK.