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Abstract

Human immunodeficiency virus prevention and testing strategies among men who have sex with men in the UK: the PANTHEON research programme including the SELPHI RCT

Janey Sewell[1], Charlie Witzel[2], David Dunn[3], Fiona Lampe[1], Fiona Burns[1], Peter Weatherburn[2], Sheena McCormack[3], Leanne McCabe[3], Alec Miners[2], Valentina Cambiano[1], Roger Pebody[4], Roy Trevelion[4], Nadia Hanum[1], Andrew Phillips[1] and Alison Rodger[1*]

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Background: Rates of human immunodeficiency virus diagnoses in United Kingdom men who have sex with men were at a 10-year high in 2014; many recent infections indicated ongoing transmission. There was a need to increase testing rates, reduce late diagnosis and understand how to best allocate human immunodeficiency virus prevention resources.

Objective: We aimed to assess (1) the feasibility of human immunodeficiency virus self-testing among men who have sex with men, (2) whether the offer of free human immunodeficiency virus self-testing resulted in earlier diagnosis of human immunodeficiency virus in an online randomised controlled trial, (3) the cost-effectiveness of strategies for preventing human immunodeficiency virus in men who have sex with men, including free human immunodeficiency virus self-testing.

Design:

1. We produced a systematic evidence map and conducted focus groups and interviews with men who have sex with men and relevant stakeholders to identify barriers and facilitators to human immunodeficiency virus self-testing.
2. We conducted an internet-based randomised controlled trial (a human immunodeficiency virus Self-testing Public Health Intervention to assess whether free human immunodeficiency virus self-testing with reminders results in earlier diagnosis of human immunodeficiency virus compared with standard of care.
3. We evaluated the cost-effectiveness of human immunodeficiency virus prevention strategies in men who have sex with men in the United Kingdom using a simulation model.

Data sources: Databases included MEDLINE, EMBASE, Global Health, Social Policy and Practice, PsycInfo, Health Management Information Consortium, EBSCO CINAHL Plus, Cochrane Library and Web of Science.

Review methods: Searches combined key terms relating to human immunodeficiency virus with terms related to self-testing. Data were manually extracted through a standard form and then entered into an open-access relational map (HIVST.org).

Setting: Internet-based study conducted in England and Wales.

Participants: Participants were men (including *trans* men) and *trans* women aged ≥ 16 years old, resident in England or Wales, and not known to be human immunodeficiency virus-positive, who had ever had anal sex with a man. The qualitative work also included human immunodeficiency virus service providers and commissioners.

Intervention: At baseline participants were randomised (randomisation A) to the offer of a single, free baseline human immunodeficiency virus self-test versus no free human immunodeficiency virus self-test (no baseline test). At 3 months, eligible participants from the baseline test group were randomised (randomisation B) to regular offers of free human immunodeficiency virus self-testing every 3 months for up to 24 months (regular test) versus no offer of free self-tests (no regular test).

Main outcome measure: The primary outcome for randomisation A was a confirmed new human immunodeficiency virus diagnosis within 3 months of randomisation (detection of prevalent infections, binary outcome). The primary outcome for randomisation B was the time from randomisation to a confirmed new human immunodeficiency virus diagnosis (detection of incident infections, time-to-event outcome).

Results: Focus groups (n = 47 men who have sex with men) and interviews (n = 18 key informants) showed that human immunodeficiency virus self-testing was a highly acceptable intervention for men who have sex with men, with potential to reduce barriers related to convenience, stigma and privacy.

The Self-testing Public Health Intervention randomised controlled trial randomised 10,135 men who have sex with men and *trans* women 3 : 2 to baseline test or no baseline test. There was no significant difference at 3 months in confirmed new human immunodeficiency virus diagnoses [p = 0.64, 19/6049 (0.3%) in baseline test vs. 15/4062 (0.4%) in no beseline test], but human immunodeficiency virus testing rates were higher in baseline test. Following the second randomisation (n = 2308) to regular test versus no regular test there was no significant difference between groups in confirmed human immunodeficiency virus diagnoses although there was a substantial increase in testing rate in regular test versus no regular test with no reduction in sexually transmitted infection testing.

Modelling suggested that provision of oral tenofovir/emtricitabine pre-exposure prophylaxis increased human immunodeficiency virus testing, with anti-retroviral therapy initiation at diagnosis, and reductions in the level of condom-less sex, that each played an important role in decreasing human immunodeficiency virus incidence among men who have sex with men, and that the current human immunodeficiency virus incidence would have been double what it is if any one of them had not occurred. A combined substantial increase in human immunodeficiency virus testing and pre-exposure prophylaxis could avert 34% of infections. However, at the current cost-effectiveness threshold, a 16% reduction in the cost of delivery of testing and pre-exposure prophylaxis would be required for this scenario to offer value for money.

Limitations: The decline in human immunodeficiency virus incidence over the study period resulted in under-powering of the trial. However, we recruited a large number of men at risk of human immunodeficiency virus. A further limitation of the study is the low (but typical) completion rates of surveys, which may have introduced bias into the analysis of the secondary end points, although not the primary end point. Finally, the majority of the participants were white gay men, which may make our results less generalisable.

Conclusions: Human immunodeficiency virus self-testing is highly acceptable to men who have sex with men with potential to increase first and repeat human immunodeficiency virus testing and broaden testing options, particularly in among key sub-populations at risk of human immunodeficiency virus. The trial did not demonstrate that self-testing increased human immunodeficiency virus diagnoses linked to care, but was underpowered to do so.

Future work: Future research includes investigating the role of marginalisation based on ethnicity, migration status, sexual orientation and education in making testing decisions, and how social exclusion and health inequalities shape engagement with human immunodeficiency virus self-testing.

Study registration: This study is registered as ISRCTN20312003.

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List of abbreviations

ART	antiretroviral treatment
AURAH2	Attitudes to and Understanding Risk of Acquisition of HIV
BT	baseline test
CAG	Community Advisory Group
CAI	condom-less anal intercourse
CAS	condom-less anal sex
CD4	cluster of differentiation 4
CLS	condom-less sex
CMG	Core Management Group
COM-B	capability, opportunity, motivation, behaviour
DoH	Department of Health
EPR	electronic patient record
FGD	focus-group discussion
FSW	female sex workers
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GUM	genito-urinary medicine
HARS	National HIV and AIDS reporting system
HIV	human immunodeficiency virus
HIVSS	HIV self-sampling
HIVST	HIV self-testing
HIVSTI	HIV and STI
IPV	intimate partner violence
IRR	incidence rate ratio
MSM	men who have sex with men
NAM	National AIDS Map
nBT	no baseline test
NIHR	National Institute for Health and Care Research
nRT	no regular test
PE	process evaluation
PEP	post-exposure prophylaxis
PI	principal investigator
PLWH	person living with HIV
PPI	patient and public involvement
PrEP	pre-exposure prophylaxis
PROUD	pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection
PY	person years
RCT	randomised controlled trial
RT	regular test
SELPHI	a HIV Self-testing Public Health Intervention
STI	sexually transmitted infection
TMG	Trial Management Group
UKHSA	United Kingdom Health Security Agency
WHO	World Health Organization
WS	workstream

Plain language summary

Background

In 2014, new human immunodeficiency virus diagnoses among gay men in the United Kingdom were increasing year on year. New ways of testing for human immunodeficiency virus, such as self-testing (whereby a person can do the test themselves without a health worker there and then read the result within 15 minutes) had been developed, but it was not known whether offering self-testing would increase the number of new human immunodeficiency virus diagnoses in gay men.

Methods

We did an internet trial to see whether giving gay men a free human immunodeficiency virus self-testing kit would increase the number diagnosed with human immunodeficiency virus compared to not being given a free human immunodeficiency virus self-testing kit. We also looked at whether regular provision of human immunodeficiency virus self-testing kits every 3 months over a 2-year period would allow a more prompt diagnosis among those who got a new human immunodeficiency virus infection. Finally, we looked at value for money of providing free human immunodeficiency virus self-testing and other interventions including pre-exposure prophylaxis and early human immunodeficiency virus treatment (at the point of diagnosis), to prevent human immunodeficiency virus infection.

Results

The ease and privacy of human immunodeficiency virus self-testing meant that it was an acceptable way of testing for men who have sex with men. Over 10,000 men who have sex with men and *trans* people took part in the trial but there was no difference after 3 months in the number of gay men who were newly diagnosed with human immunodeficiency virus who had been provided with a free self-test kit compared to the group that had not.

We found that a combination of human immunodeficiency virus-prevention interventions including an increase in human immunodeficiency virus testing, pre-exposure prophylaxis, early human immunodeficiency virus treatment at the point of diagnosis, and a reduction in the levels of condom-less sex each played an important role in decreasing human immunodeficiency virus incidence among men who have sex with men.

Conclusions

Human immunodeficiency virus self-testing was acceptable to men who have sex with men. Although human immunodeficiency virus self-testing increased how often men who have sex with men tested, it did not increase human immunodeficiency virus diagnosis.

Scientific summary

Background

In 2014, the number of newly human immunodeficiency virus (HIV) diagnosed men who have sex with men (MSM) was at an all-time high and the 3000 new infections/year were a significant cost to the NHS, accruing £1 billion in future costs every year. Approximately 25% of all HIV-positive MSM were unaware of their infection and disproportionately contributed to onward transmission (between 60% and 80% of transmissions) and late presentations, with greatly increased risk of death. Uptake and frequency of HIV testing among MSM in 2014 was low. Innovative strategies, such as HIV self-testing (HIVST), which, due to associated confidentiality and convenience, could increase initial and repeat testing rates and diagnosis, had not been evaluated. It was also unclear whether other HIV prevention initiatives in addition to self-testing could offer value for money. In practice, assessing the cost-effectiveness of a range of prevention interventions required modelling.

Aims and objectives

Our aim was to assess the acceptability, effectiveness and cost-effectiveness of HIVST, and to examine the best economic value of a wider set of HIV prevention initiatives.

Main research questions

For MSM in the UK:

1. Does provision of free HIVST result in the earlier diagnosis of HIV infection?
2. Which HIV prevention initiatives are most cost-effective?

Specific objectives

Workstream 1: feasibility

- To identify the most up-to-date evidence of HIVST among MSM (systematic review and systematic mapping process).
- To increase understanding of accessibility and feasibility of HIVST among MSM and identify barriers and facilitators to HIVST in a range of models and contexts (focus groups and interviews).
- To explore how those utilising self-tests experience HIVST and the implications for further intervention development and scale-up.
- To explore how the HIV Self-testing Public Health Intervention (SELPHI) intervention might be experienced by and the pathways to impact on behaviour for different groups of randomised controlled trial (RCT) participants.
- To develop and undertake a process evaluation to assess what worked well about the RCT intervention and for whom.

Workstream 2: intervention

- To assess whether free self-testing for HIV with reminders to test results in earlier diagnosis of HIV infection compared with standard of care through an internet-based, randomised trial (SELPHI).

- To explore testing pathways, practices, effects and perspectives on self-testing through qualitative interviews, including in key groups (Asian, black and Latin American MSM and *trans* people).

Workstream 3: modelling and economic evaluation

- To estimate HIV incidence and predictors and describe risk behaviours in HIV-negative MSM at the time of HIV infection and after diagnosis through a web-based longitudinal cohort study to provide key parameters for the cost-effectiveness model.
- To identify efficacious existing HIV prevention strategies in MSM from high-income countries (systematic review).
- To estimate the cost of health care for people diagnosed with HIV living in England and Wales.
- To model the cost-effectiveness of HIV prevention strategies, including HIV testing interventions, using a simulation model to determine the cost-effectiveness (from an NHS perspective with outcomes as quality-adjusted life-years) of strategies for preventing HIV transmission, alone and in combination.

Methods

We divided the programme into three workstreams that were undertaken between 2015 and 2021.

Workstream 1: feasibility

Study 1A: we conducted a systematic mapping process from which the outputs were used to populate the HIV self-testing and research policy hub website HIVST.org. We collaborated with the World Health Organization (WHO) on four systematic reviews to provide the foundation for the updated WHO Global Guidelines on HIVST, which was launched in December 2019.

Study 1B: we undertook six focus-group discussions (FGDs) with MSM to increase understanding of accessibility and feasibility of HIV self-testing among MSM and identify barriers and facilitators in a range of models and contexts to inform development of the intervention.

Eighteen key informant interviews were conducted with service providers and commissioners to explore similar themes as the MSM FGD.

Study 1C: development of manual and materials to promote and support the interventions in the RCT and RCT study website design.

Study 1D: we undertook a process evaluation to examine the implementation of the planned intervention in the SELPHI RCT. The process evaluation explored the mechanisms of impact, and contextual factors that affect impact and potential normalisation of the intervention with the target population.

Workstream 2: intervention

Study 2A: building on the work from workstream (WS) 1 to inform the design of the trial and intervention, we undertook a RCT to assess whether offering free HIVST kits via the internet increased the rate of HIV diagnosis in MSM and *trans* people with linkage to clinical care. The trial aimed to enrol 10,000 HIV-negative participants, age > 16 years, resident in England or Wales, who were willing to provide name, date of birth and a valid e-mail address and who gave consent to linkage with surveillance and clinical databases. Online advertising was used to recruit men potentially interested in HIVST through the geo-location social-sexual networking applications (apps) (Grindr, Growlr, Scruff and Hornet) as well as targeted Facebook advertising.

In a two-stage randomisation process, participants were first randomised (3 : 2) to receive a free baseline HIVST or no free baseline HIVST (randomisation A). At 3 months, participants allocated to

receive a baseline HIVST were subsequently randomised (1 : 1) to receive the offer of regular (every 3 months) free HIVST, with testing reminders, versus no such offer (randomisation B) if they met further eligibility criteria. The primary outcome for randomisation A was a confirmed new HIV diagnosis within 3 months of randomisation (detection of prevalent infections, binary outcome). The primary outcome for randomisation B was the time from randomisation to a confirmed new HIV diagnosis (detection of incident infections, time-to-event outcome). The primary analyses compared the randomised groups as allocated (intention to treat). New HIV diagnoses were principally identified through linkage to national HIV surveillance databases maintained by the UK Health Security Agency (UKHSA). During the pilot phase, we conducted a mixed-methods study to assess trial feasibility and intervention acceptability using quantitative data from advertising sources and RCT surveys alongside qualitative data from a nested substudy.

Study 2B: as part of the extensive qualitative work in WS2, we conducted a series of face-to-face and remote interviews with MSM and *trans* people participating in SELPHI (from both intervention arms) to examine experiences of those utilising HIVST and the implications for further intervention development and scale-up. We focused on interviewing specific groups of participants who may have unique experiences with HIVST, including *trans* people, and MSM from Asian, black and Latin American backgrounds and a small group of MSM who reported harm from the study.

Workstream 3: modelling and economic evaluation

Study 3A: we conducted a 3-year web-based longitudinal prospective cohort study in MSM, the Attitudes to and UnderstandingRisk of Acquisition of HIV (AURAH2) study, which used 4-monthly online questionnaires to collect information on HIV status, HIV testing history, recent sexual behaviour, health and lifestyle factors and sexually transmitted infection (STI) diagnoses from 2015 to 2018. We linked all AURAH2 study participants data to the national HIV surveillance database managed by UKHSA (previously called Public Health England till October 2021).

Study 3B: to inform the cost-effectiveness modelling, we undertook a systematic review of HIV prevention strategies for MSM among high-income settings using published studies from 2012 up until 2021. The systematic review identified and described studies evaluating the efficacy or effectiveness of behavioural HIV-prevention interventions for reducing HIV incidence among MSM in high-income countries.

Study 3C: to better understand the cost-effectiveness of preventing HIV infection, we estimated the healthcare costs of people diagnosed with HIV living in England and Wales using data from a large English HIV treatment centre's electronic patient record system which was combined with National Reference Costs for England to estimate the frequency of hospital attendances (including inpatient episodes, day-case visits and outpatient visits) and costs.

Study 3D: finally we developed an existing individual-based stochastic model that simulates the UK population of MSM from the start of the epidemic, tracking detailed levels of condom-less anal sex with long-term and casual partners and hence risk of HIV acquisition. The Synthesis model was calibrated using longitudinal patterns of condom-less sex, particularly around the time of HIV infection, changes in risk behaviour as a result of receiving a diagnosis of HIV in MSM, and the proportion of men likely to have been infected by a long-term partner, so that the cost-effectiveness of all relevant prevention activities could be estimated.

Results

Workstream 1: feasibility

The systematic map consolidated all emerging evidence related to HIVST and populated HIVST.org by systematically searching databases and the abstracts of five conferences from 2006, with monthly

automated database searches until June 2019. We conducted four systematic reviews using the results from the systematic map to identify eligible studies for each review. The main review was a meta-analysis of RCT data relating to key populations that compared the effects of HIVST with standard HIV testing. It demonstrated that HIVST was safe and increased testing uptake, frequency and yield of positive results for MSM and *trans* people without negative effects on linkage to HIV care, STI testing, condom use or social harm for MSM and *trans* people.

The FGDs showed that HIVST was a widely acceptable intervention. MSM reported that HIVST reduced barriers related to convenience, stigma and privacy concerns and that HIVST facilitated more frequent testing, with the potential to reduce STI screening frequency. Interviews with key informants demonstrated the value of the increased choice that HIVST provides but highlighted the need to provide direct pathways into standard testing services and HIV care.

Workstream 2: intervention

An internet-based, open-label, randomised trial was developed informed by the feasibility work in WS1. The mixed-methods study evaluating the pilot phase of the RCT demonstrated that recruiting to the RCT was feasible, that the intervention was acceptable to participants and the kit had high reported usability.

In total 10,111 men were randomized, 6049 to a free HIV self-test at baseline (BT), and 4062 to no baseline test (nBT). Results from randomisation A demonstrated that of those randomised to a free HIV self-test at baseline, 73.5% reported using the HIVST kit. There were 34 new HIV diagnoses across both arms of the study (19 in BT and 15 in nBT) and, of those newly diagnosed, a large proportion had not tested for HIV in the previous 12 months. There was no significant difference between arms at 3 months in confirmed new HIV diagnoses that had linked to care (the primary outcome of the trial). Participants randomised to BT were more likely to self-report testing for HIV in the 3 months after enrolment than nBT [BT 4368/4511 (97%) vs. nBT 670/1574 (43%)].

In randomisation B, 2308 men were randomised, 1161 to the offer of regular (3-monthly) HIVST [regular test (RT)] and 1147 to no regular HIVST offer (nRT). Men in RT were much more likely to HIV test in each 3-month period compared with men in nRT. As expected, survey completion rates decreased over time and ranged from 47% to 4%. However, there was no significant difference in confirmed HIV diagnoses between arms [RT 10/1161 (0.9%) vs. nRT 8/1147 (0.7%)]. There were also no statistical differences in STI testing, STI diagnoses, or reported CAI between the groups.

HIVST facilitated more frequent testing, with the potential to reduce STI screening frequency.

Our mixed-methods substudy which interviewed *trans* people, and also used trial data, demonstrated that HIVST increased testing uptake and frequency by three times compared with standard care. *Trans* people reported HIVST benefits included increased autonomy, privacy, convenience and the avoidance of healthcare providers perceived to be discriminatory and services that increased gender dysphoria. The study of Asian, black and Latin American MSM showed that these groups were often excluded from lesbian gay bisexual trans queer + social environments because of their ethnicity. This had a potential downstream impact constraining the development of testing norms drawn from community and society. In addition, MSM from ethnic minority backgrounds sometimes had difficulty accessing bricks-and-mortar sexual health services, which HIVST mitigated.

The study of harms arising in the RCT found that these were very uncommon (reported by 1–2%). Harms were transient and most resolved without requiring intervention.

Workstream 3: modelling and economic evaluation

The AURAH2 study recruited 1167 MSM into the baseline study, of whom 622 joined the online component and were followed up over 3 years. In line with national data, the study demonstrated that

there had been a substantial decline in HIV incidence among MSM over the study period and that factors associated with incident HIV were injecting drug use, chemsex and high-risk sexual behaviour. Results from the study also showed that pre-exposure prophylaxis (PrEP) awareness and use increased substantially over the study period.

The systematic review of HIV prevention strategies among MSM in high-income countries identified 36 original papers, which were included in the review. Overall, PrEP was identified as the most effective intervention for reducing HIV incidence.

The cost of caring for people with diagnosed HIV infection using routinely collected data in combination with information on national unit costs was estimated to be £522 per quarter, excluding the costs of antiretroviral treatment. Outpatient visits accounted for most of the hospital activity, and for total costs. A higher quarterly cost was associated with being a new patient and having a low cluster of differentiation 4 count category, followed by current viral non-suppression or previous virological failure.

Results from the model-based economic evaluation showed that combination prevention, including a PrEP strategy, played a major role in the reduction in HIV incidence observed so far in the UK among MSM. Continuation of current activities may allow achievement of virtual HIV elimination among MSM in the UK and our modelling suggests they are likely to be cost-effective activities according to standard UK norms.

Future steps

Further work should aim to support the roll-out of HIVST at a national level to help address inequalities in access to HIV testing services that are experienced in particular by marginalised groups of MSM.

Conclusion

Human immunodeficiency virus self-testing is an acceptable and feasible HIV prevention tool for MSM and *trans* people. Although HIVST broadens the options for testing, and increases testing regularity, the trial results did not demonstrate that HIVST increased rates of HIV diagnosis. This likely reflects major national declines in HIV infections in MSM in the UK, which occurred after the study was planned and meant the study was not sufficiently powered to detect a difference. There were also no statistical differences in STI testing, STI diagnoses, or reported CAI between the groups. The cost-effectiveness evaluation found that strategies to increase the demand for HIV testing and condom and PrEP use are likely to substantially improve health outcomes. A reduction in the cost of delivery of HIV testing and PrEP is necessary in order to provide value for money.

Trial registration

This study is registered as ISRCTN20312003.

Funding

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Involvement of patients and public

The most successful responses to human immunodeficiency virus (HIV) in the UK have been community-led and/or involved collaborations with the people most directly affected. Even 40 years into the epidemic, men who have sex with men (MSM) remain at the highest risk for reasons that are complex, but which are likely to still be related to a degree of social marginalisation. While new strategies have been proven in clinical studies to dramatically reduce the risk of HIV transmission, these have yet to be integrated into routine healthcare options and our research proposed to find the most cost-effective ways to do this. This programme of research specifically aimed to not only include community advocates but for them to play a central role in the development and oversight of all aspects of the research. Therefore, the HIV and MSM community were included in the core team for all studies in the programme, and budget was included to support this.

Patient and public involvement (PPI) representatives from HIV i-Base, National AIDS Map (NAM) and other organisations were co-applicants and also part of the Programme Management Group (PMG) and the Trial Management Group (TMG). Additional PPI members were recruited through adverts on relevant networks such as the Community Advisory Board and through existing partnerships with the HIV community. This led to the establishment of a study-specific Community Advisory Group (CAG) in July 2016, which was co-chaired by the two co-applicant PPI members and consists of academics with extensive experience of working with service users and the voluntary sector. There were 28 members of the CAG who were either linked to organisations working in the field of HIV, affiliated to the UK CAB, or individual participants in the Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD) pre-exposure prophylaxis (PrEP) trial. The group met quarterly and produced a PPI strategy, which can be found on the HIV Self-testing Public Health Intervention (SELPHI) website (www.selphi.org). The strategy was discussed at the monthly TMG meetings and, to ensure implementation, there was a standing PPI agenda item on the SELPHI TMG. The CAG co-chairs attended each TMG meeting and raised potential PPI activities in addition to completing a template from the start to the end of each PPI activity to assess impact.

Key areas of the methodology that PPI informed are listed as follows: the development of the trial design, protocol, participant information and consent materials, impact assessments, surveys, recruitment strategy, advertising materials and diffusion of information to trial participants. The CAG was consulted regarding the content and format of study materials aimed at participants to ensure that they were understandable and accessible, notably establishing a simplified language style for the participant information sheets. Following PPI feedback, documents were amended as suggested in readiness for submission for the relevant ethics approval.

In addition, the group suggested the expansion of SELPHI study entry criteria to include *trans* women, even though the original grant was limited to gay and bisexual men (including *trans* men). The change was driven by the lack of specific research and access for *trans* women and the precedent of broader inclusion in other prevention studies (e.g. with PrEP). This resulted in the production of novel evidence relating to research in the *trans* population and multiple publications. A *trans* researcher was also employed to inform the *trans* qualitative work.

Another key area where our PPI group were invaluable was the dissemination of research progress and study outputs. The PPI co-applicants and co-chairs of the CAG collaborated with the research team to produce regular updates that were shared on the study website (www.selphi.org) as well as community websites, such as National AIDS Map (NAM) and HIV i-base; they also contributed to writing academic outputs, conference presentations and this report.

Upon reflection, PPI input was incredibly valuable throughout the programme of research. A particular success was the integration of PPI activities at the pre-application stage of the grant, which meant that their input was significant throughout, and that they worked as an integral part of the research team.

Programme management

A Programme Steering Committee oversaw the entire programme. The Programme Steering Committee with an independent chair met annually from 2014 through to 2019 and included members with expertise in PPI, HIV, health services research and biostatistics. The programme was managed by a day-to-day Core Management Group (CMG), a Steering Group and a PPI Advisory Group (*Figure 1*). The principal investigator (PI) had overall responsibility for the successful delivery of the programme of research. The CMG were responsible for programme management ensuring that all stages of the project were completed in a timely manner and met 2-weekly for the duration of the project. Each workstream was managed by an expert WS lead(s) linked to the CMG by the PI, who sat on all WS groups. A TMG oversaw implementation and conduct of the trial linking with the WS1 team on qualitative inputs. The TMG met monthly, and others joined according to stage of development. Two PPI representatives attended these meetings. The frequency of meetings of each WP group varied according to stage of the project and need.

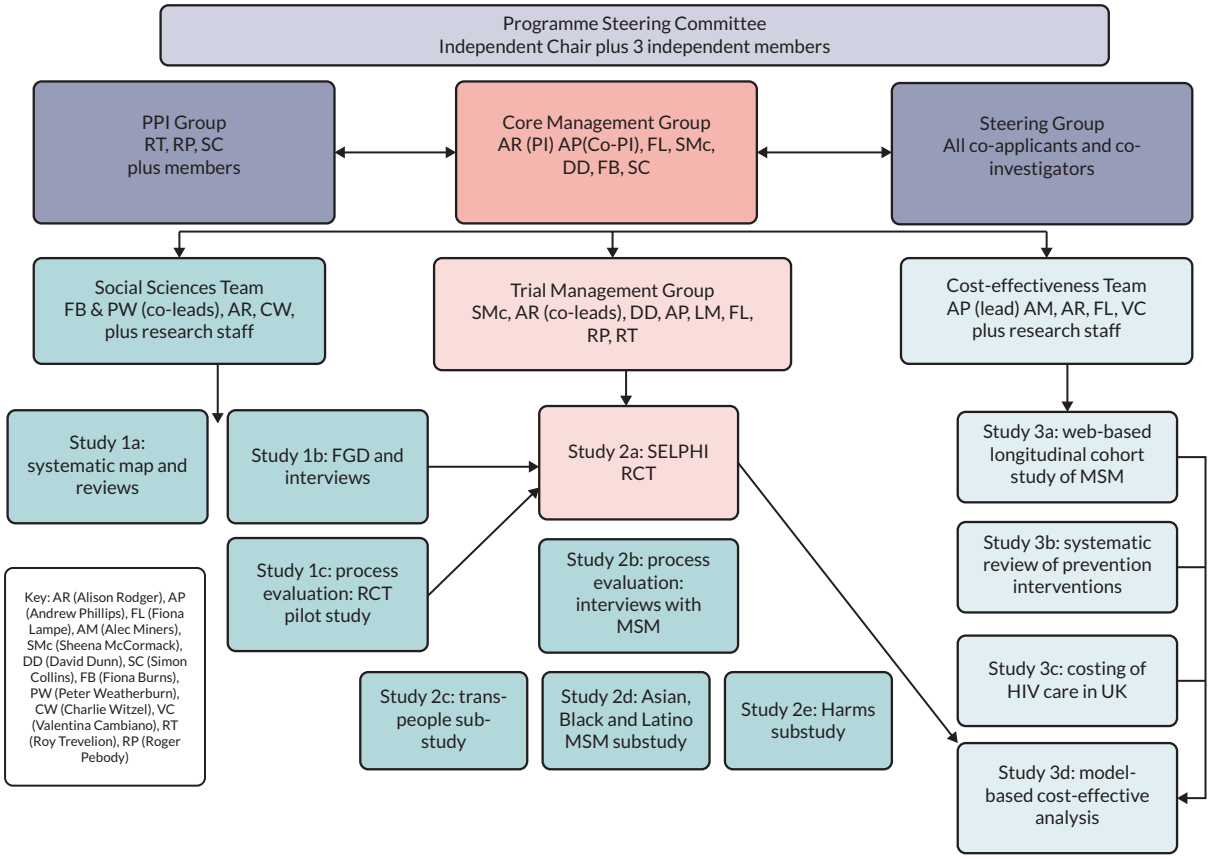

FIGURE 1 Diagram depicting the PANTHEON programme and its inter-relationships.

Synopsis

Research summary

The research programme was undertaken from March 2015 to February 2021. Our original proposal stated that the PANTHEON programme of research would include three linked WSs that aimed:

1. to understand barriers and facilitators among MSM in order to optimise accessibility and feasibility of HIV self-sampling (HIVSS) and self-testing interventions
2. to conduct a randomised controlled trial (RCT) in MSM to assess whether the offer of free self-testing with reminders leads to earlier diagnosis of HIV infection compared with standard of care for testing
3. to assess the cost-effectiveness of HIV prevention strategies, including HIV self-testing (HIVST), individually and in combination, to prevent HIV in MSM.

Summary of alterations to the programme

Over the 6 years of our programme of applied research, we completed all planned work. We modified certain aspects the programme as follows:

1. extended the process evaluation (PE) to cover not just the initial phase of the RCT (WS1), but the whole trial to provide more in-depth interpretation of outcomes and to assess what works well about the intervention and for whom
2. extended the follow-up time of the trial (WS2) in a no-cost extension to achieve 2 years follow-up of all participants in randomisation B
3. expanded the qualitative work in WS2 to contextualise trial quantitative data in key populations to allow maximal impact and benefit from HIVST; the groups that we conducted further qualitative work with were (i) *trans* people, (ii) Asian, black and Latin American MSM and (iii) those who reported any harms arising from the RCT
4. estimated the healthcare costs of caring for people diagnosed with HIV using data from a single English HIV treatment centre instead of linking to national Hospital Episode Statistics.

Setting the scene

Ongoing human immunodeficiency virus transmission, low rates of testing and late diagnosis in men who have sex with men and the trans community in the United Kingdom

In 2014 the HIV epidemic in MSM continued to grow, with 3000 new infections occurring per year despite intensive prevention efforts.[1,2] This was probably due to modest increases in condom-less anal intercourse (CAI) among MSM since the late-1990s, coincident with realisation of the health benefits of antiretroviral treatment (ART)[3–5] and as HIV infection was seen as less of a threat to health.[6] This was also against a background from 2011 of HIV-positive people being shown to be dramatically less infectious if using effective ART.[6]

Uptake and frequency of HIV testing among MSM in the UK remained low (estimated 30% never tested, 75% not in past year).[7] Approximately 25% of HIV-positive MSM were unaware of their HIV infection and disproportionately contributed to onward transmission (60–80% of new HIV transmissions come from people not diagnosed) as well as presenting late with consequent increased risk of death.[8,9] An estimated 14% of diagnoses made in MSM in the UK were diagnosed late in the course of their HIV infection with advanced immunodeficiency.[10]

Additionally there were no reliable data on HIV prevalence, incidence or HIV testing among *trans* women or *trans* men in the UK in the UK as historically gender identity had only been captured as male or female, although the UK Health Security Agency (formerly Public Health England) were expanding this categorisation.

While most HIV tests were conducted in genito-urinary medicine (GUM) clinics,[11] some initiatives had offered HIVSS, which involves an individual taking their own blood sample, which they post back to the relevant laboratory for testing, and they are subsequently contacted with the result. A further approach was to offer HIVST where the person not only takes the sample but also immediately processes it themselves, so only they are aware of the result. The potential advantage of the self-testing method was that the associated privacy and convenience could increase initial and repeat testing rates and therefore diagnosis. Self-testing was made illegal in the UK in 1992 because of concern, among other factors, that a person could discover they had HIV without ready access to counselling, which may lead to distress or self-harm. With the new climate that effective ART had engendered, the Department of Health (DoH) announced that HIVST would become legal from April 2014, meaning that an immediate assessment of the feasibility, efficacy and cost-effectiveness of providing this technology free to MSM through the NHS was required. Despite theoretical potential, there was an absence of evidence on the potential impacts of self-testing approaches,[12] and limited qualitative data to inform how such interventions would be perceived, used and experienced among MSM.

Evaluating the cost-effectiveness of human immunodeficiency virus-prevention intervention options

In addition to increasing HIV testing, other HIV prevention strategies in addition to self-testing include PrEP (where high-risk HIV-negative people take HIV drugs regularly to prevent infection), immediate treatment for all people with diagnosed HIV (not standard of care at the time this programme was planned), behaviour-change interventions and interventions prioritising partner notification of newly diagnosed cases. However, it was unclear which offered the greatest benefit for cost. Most of the relevant existing cost-effectiveness studies were either non-UK focused and/or excluded MSM. A search of PubMed and the NHS Economic Evaluation Database identified only one directly relevant study published in the 5 years preceding 2014.[13]

In practice, assessing the cost-effectiveness of a range of prevention interventions can only be achieved by modelling, by synthesising the relevant evidence in order to quantify the long-term impact of reduced HIV population spread. A key part of our proposal was that a 'comprehensive' assessment of all relevant prevention activities using a single model would allow prevention activities, singly and combined, to be compared in a coherent and consistent manner. This was done by adapting our existing individual-based simulation model, which had already been used to explain why the incidence of HIV in MSM had been increasing in the UK despite the increase in ART coverage.[1] The model simulates the UK population of MSM from the start of the HIV epidemic, tracking in detail levels of condom-less anal sex (CAS) with long-term and casual partners, risk of HIV acquisition, ART use and risk of HIV disease progression.[1]

Original aims, objectives and outputs

The overarching aim of this research was to reduce HIV incidence among MSM by determining the most cost-effective HIV prevention and testing policies and work with policy-makers to ensure their adoption.

Our main research questions were to address for MSM in the UK:

1. Does provision of free HIVST increase rates of diagnosis?
2. Which HIV prevention initiatives for reducing HIV incidence are most cost-effective?

To answer these research questions, we developed three inter-related WSs composed of a series of studies to meet each WS objectives (see *Figure 1*):

- WS1 – to increase understanding of accessibility and feasibility of HIVSS and self-testing among MSM, while collating evidence about ideal intervention designs. This WS directly informed the design and processes for the RCT in WS2.
    - Study 1A: systematic mapping and systematic review to identify most up to date evidence on HIVSS in MSM.
    - Study 1B: focus groups and interviews with MSM and HIV prevention and testing service providers to identify barriers and facilitators to HIVSS and self-testing in a range of models and contexts.
    - Study 1C: process evaluation to assess the interventions in the RCT, including the feasibility and acceptability in the internal SELPHI pilot.
- WS2 – to conduct an internet-based, randomised controlled trial with a two-stage randomisation process, to assess whether free self-testing for HIV with reminders to test results in earlier diagnosis of HIV infection compared with standard of care.
    - Study 2A: randomised control trial – the SELPHI study (Self-testing Public Health Intervention).
    - Study 2B: qualitative interview study with men from different arms of the trial to explore testing pathways, practices and effects, to gain a deeper understanding of perspectives on self-sampling and self-testing.
    - Study 2C: *trans* substudy investigating uptake and acceptability of HIVST.
    - Study 2D: Asian, black and Latin American substudy exploring testing barriers and HIVST's potential role.
    - Study 2E: HIVST harms qualitative study.
- WS3 – to assess the cost-effectiveness of strategies for preventing HIV in MSM, including free-self-testing.
    - Study 3A: web-based, observational, longitudinal, cohort study of HIV-negative (at the time of recruitment) MSM to assess predictors of HIV incidence and changes in risk behaviours over time and after HIV diagnosis. This study would provide key parameters for the cost-effectiveness model in Study 3C.
    - Study 3B: systematic review to identify HIV prevention strategies in MSM from high-income countries.
    - Study 3C: economic evaluation to characterise costs of being diagnosed with HIV in the UK.
    - Study 3D: modelling the cost-effectiveness of HIV prevention strategies, including HIVST, using a simulation model to determine the cost-effectiveness (from an NHS perspective with outcomes as quality-adjusted life-years) of strategies for preventing HIV transmission, alone and in combination.

Outputs

The overall primary anticipated outputs were to provide:

1. an estimate from a RCT of the effectiveness of offering free self-testing for HIV, with reminders to test, in increasing HIV diagnosis compared to standard of care.
2. a comprehensive evaluation of the cost-effectiveness of combinations of potential HIV prevention strategies.

Workstream 1: feasibility studies to increase understanding of accessibility and feasibility of human immunodeficiency virus self-testing among men who have sex with men to inform the design and processes for the randomised controlled trial in Workstream 2

Workstream 1: overview

The main objective of this WS was to consolidate the existing evidence on HIVST and gain an understanding of the values and preferences, and the potential barriers, relating to HIVST among MSM and *trans* people in England and Wales. This initial work would directly feed into the design and implementation of the RCT planned in WS2. To consolidate the existing evidence on HIVST we planned to undertake a series of systematic reviews and produce a systematic map, in collaboration with the World Health Organization (WHO), in order to update HIVST policies and guidance. Simultaneously we ran focus groups and interviews with key stakeholders, including MSM and healthcare professionals, to gain insight into the relatively new concept of HIVST, using the COM-B (capability, opportunity, motivation, behaviour) framework for understanding behaviour.[14] A further objective was to develop and undertake a process evaluation to assess the feasibility and acceptability of the intervention (HIVST) used in the RCT in WS2, including using data from the pilot phase of the study.

Workstream 1: introduction

With pending legalisation of HIVST in 2014, individuals would soon have the ability to perform unsupervised a rapid diagnostic test at home. This innovation was not without complications; in particular, there were no means to ensure that those with a reactive result presented for care or support and that self-test kits were used free from coercion or violence. Additionally, the impact of self-testing on risk behaviours, other sexually transmitted infections (STIs), and engagement in HIV and STI prevention initiative was unclear.

Workstream 1: research aims and objectives

Aims

To understand barriers and facilitators among MSM in order to optimise accessibility and feasibility of a HIVST intervention. This directly informed design and processes for the RCT proposed in WS2.

Objectives

1. To consolidate emerging evidence related to HIVST.
2. To examine the values and preferences of MSM for HIVST interventions considering key domains of intervention design.
3. To explore the potential barriers and facilitators of HIVST for MSM using COM-B as a framework.
4. To understand how HIVST complemented existing testing strategies considered or adopted by MSM.

Study 1A: producing a systematic map to identify most up-to-date evidence of human immunodeficiency virus self-sampling and self-testing in men who have sex with men

This work was carried out to consolidate emerging evidence related to HIVST, specifically meeting objective 1 of WS1. This was a collaborative project with the WHO, with the intention of updating their normative HIVST guidance.

Methods

We developed a systematic map to consolidate emerging evidence around HIVST. We systematically searched databases and the abstracts of five conferences from 2006 to June 2019, with monthly automated database searches. The methods for this process have been published.[15] We performed meta-analyses (divided into key and general populations) and analysed acceptability and values and preferences. This was used to update the WHO HIVST global guidelines and resulted in three additional publications.

Findings

In the key populations' meta-analysis we found that HIVST (compared to standard HIV testing) increased testing uptake by 1.45 times [risk ratio (RR) = 1.45; 95% confidence interval (CI) 1.20, 1.75] and increased the mean number of HIV tests by 2.56 over follow-up (mean difference = 2.56; 95% CI 1.24, 3.88) for MSM and *trans* people, and increased numbers of those with a positive result (MSM and *trans* people only).[16] Linkage to care was reduced overall.[16] There were no negative impacts on condom use and social harm was very rare. In general populations, HIVST also increased testing uptake overall. The number of persons diagnosed HIV-positive among those tested and the number linked to HIV care/treatment among those diagnosed were similar between HIVST and standard testing.[17] In terms of acceptability, values and preferences, our review found that the majority of participants were willing to self-test. Key reasons for desiring HIVST included privacy, convenience and ease of use. Few participants expressed concerns and the most common were about accuracy, user errors and lack of counselling. Many healthcare workers would welcome the introduction of HIVST, though some felt HIVST could threaten their jobs.

Successes

We successfully collaborated across several reviews,[16–18] which continue to inform policy-making and commissioning of HIVST in a variety of settings internationally. Most importantly, the completion of this work directly informed the WHO normative guidance on HIVST delivery.[19] These guidelines are extensively used in low- and middle-income countries, directly informing global HIVST provision.

Limitations

Our three meta-analyses followed, as far as possible, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to systematic reviewing. HIVST as an intervention by definition cannot be blinded and therefore this criterion has limited relevance. Very small numbers of *trans* people (*n* = 72) were included in key population RCTs and their data were not disaggregated from *cis*-MSM. This means our understanding of HIVST impacts for *trans* people is partial.

Study 1B: focus groups and interviews with men who have sex with men, human immunodeficiency virus prevention and testing service providers to identify barriers and facilitators to human immunodeficiency virus self-testing in a range of models and contexts

The focus groups and interviews were specifically designed to address Objectives 2, 3 and 4:

- to examine the values and preferences of MSM for HIVST interventions considering key domains of intervention design
- to explore the potential barriers and facilitators of HIVST for MSM using COM-B as a framework
- to understand how HIVST complements existing testing strategies considered or adopted by MSM.

Methods

We recruited 47 MSM to 6 focus groups in London, Plymouth and Manchester. Gay, bisexual and other MSM (*cis* or *trans*) over the age of 18 were eligible. Four groups were for a general sample of MSM, one was for those who had not previously tested and one for men reporting CAI in the preceding 3 months. We assessed that further groups beyond these six would not provide substantial new data. Men were recruited through geo-location sexual networking apps (Scruff, Grindr and Growlr) and through community-based organisations in the three cities. OraQuick™ (Pennsylvania, USA) saliva-based and BioSure™ (Waltham Abbey, UK) blood-based testing second-generation HIVST kits were demonstrated for participants, who were asked to comment on procedure, design and instructions.

Focus-group discussions (FGDs) were transcribed verbatim. All authors familiarised themselves with the transcripts and agreed a thematic framework based on higher-level codes, such as barriers/facilitators, intervention preferences and impacts.

Findings

Objective 2: to examine the values and preferences of men who have sex with men for human immunodeficiency virus self-testing interventions considering key domains of intervention design Our results demonstrated the range of preferences relating to HIVST designs and kit types that exist among MSM in England, and the reasons underpinning them.[20] A strong preference for fourth-generation testing was found, as tests with this short window period most closely match what is routinely available in clinical settings and have the shortest time between initial infection and detection.[20] Sample type preferences were divergent. Although a preference for blood-based testing was observed because of higher perceived accuracy, a significant minority had a strong preference for oral fluid testing because of their aversion to drawing and collecting a blood sample. This was broadly in line with existing evidence from this time.[21,22]

Men who have sex with men tended to prefer HIVST interventions which delivered kits through the postal system.[20] These were perceived to be exceptionally convenient for most and were generally unproblematic, providing packaging was discreet and the kit could fit through a standard letterbox. Instructions that were simple to understand and relied on small volumes of text were preferred. In this study the kits which were shown to participants were disliked as their relatively opaque instructions gave the impression that the tests were significantly more challenging to perform than they were.[20] Video instructions were also valued. In terms of support and follow-up, it was felt to be essential that interventions provided a helpline in order to mitigate potential harm and to support correct use, and that an intervention had a means to record results and signpost to care if necessary. This type of support tool mimics what has been implemented with MSM in the UK and in other high-income settings.[23–25]

Objective 3: to explore the potential barriers and facilitators of human immunodeficiency virus self-testing for men who have sex with men using capability, opportunity, motivation, behaviour as a framework We explored the primary barriers and facilitators that potential intervention beneficiaries face when considering uptake of HIVST, described using COM-B. Capability, both physical and psychological, was largely associated with barriers, such as difficulty performing the test. Opportunity and motivation had both associated facilitators and barriers.[20] When considering potential HIVST interventions, concerns around capability (physical) were initially a significant issue for MSM, but lessened as experience with the HIVST increased. Any concerns were largely due to the instructions in the existing HIVST kits in the first formative study, but also because of concerns regarding their own abilities in undertaking a rapid diagnostic test properly, and the potential risks associated with failure, such as an incorrect result.[20] This was in line with existing literature at the time, although perhaps more pronounced.[26,27]

Objective 4: to understand how human immunodeficiency virus self-testing complements existing testing strategies considered or adopted by men who have sex with men We found three clear motivations for accessing HIV testing: in response to risk; for reassurance; out of routine.[28] Testing in response to risk was a normative practice and was understood universally as a primary testing motivation in MSM. Frequent HIV testing was strongly viewed as a normative behaviour for many MSM in this study.[28,29] Testing norms were so widely held that MSM who had never tested for HIV struggled to disclose this in FGDs. HIVST was felt to be exceptionally useful in response to testing norms disseminated through friends and peers, as the technology allowed individuals to meet these expectations with limited effort.[28] However, for some, self-testing transgressed other norms by bringing HIV testing into the home. The results indicated ways in which HIVST complemented existing testing strategies adopted and considered by MSM. Based on these results, self-testing would likely be confined to testing when there was not perceived to be a significant risk of a positive result, except for when major barriers to clinic access exist.[30]

Successes

The results of these FGDs have substantially shaped HIVST delivery in the UK and more widely by providing the first evidence on the values and preferences of MSM in England for HIVST interventions. The first published paper[20] has become a key reference in the literature and is currently, to our

knowledge, the most cited HIVST paper in a European setting. The results have also been used by community-based organisations in their design and delivery of HIVST services.

Limitations

The research has some important limitations. First, very few participants had previously tested for HIV using a self-test, meaning that the initial research on values and preferences discussed was largely speculative. It is likely that this overemphasised some negative aspects of the intervention, such as capability concerns and issues around access to care.

In addition, although focus groups are exceptionally useful for gaining normative understandings of intervention potential, the group nature of the method produces a barrier for those with the most confidentiality concerns. This means that the perspectives of the most marginalised may not have been captured in this research.

Study 1C: process evaluation to assess the interventions in the randomised controlled trial

The process evaluation (PE) was initially planned to cover the pilot phase of the RCT (WS1) to assess feasibility and acceptability. However, it was extended to cover the whole trial to provide more in-depth interpretation of outcomes and to assess what works well about the intervention and for whom. In this section, we outline the pilot study while the rest of the process evaluation is outlined in WS2 qualitative studies.

Methods

We used a mixed-methods approach to assessing feasibility of recruitment and intervention acceptability during the pilot phase of the SELPHI RCT. Full methods for the RCT are detailed later in WS2 and published.[31] In brief, eligible participants were men (*cis* and *trans*) and *trans* women, all who reported ever having had anal sex with a man. Participants were recruited online, through social media [Facebook (Facebook, Inc., Menlo Park, CA, USA), Twitter (Twitter, Inc., San Francisco, CA, USA)], geolocation sexual networking apps (Grindr, Scruff, Growlr, Hornet) and through the networks of community organisations. We conducted 10 interviews in May 2017 during the pilot phase of the RCT to explore the usability and experiences of HIVST by MSM in the study; this is detailed in WS2, Study 2B.

Findings

Recruiting MSM to the pilot phase proved recruitment was feasible, and the HIVST intervention highly acceptable among those who received it. This provided the first European data about usability of HIVST among end-users, providing a vital piece of evidence to support implementation efforts. We demonstrated the feasibility of recruiting a broadly representative sample of MSM to the RCT pilot using a range of online platforms.[32] The results also highlighted the need to design future interventions which require minimal steps. In the pilot phase, 25% of participants did not link through from the recruitment to enrolment surveys, leading to attrition at this stage, which was probably due to the demands of trial processes.[32]

We found that HIVST outperformed HIVSS tests on test completion when comparing our results to self-sampling service evaluations. In total, 95% of those who filled in the 3-month survey in the pilot indicated use of the HIVST, far outperforming the 55% return rates of HIVSS.[32] Test kit usability was extremely high, with the vast majority reporting good or very good experiences. This was not expected given the capability concerns identified in the formative work,[20] although extensive efforts went into addressing these before the pilot phase of the RCT.

The instructions were perceived to be easy to understand, perhaps reflecting increased simplicity introduced following a kit redesign by the manufacturer, which also reduced the size of the box so that the kit could fit through a standard letterbox. This increased 'capability' in the COM-B model.[32] 'Opportunity', as described in COM-B, was enhanced by the provision of a free HIVST, ameliorating barriers pertaining to inconvenient clinics, and psychosocial barriers, such as privacy and stigma.

'Motivation' (reflective and automatic) was negatively affected by increased anxiety associated with the intervention as a whole, and the 15-minute waiting period for results.

Successes
Recruitment to the pilot phase of the RCT was successful and on the basis of these findings we were able to proceed to full RCT implementation. In demonstrating that HIVST use is far higher than HIVSS sample return (97% vs. 55%) we provided crucial data that self-testing outperforms other remote options.

Limitations
Substantial informed consent procedures which required extensive test information were provided for RCT participants. It is very unlikely this amount of information would be provided through NHS or voluntary-sector provision, perhaps negatively impacting on usability in a real-world setting.

Workstream 1: discussion
The systematic reviews and the systematic mapping process that were conducted as part of WS1 demonstrated that HIVST increased HIV testing among key populations including MSM, and among MSM HIVST increased the mean number of tests taken over follow-up time. The reviews also demonstrated that although there was a legitimate concern over HIVST and linkage to care after a positive result, this was not the case for MSM and *trans* people [although not overall when female sex workers (FSW) were included]

Our FGDs demonstrated the diversity of patient preferences for self-testing interventions, and potential adaptations for subgroups.[20,28] The discussions highlighted the importance that MSM placed on the accuracy and window period of the HIVST, the convenience of the distribution of the test, and how HIVST may complement existing testing strategies that MSM employ, in particular to maintain regular testing when not deemed to be at particularly high risk.[28]

The process evaluation of the pilot phase of the RCT demonstrated that it was feasible and acceptable to recruit MSM online to a HIVST trial.[32] The usability of the HIVST kit (detailed in WS2 Methods) was found to be high and the experiences of the participants were good. As a result of valuable data collected from the process evaluation within the trial pilot phase, and the identification of subgroups that may particularly benefit from HIVST, the process evaluation was extended to cover the whole RCT, further detailed in WS2, Studies 2B, 2C, 2D and 2E.

Conclusion
human immunodeficiency virus self-test(ing) has the potential to increase uptake and frequency of testing among MSM. The values and preferences ascribed to HIVST by MSM included privacy, utility and convenience; however, concerns included accuracy of the test and capability to perform the test. Overall, in the SELPHI pilot study HIVST was found to be a highly acceptable form of testing that could complement and expand MSMs testing strategies.

Workstream 2: randomised controlled trial to assess whether free availability of human immunodeficiency virus self-testing leads to earlier diagnosis of human immunodeficiency virus infection

Workstream 2: overview
Formative data from WS1 were used to inform the design and implementation of the RCT in WS2. The main objective of WS2 was to conduct a RCT to measure the impact of the provision of free HIVST on new confirmed HIV diagnoses linked to clinical care. The SELPHI RCT was co-ordinated by the Medical Research Council's Clinical Trials Unit at University College London and is detailed in Study 2A. A further objective of WS2 was to undertake the extended process evaluation to cover the whole RCT.

Specifically, the process evaluation explored, through qualitative data collection, the experiences and utilisation of HIVST in Study 2B, the impact that HIVST might have for specific groups of participants such as *trans* people (Study 2C) and Asian, black and Latin American MSM (Study 2D) and finally the types of harms that may have arisen from the SELPHI RCT (Study 2E).

Workstream 2: introduction

Although several randomised controlled trials had assessed the impact of providing HIVST on rates of HIV testing,[33,34] SELPHI was designed to evaluate whether this intervention resulted in increased rates of HIV diagnoses that link to clinical care. Linking to care is the critical public health outcome enabling access to ART, which results in individual health benefits and reduction in HIV transmission.

Workstream 2: research aims and objectives

Aims

To assess in MSM whether the offer of free self-testing with reminders leads to earlier diagnosis of HIV infection compared with standard of care for testing.

Objectives

1. To examine whether the offer of a single free HIV self-test at enrolment leads to the confirmed diagnosis of prevalent HIV infections with linkage to HIV clinical care.
2. To examine among HIV-negative individuals at high risk of acquiring HIV infection whether the offer of regular free self-tests with testing reminders results in more rapid confirmed diagnosis of an incident HIV infection with linkage to HIV clinical care.
3. To generate data to inform key parameters for the cost-effectiveness model.
4. To conduct a process evaluation to assess the interventions in the RCT.
5. To describe the usage and acceptability of HIVST.
6. To describe sexual, health-seeking behaviour and HIVST intervention acceptability for *trans* people in the SELPHI RCT.
7. To describe sexual, health-seeking behaviour and HIVST intervention acceptability for Asian, black and Latino MSM in the SELPHI RCT.
8. To quantify, describe and explore the types of harms arising from participation in the SELPHI RCT.

Study 2A: randomised control trial (SELPHI: a HIV Self Testing Public Health Intervention)

This study was designed to answer the overarching question of the programme grant, whether the provision of free HIVST increases rates of diagnosis among MSM, and to specifically meet objectives 1, 2 and 3 of this workstream.

Methods

Human immunodeficiency virus Self Testing Public Health Intervention was an open-label parallel-group randomised controlled trial with a two-stage simple randomisation aiming to enrol 10,000 participants. The SELPHI protocol is published and methods are described.[31] To recruit participants, advertising campaigns placed on social networking websites and via mobile phone applications designed to facilitate sexual and social contact, such as Facebook, Grindr, Hornet and community web pages were used.

Randomisation A took place at enrolment, with participants randomly allocated (in a 3 : 2 ratio) to the offer of a free baseline HIVST (BT) versus no offer of a free baseline HIVST (nBT). An unequal allocation ratio ensured a majority of those agreeing to participate would receive a free self-test and increased the numbers eligible for randomisation B. This second randomisation occurred at month 3 after enrolment and was open only to participants who were initially allocated to the BT group in randomisation A,

completed the 3-month survey, remained HIV-negative; reported CAS with ≥ 1 male partner in the previous 3 months (indicating higher risk of incident HIV infection) and were interested in using HIV self-test kits in the future. Eligible participants were randomised (1 : 1) to receive the offer of regular (immediately and every 3 months thereafter) free HIV self-tests + testing reminders (RT) versus no such offer (nRT). Both groups were sent 3-monthly surveys over 2 years of follow-up. A flow chart depicting the study randomisations is shown in *Figure 2*.

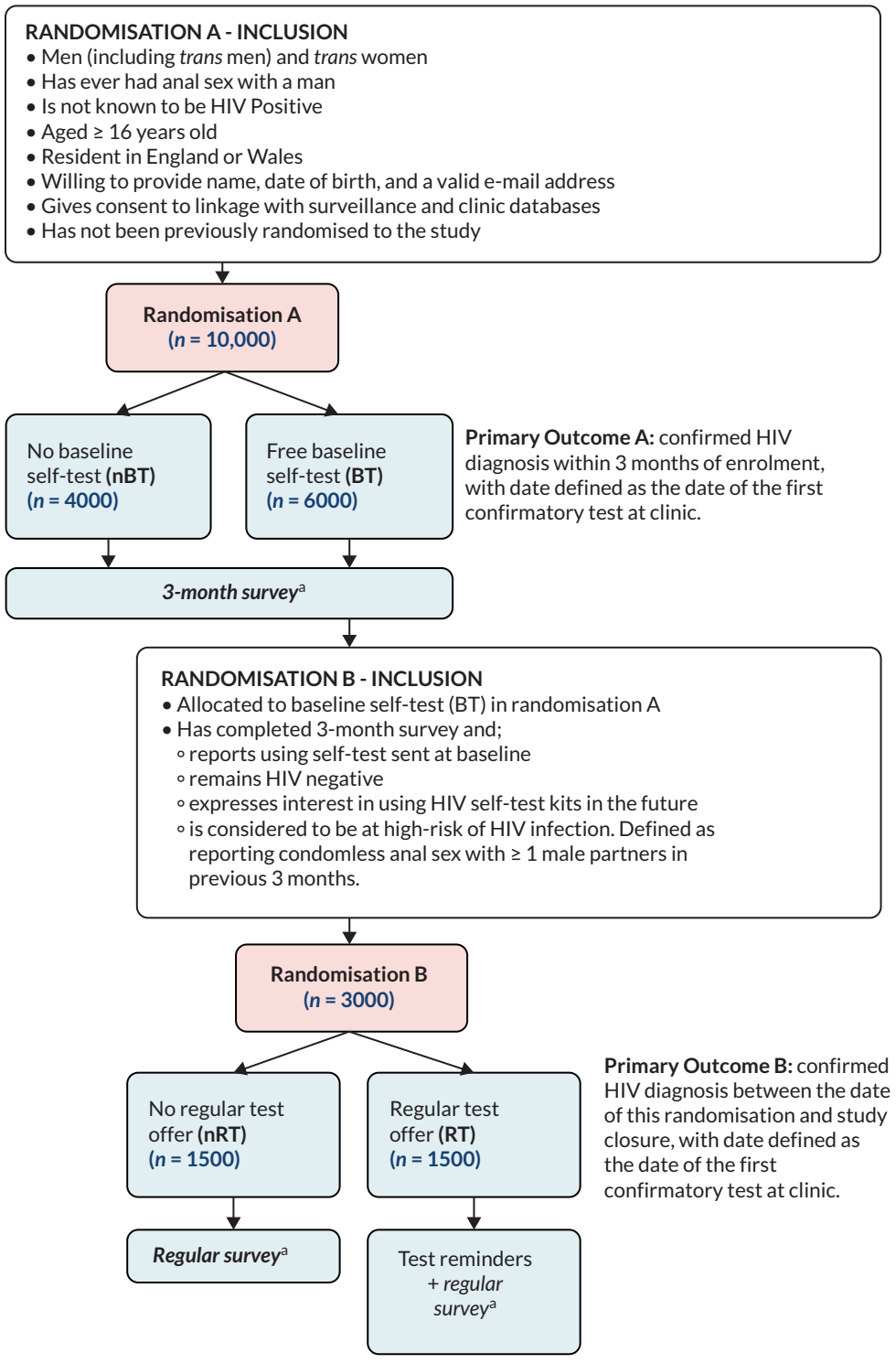

FIGURE 2 Flow chart of the randomisation process for the SELPHI RCT. a Surveys include questions on sexual behaviour and HIV testing.

Human immunodeficiency virus self-testing kits

In the UK, HIVST was legalised in April 2014, and the first CE-marked kit (BioSURE HIVST, BioSURE, UK) was released to the UK market in April 2015. The BioSURE HIVST kit is classed as a second-generation test (an antibody immunoassay detecting HIV 1/2 antibodies from approximately 28 days after infection), used a whole blood sample and retailed at £30–35 at that time.

The HIVST kit used in the study was the BioSURE® HIV Self-Test, which had an estimated sensitivity of 99.7% (95% CI 98.9 to 100).[35] In addition to written information provided with the test kit, an online video providing instructions on kit use (produced by BioSURE) (https://youtu.be/N4CAqsmN_6g) was also promoted to participants on joining the study and was available on the study website (www.selphi.org).

Primary outcome measure

The primary outcome for randomisation A was a confirmed new HIV diagnosis within 3 months of randomisation (binary outcome). The primary outcome for randomisation B was the time from randomisation to a confirmed new HIV diagnosis (time-to-event outcome). For both randomisations, the date of diagnosis was defined as the date of the first confirmatory HIV test at clinic. For randomisation B, the censoring date (31 December 2019) was based on the date of the last United Kingdom Health Security Agency (UKHSA) linkage exercise.

A HIV diagnosis primary end point is a key feature of SELPHI and distinguishes it from other randomised trials of HIVST, which have all used testing as the primary outcome. HIV diagnoses were primarily obtained from linkage to the national HIV surveillance database, the HIV and AIDS Reporting System (HARS), which is maintained by UKHSA.

Analysis

Analyses of the primary outcome were performed using the intention-to-treat principle, including participants who did not order a kit or ordered a kit and did not use it. Participants were only excluded if they were determined to be ineligible after randomisation or asked for all their data to be removed. Comparisons of outcomes between randomised groups used chi-square tests for categorical data, Mann–Whitney U tests for ordinal data. The time to HIV diagnosis (for randomisation B) was examined using a Kaplan–Meier plot. HIV diagnosis data were last received from UKHSA (known as Public Health England until October 2021) on 17 April 2020 and were assumed to be complete to the end of 2019 (censoring date 31 December 2019).

Key findings

Randomisation A

Ten thousand seven hundred and ninety-one participants were randomised between 16 February 2017 and 1 March 2018. Of those, 648 were later deemed ineligible (details in *Figure 3*, 9 asked for all of their data to be withdrawn, and 24 were *trans* women whose data are reported elsewhere.[36] This left 10,111 participants in the analysis data set, 6049 of whom were allocated to BT and 4062 to nBT. Two hundred and sixty-two (3%) participants subsequently withdrew or unsubscribed from further contact but were assessed for the primary outcome.

Baseline characteristics

Participants' baseline characteristics and previous HIV testing behaviour have been described.[37] Median age was 33 years [inter-quartile range (IQR) 26–44], 9000 (89%) participants were white, 8118 (80%) were born in the UK, and 4706 (47%) were university-educated (*Table 1*). Only 81 (1%) participants were *trans* men. One thousand six hundred and ninety-five (17%) participants had had a HIV test in the 3 months before enrolment, and 1537 (15%) had never HIV tested. The most recent HIV test was conducted at a sexual health clinic for 5089 (61%) of the participants who had tested before, using a self-sample for 1380 (17%), a self-test for 556 (7%), and other modalities for 1291 (16%). In terms of numbers of CAI partners in the 3 months before enrolment, 3330 (33%) of participants reported 1

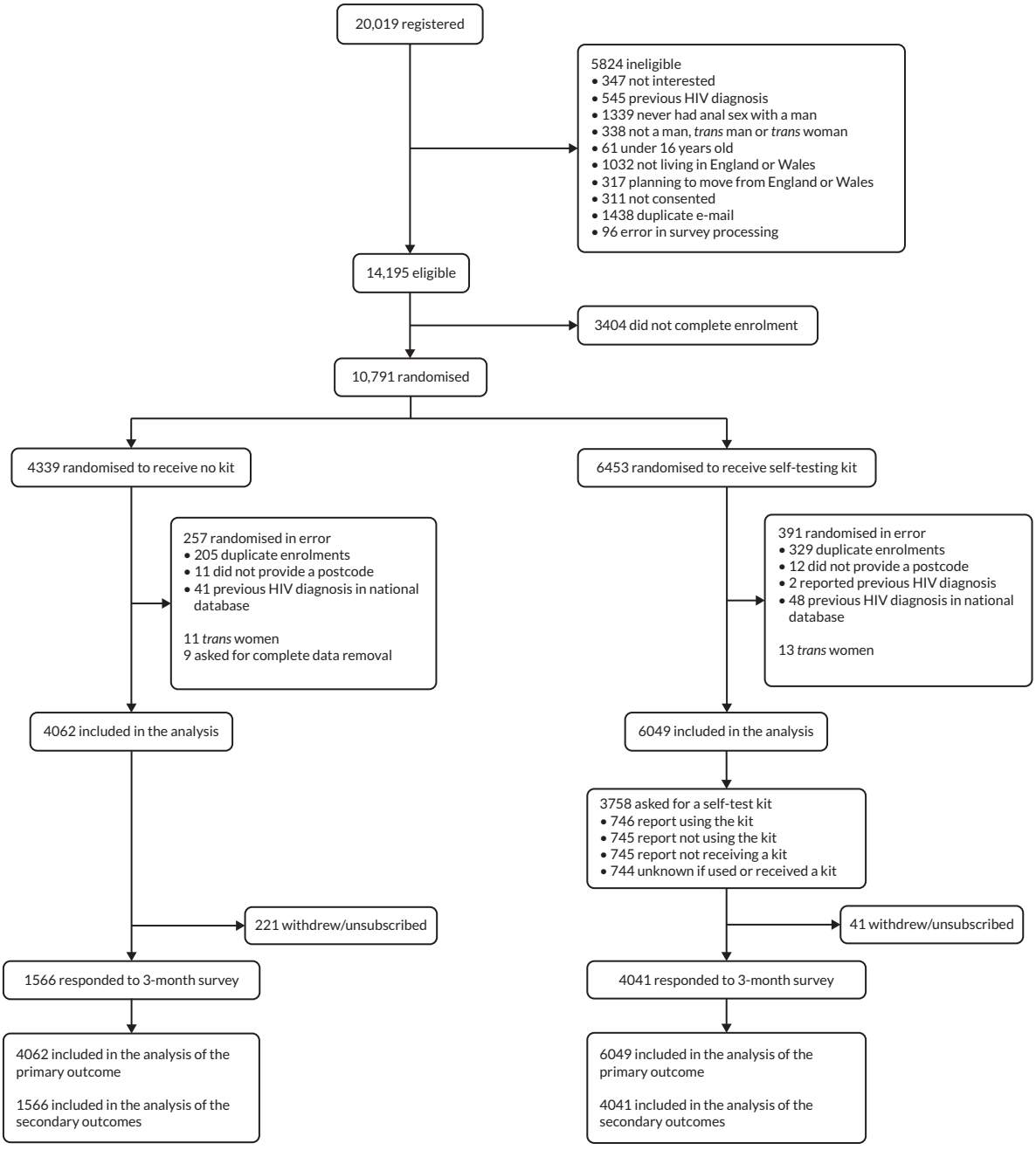

FIGURE 3 Consolidated Standards of Reporting Trials diagram for randomisation A.

partner only, 2943 (29%) reported 2–4 partners and 1009 (10%) reported 5 or more partners. At the time of enrolment, 389 (4%) were taking PrEP. Baseline characteristics were reasonably balanced over the two groups.

Survey response rates

Three thousand eight hundred and ninety-five (64%) BT participants completed the 2-week survey, of whom 167 (4%) reported not having received the kit, 110 (66%) of whom later reported receiving the kit. The 3-month survey was completed by 4041 (67%) participants in the BT group and 1566 (39%) in the nBT group. Completion rates were higher among participants who were older, more highly educated, those who had HIV tested more recently and those reporting more CAI partners (data not shown). The final survey was completed by 1695 (28%) participants in the BT group and 1069 (26%) in the nBT group.

TABLE 1 Baseline characteristics (randomisation A)

	Free baseline test	No baseline test	Total
Randomised	*N* = 6049	*N* = 4062	*N* = 10111
Median (IQR) age (years)	33 (26–44)	33 (26–44)	33 (26–44)
Trans man	47 (1%)	34 (1%)	81 (1%)
Born in the UK	4849 (80%)	3269 (80%)	8118 (80%)
White	5347 (88%)	3653 (90%)	9000 (89%)
University-educated	2854 (48%)	1852 (46%)	4706 (47%)
Last HIV test			
< 3 months	989 (17%)	706 (18%)	1695 (17%)
3–12 months	2250 (38%)	1471 (36%)	3721 (37%)
> 1 year	1813 (30%)	1248 (31%)	3061 (31%)
Never	929 (16%)	608 (15%)	1537 (15%)
Location of last HIV test			
Sexual health clinic	3030 (61%)	2059 (61%)	5089 (61%)
Other NHS or clinic setting	430 (9%)	279 (8%)	709 (9%)
Self-sample	826 (17%)	554 (17%)	1380 (17%)
Self-test	336 (7%)	220 (7%)	556 (7%)
Elsewhere	340 (7%)	242 (7%)	582 (7%)
Last STI test			
< 3 months	896 (15%)	631 (16%)	1527 (15%)
3–12 months	1814 (30%)	1225 (30%)	3039 (30%)
> 1 year	2090 (35%)	1386 (34%)	3476 (35%)
Never	1223 (20%)	797 (20%)	2020 (20%)
Number of CAI partners in previous 3 months			
0	1716 (28%)	1112 (28%)	2828 (28%)
1	2000 (33%)	1330 (33%)	3330 (33%)
2–4	1745 (29%)	1198 (29%)	2943 (29%)
5 +	587 (10%)	422 (10%)	1009 (10%)
Currently taking PrEP	241 (4%)	148 (4%)	389 (4%)

CAI, condom-less anal intercourse.

Human immunodeficiency virus testing

Five thousand nine hundred and ninety-six (99%) participants allocated to BT accepted the offer of a free HIV self-test kit. Of these, 4263 (71%) participants in the BT arm reported having used the SELPHI self-test kit by the 3-month survey: 530 at the 2-week survey and 3733 at the 3-month survey. Of the 182 remaining BT participants who completed the 3-month survey, 97 (68%) had accessed another HIV test in the previous 3 months. Additionally, linkage with UKHSA data indicated that eight participants HIV tested who did not respond to either survey. Thus overall, 4368 (97%) of BT participants had evidence of any HIV test before 3 months, significantly higher than the proportion in the nBT group

(670, 43%) ($p < 0.001$). Of the 3722 BT participants who had used the SELPHI self-test kit and responded to further questions, 892 (24%) reported having had an additional HIV test after the self-test.

Self-tests and linkage to care

Four thousand four hundred and forty-nine (76%) participants reported having used the self-test kit at either the 2 weeks, 3 months, or final survey. Of these, 4378 (98.4%) participants obtained a non-reactive result, 14 (0.3%) a reactive result, and 57 (1.3%) obtained no result, that is, no lines appeared or there was another problem with the test. Of the 14 participants with a reactive result, 10 either reported a positive confirmatory clinic result or linked to the UKHSA database (implying a positive confirmatory result in a clinic), and one reported a negative confirmatory clinic result. There were no reported false negatives; however, this would have been difficult to ascertain through the surveys. A study clinician attempted to contact the remaining four participants, but was not successful. Median time between enrolment and linkage to care for those reporting using the self-test kit was 9 days (IQR 6–12).

Confirmed human immunodeficiency virus diagnoses

A total of 34 (0.3%) participants had a confirmed HIV diagnosis within 3 months, the primary outcome for randomisation A (*Table 2*). There was no evidence of a difference between the two groups ($p = 0.64$),

TABLE 2 Outcome measures at 3 months

	BT	nBT	Total	Risk difference (95% CI)	*p*-value
Randomised	*N* = 6049	*N* = 4062	*N* = 10,111		
Diagnosed with HIV	19 (0.3%)	15 (0.4%)	34 (0.3%)	−0.1% (−0.3% to 0.2%)	0.64
Completed 3 months survey	4041 (67%)	1566 (39%)	5607 (55%)	–	
	N = 4511	*N* = 1574	*N* = 6085		
Reporting any HIV test	4368 (97%)	670 (43%)	5038 (83%)	54% (52% to 57%)	< 0.001
Number reporting > 1 HIV test	940 (22%)	125 (19%)	1065 (21%)	3% (−0.4% to 6%)	0.10
Reporting using any self-test kit	4266 (95%)	89 (6%)	4355 (72%)	89% (88% to 90%)	< 0.001
	N = 756	*N* = 325	*N* = 1081		
Reporting any HIV test in those who tested < 3 months prior to enrolment	742 (98%)	222 (68%)	964 (89%)	30% (25% to 35%)	< 0.001
	N = 4028	*N* = 1563	*N* = 5591		
Reporting a STI test	903 (22%)	397 (25%)	1300 (23%)	−3% (−5% to −0.5%)	0.02
	N = 4039	*N* = 1566	*N* = 5605		
Any CAI partners	2542 (63%)	927 (59%)	3469 (62%)	4% (1% to 7%)	0.01
	N = 2542	*N* = 927	*N* = 3469		0.07
Reporting a STI test and ≥ 1 CAI partner	663 (26%)	281 (30%)	944 (27%)	−4% (−8% to −1%)	0.01
Number of CAI partners					
1	1292 (51%)	451 (49%)	1743 (50%)		
2–4	543 (21%)	187 (20%)	730 (21%)		
5 +	319 (13%)	148 (16%)	467 (13%)		

CAI, condom-less anal intercourse.

Note

p-values calculated using chi-square tests. The numbers reporting HIV tests are taken from the 2-week, 3-month and final survey, multiple surveys and from HIV diagnosis linkage data.

with 19 (0.3%) BT participants versus 15 (0.4%) nBT participants diagnosed (risk difference 0.0%, 95% CI −0.2% to 0.3%). This finding was unchanged in sensitivity analyses that explored looser and stricter criteria for a HIV diagnosis (data not shown).

Randomisation B

Two thousand four hundred and ninety-nine participants were randomised between 17 May 2017 and 21 June 2018. Of those, 191 were later deemed ineligible, leaving 2308 participants in the analysis data set, of whom 1161 were allocated to RT and 1147 to nRT. This was a smaller number than the estimated sample size of 3000 participants for randomisation B.

Baseline characteristics

Baseline characteristics of randomisation B closely mirrored those of randomisation A. The median age was 34 (IQR 27–44), the majority were of white ethnicity [2052 (89%)], and nearly half were educated to degree level or above [1092 (47%)]. All participants, by definition, had at least one condom-less male anal sex partners within the past 3 months. One thousand one hundred and eighty-seven (51%) participants reported one such partner, 490 (21%) two partners, 616 (27%) three or four partners and 678 (29%) five or more partners. Two hundred and fifty-three (11%) participants had ever taken PrEP, with 148 (6%) being current users.

Survey response rates

Participants were asked to complete a survey every 3 months for 2 years. The number of eligible participants fell sharply after the sixth survey, related to the timing of recruitment. Until this point, the response rate decreased slowly but steadily in each arm (from 84% to 64% for RT, from 83% to 54% for nRT).

Human immunodeficiency virus testing

Overall, a total of 5085 self-test kits were requested by participants in the RT arm (*Table 3*); 78% kits were reported as having been used at the subsequent survey. The main reason for not having used the test was an intention to use the test at a later date.

Considering all types of HIV testing, 87% of participants in the RT arm reported at least one HIV test during follow-up compared with 45% in the nRT arm, giving a risk difference of 42% (95% CI 31% to 53%, $p < 0.001$). The proportion of participants reporting the use of a HIV test in the previous 3 months was stable over the course of follow-up, with a range of 84–87% in the RT arm and a range of 34–44% in the nRT arm. Most of the testing in the RT arm was done with a SELPHI kit; self-testing was used infrequently in the nRT arm.

Confirmed human immunodeficiency virus diagnoses

A total of 16 (0.7%) participants had a confirmed HIV diagnosis during follow-up according to the primary definition (*Figure 4*). There was no evidence of a difference between the two groups ($p = 0.63$), with nine (0.8%) RT participants versus seven (0.6%) nRT participants diagnosed (hazard ratio 1.27, 95% CI 0.47 to 3.41). This finding was unchanged in sensitivity analyses that explored looser and stricter criteria for a HIV diagnosis (data not shown).

Successes

Human immunodeficiency virus Self-testing Public Health Intervention clearly achieved its first objective in demonstrating the feasibility and acceptance of the online promotion and postal delivery of free HIV self-test kits, both as a cross-sectional (randomisation A) and a longitudinal intervention (randomisation B). It also demonstrated an important methodological principle: via linkage with the UK surveillance system run by PHE it was possible to use confirmed HIV diagnoses as the primary outcome, this being a more clinically relevant outcome than rate of testing per se.

TABLE 3 Overall acceptance and uptake of kits after randomisation into randomisation B in the RT arm

Total surveys sent out in RT arm	*N* = 8025
Completed surveys (% expected)	5733 (71%)
Test kit use (% completed surveys)	
Used test	4460 (78%)
Not used test	262 (5%)
Not received test	267 (5%)
Not requested a test[a]	741 (13%)
Missing	3 (< 1%)
Reasons for not using the test (% not tested)	
Tested elsewhere	57 (22%)
Changed mind	2 (1%)
Gave test to a friend	29 (11%)
Using later	161 (61%)
Other	12 (5%)
New kit requests (% eligible for another kit[b])	5085 (89%)
Reporting reactive test result (% used kit)	4 (0.1%)
Attending clinic for confirmation	4 (100%)
Clinic results (% attended clinic)	
Positive	3 (75%)
Negative	1 (25%)
Waiting result	0

a This is participant-reported and may not reflect actual kit requests. If a participant reports not requesting a kit, they are not asked any questions relating to kit use.
b Participants are eligible for another kit if they have not reported a positive clinic result or are waiting for a clinic result and have completed the 3-month regular survey.

Limitations

No significant effect of the intervention was found in terms of revealing undiagnosed prevalent infection (randomisation A) or decreasing the interval between infection and diagnosis among incident infections (randomisation B). This likely reflects rapid declines in HIV infections in MSM in the UK during the study period, which reduced the statistical power of the study. The wide confidence intervals (CIs) indicate that an important effect of HIVST cannot be ruled out. The validity of the analysis for randomisation B (randomisation A is not affected) would be jeopardised if the intervention affected the underlying HIV incidence, for example if performing regular HIV self-tests was associated with participation in more risky sex.

Generalisability of the findings is another concern. First, the trial was not accessible to those who do not use apps or are not online, although this became increasingly less important over time. Second, the trial participants were, by the fact they chose to enrol in the trial, interested in HIVST or potentially interested in testing in any case. However, we recruited a significant proportion of men who, based on self-reported risk behaviours, were at significant risk of HIV. Third, the trial only included those willing to provide name and address (to enable linkage to the UK surveillance database) and allow contact from the study team, whereas one of the main reported potential benefits of HIVST was its capacity for

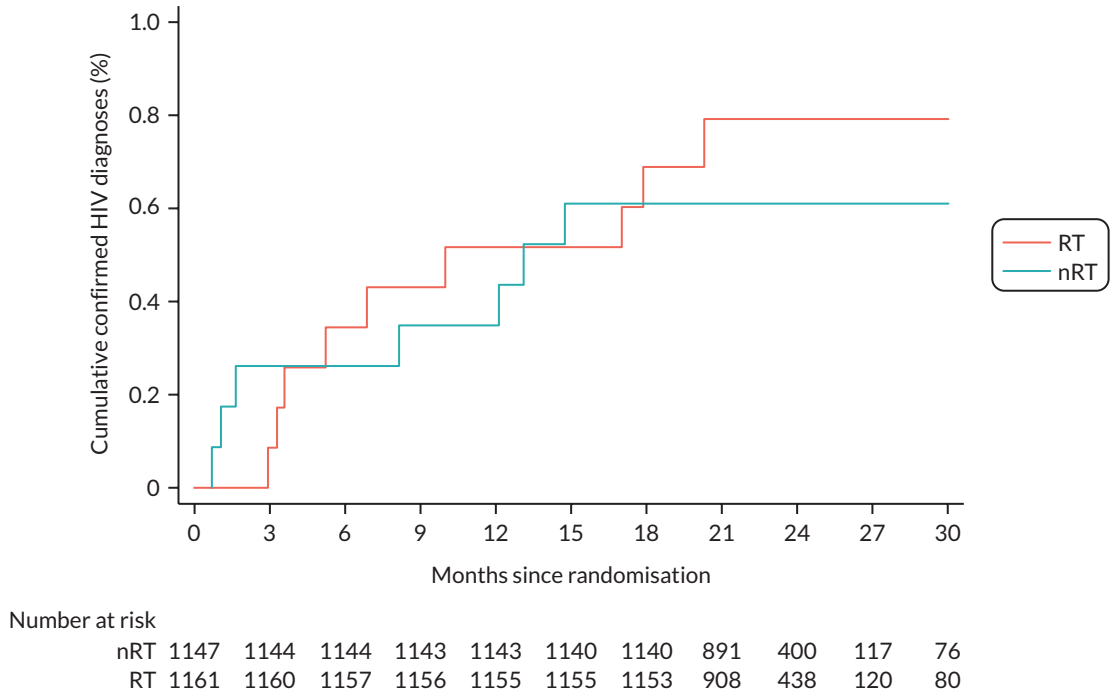

FIGURE 4 Kaplan–Meier plot of time to confirmed HIV diagnosis in randomisation B (*n* = 2308).

confidentiality compared to all other modes of testing. Fourth, we recruited low numbers of Asian, black and Latino men and *trans* people, who are at increased risk of HIV.

Study 2B: qualitative interviews with an human immunodeficiency virus Self-testing Public Health Intervention participants

This qualitative study was part of the process evaluation from WS1 which was extended to cover the RCT and aimed to:

1. explore how those utilising self-tests experience HIVST and the implications for further intervention development and scale-up.
2. explore how the SELPHI interventions might be experienced by, and the pathways to impact on behaviour for, different groups of RCT participants.

This study would specifically meet objective 4 of this WS.

Methods

We conducted a qualitative substudy in which 37 *cis*-MSM participants from the SELPHI RCT were interviewed: 10 during the pilot phase (May 2017) and the remainder during the main trial (January–October 2018). Interviews were conducted remotely (*n* = 17) or face to face (*n* = 20) based on location and geography.[38,39] Sampling was purposive and aimed for maximum diversity first based on HIV testing experience, then age and ethnicity.[38,39] Our topic guide was developed within the WS1 team and covered testing history, engagement with SELPHI, experience of the interventions and preferences for future HIVST interventions. Interviews were audio-recorded and transcribed verbatim.

Key findings

Aim 1: MSM were motivated to access the intervention because of a reduction of barriers related to stigma from clinic staff and attendees, as well as simultaneous increases in privacy and in convenience.[39] Overall, we found that individuals who had higher barriers to clinic access based on stigma, privacy concerns or geographic issues tended to describe HIVST as facilitating increased testing frequency, but with the potential to reduce STI screening by reducing incentives to access clinical services. However,

some minor adverse outcomes (*n* = 2; fainting, relationship discord) reported by two individuals were discovered spontaneously.[39] Finally, both individuals who had positive HIVST results linked to confirmatory care within 24 hours and described very high intervention acceptability, crediting the technology with 'saving their lives'.[39]

Aim 2: this analysis identified three groups: 'inexperienced testers', 'pro self-testers' and 'opportunistic adopters' (*Figure 5*).[38] Inexperienced testers were those who had little or no testing history and did not test out of routine; they were typically early in their sexual or testing careers and tended not to be very open about their sexual orientation or practice. They had high psychosocial barriers to testing relating to the COM-B domains of motivation (reflective and automatic), opportunity (social and physical) and capability (psychological).[38] These barriers included lack of risk perception, shame, fear of stigma, privacy concerns and low self-efficacy when considering testing in a clinic. HIVST ameliorated many of these concerns, facilitating testing uptake. The intervention performed most closely to hypothesised mechanisms of action for this group, with strong or moderate evidence across all intervention components (see *Figure 5*).[38]

'Pro self-testers' were often at an intermediate point in their sexual careers and sometimes lived partly hidden lives in terms of their sexual orientation. This group tended to have a testing history and were somewhat motivated to access testing, but their frequency was constrained by the high barriers to clinic access they faced (see *Figure 5*).

'Opportunistic adopters' were men who are well served by existing testing opportunities with few distinct COM-B barriers, except for some minor issues with opportunity (physical).[38] Some in this group used HIVST because of increased convenience, but the majority engaged with the intervention out of novelty and to respond to social norms around testing. The intervention largely did not perform as hypothesised for this group, with weak or moderate evidence across the majority of hypothesised mechanisms of action (see *Figure 5*).

Limitations

The SELPHI RCT required informed consent for the HIVST to be delivered to an address, residential or otherwise. This likely excluded the most marginalised and/or those with greatest concerns surrounding domestic privacy. Second, despite substantial outreach, we were only able to interview two participants

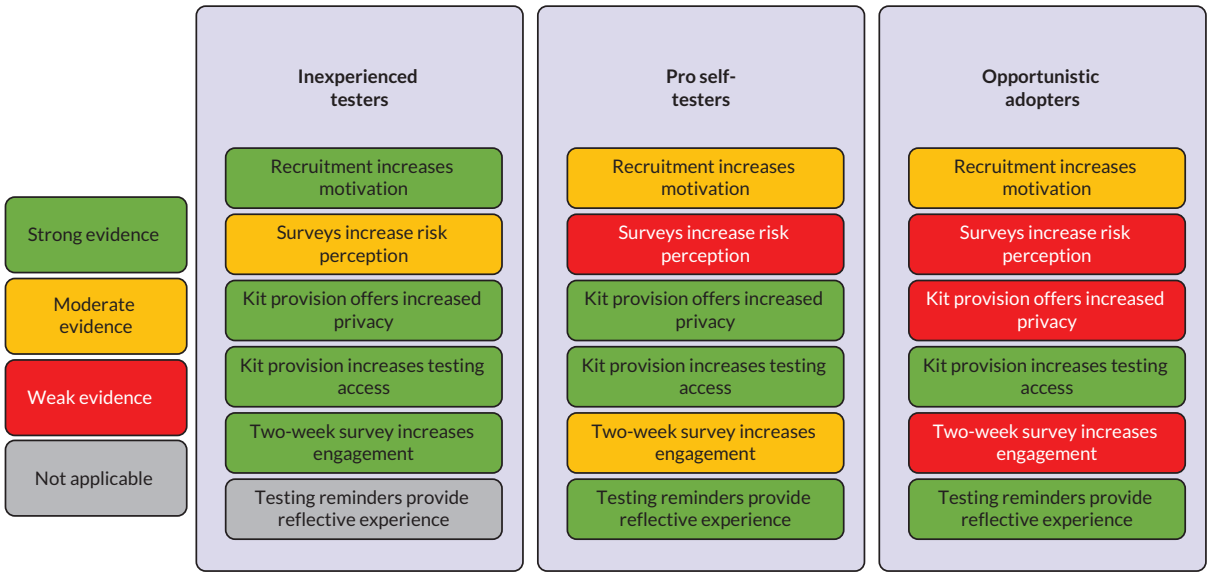

FIGURE 5 Groups of testers in SELPHI RCT.

who reported positive results. These accounts are therefore likely not reflective of the range of experiences within this group.

Successes

The study provided important and current data on HIVST acceptability after use. Prior evidence was largely prospective and explored the *perceived* acceptability and values and preferences of groups for HIVST. We also provided critical data demonstrating that these tests were feasible to use by a wide range of MSM. We found that the experiences of Asian, black and Latin American MSM were likely to be different from those of white ethnicity and therefore planned a follow-on study specifically exploring these, which is detailed below. In addition, the reports by two participants of adverse events prompted further study of the experiences of those who reported harms in the main trial.

Study 2C: human immunodeficiency virus Self-testing Public Health Intervention *trans* substudy

The aim of the SELPHI *trans* substudy was to:

1. describe key HIVST outcomes (HIV testing uptake/frequency, STI testing uptake/frequency, sero-status) and HIVST acceptability for *trans* people
2. describe *trans* people's experiences on the pathway to and experiences of gender-affirming health care and identify key issues and best-practice approaches.

This substudy specifically met objective 4 of WS2.

Methods

We undertook a *trans* peer-led qualitative substudy with *trans* participants in the SELPHI RCT in order to better understand their experiences of using HIVST. We conducted 20 interviews largely for practical reasons; this was the largest feasible sample with relatively limited numbers of *trans* participants who agreed to follow-up contact for qualitative research. The topic guide covered experiences of health care, mental health and gender identity services, previous HIV testing experiences, motivations for seeking HIVST, experiences of SELPHI trial infrastructure and potential intervention adaptations.

Analysis

Analysis combined framework and thematic approaches. Our framework drew from emerging themes identified during data generation, the wider literature around *trans* peoples' experiences of HIVST/sexual health services, theorised key components of intervention acceptability from formative and RCT acceptability work and systematic reviews. Our analysis plan for this subgroup mirrored that of the larger RCT within which it was contained. All analyses were complete case intention-to-treat.

Key findings

Human immunodeficiency virus Self-testing Public Health Intervention recruited and randomised 118 *trans* men and *trans* women (94 *trans* men, 24 *trans* women), of whom 20 (16 *trans* men, 4 *trans* women) underwent the second randomisation. At baseline 31% had never tested for HIV.[36] Sixty-two per cent (n = 59) of *trans* men completed the 3-month survey, but survey completion by *trans* women in nBT was too low (1/11) for randomised comparison. In *trans* men HIV testing uptake by 3 months was significantly higher in BT (95% 36/38) versus nBT (29%, 6/21) (RR = 3.32; 95% CI 1.68 to 6.55; $p < 0.001$). *Trans* people randomised to RT reported three-times higher rate of HIV testing compared to nRT during the 2-year follow-up [incidence rate ratio (IRR) = 3.66; 95% CI 1.86, 8.01; $p < 0.0001$].[36] Acceptability was very high in BT: 97% (38/39) found instructions easy to understand, 97% (37/38) found the HIVST simple to use and 100% (39/39) reported good overall experience. In interviews, reported HIVST benefits included increased autonomy, privacy, convenience and avoidance of healthcare providers perceived to be discriminatory and services that increased dysphoria.

Successes

This was the first HIVST RCT analysis which presents *trans* participants separately from *cis*-MSM and contributes to addressing an evidence gap identified in WHO guidelines.[16] We demonstrated the utility and potential of HIVST for this key group, and highlighted the unique challenges *trans* people face when accessing sexual health services.

Limitations

The number of *trans* people in the trial was small. Retention specifically of *trans* women was too low to enable randomised comparisons, meaning these results reflect the experiences of *trans* men rather than *trans* people overall. In addition, non-binary people were excluded from the RCT. This is a substantial evidence gap and an urgent priority for further research.

Study 2D: human immunodeficiency virus Self-testing Public Health Intervention Asian, black and Latin American men who have sex with men substudy

The aim of this substudy was to describe the experiences of and attitudes towards HIV testing for black, Asian and Latin American MSM who took part in the SELPHI RCT in England and Wales, and the implications for HIVST in these groups. This study specifically addressed objective 6 in WS2.

Methods

In order to understand the experiences of Asian, black and Latin American MSM within SELPHI, we conducted 29 interviews with these groups between April and July 2020. Interviews were conducted by various members of the WS1 team and by a peer researcher, a young black gay man. We initially sought a sample of 25 but found the research would benefit from further participants of Black African ethnicities; we therefore conducted a further four interviews with Black African MSM. Interviews were transcribed verbatim and the Framework Method[40,41] was employed to analyse interview transcripts.

Key findings

Men who have sex with men from minority ethnic backgrounds describe marginalisation and exclusion when engaging with the commercial gay scene in both offline and online spaces. In addition, men describe links between the gay scene, HIV testing and sexual health through peer interactions and exposure to sexual cultures. In accessing the scene MSM gain knowledge and are exposed to norms reinforcing the importance of protective behaviours.

Men from minority ethnic backgrounds faced difficulties in accessing sexual health services based on their experiences in waiting rooms and with clinical providers. Overall, HIVST was felt to be an empowering intervention, which led to increases in self-efficacy and provided the opportunity to test without accessing health services, more so for those who had complex relationships with GUM clinics.

Successes

The results from this substudy are novel in the UK where MSM from minority ethnic backgrounds are rarely the focus of HIV testing or prevention research. Further, our focus on Latin American MSM is a key strength as this group is profoundly underrepresented in sexual health research despite facing additional barriers to service access.

Limitations

Although focusing on the experiences of Asian, black and Latin American MSM has allowed for some comparison between these groups, it also meant that there were relatively small numbers of interviewees representing each of specific ethnicity. There are likely to be vast differences of experience and circumstance both within and between groups, which has implications for the generalisability of this work.

Study 2E: human immunodeficiency virus Self-testing Public Health Intervention harms substudy

The discovery of two adverse events (fainting and relationship discord) as part of the process evaluation for the pilot study prompted a need to quantify, describe and explore the types of harms that arose in the SELPHI RCT.

Methods

In order to develop nuanced understanding of the experiences of those reporting harm, we conducted a qualitative substudy examining participant accounts of their experiences of unintended negative outcomes in the trial and interviewed nine participants. We identified participants who reported one or more types of harm on the surveys (false positives, harm to relationships, harm to well-being, coercion to test) and invited them to participate in the interviews.

Analysis

Analysis of the qualitative data was conducted using QSR NVivo 12 (QSR International, Warrington, UK) and followed a narrative approach. Each participant account was treated as a self-contained story and important elements were coded based on their position within the narrative and the importance placed on that element (e.g. initial explanation, contributing features, critical point, resolution).

Key findings

The qualitative analysis demonstrated that harms were clustered in three main areas: technological harms (false-positive and false-negative results), intervention harms (related to the functioning of the intervention more broadly, e.g. psychosocial components) and socially emergent harms (harms to relationships or well-being, and coercion to test).

Successes

This was the most comprehensive study of HIVST harms in a high-income setting to date. We demonstrated that these are very rare and largely are related to the social circumstances of the individuals who experience them.

Limitations

The number of people reporting harms in SELPHI was low, making the results hard to generalise. We did not systematically collect data on intimate partner violence (IPV) within SELPHI. Although none of the participants who were interviewed because of 'harm to relationship' reported IPV, it may have been experienced by others during the trial.

Workstream 2: discussion

The SELPHI RCT recruited over 10,000 MSM into the study and showed that, across England and Wales, the online promotion and subsequent postal delivery of free HIVST self-testing kits were highly acceptable to MSM. Overall, the numbers of new HIV diagnoses in both arms of the trial were low (34 in total) after 3 months of follow-up, which reflected the national decline in HIV diagnoses at the time that SELPHI was conducted. STI testing rates were similar in both arms. Importantly in terms of linkage to care, the majority (10 of the 14 participants) who received a reactive result in the BT arm either had a clinic-confirmed positive result or were linked to the UKHSA database (implying a positive confirmatory result). HIV testing rates were higher in the BT arm and in the subsequent RT arm with no decrease in STI testing or increases in STI diagnoses or CAI, suggesting that while HIVST may be used to mitigate HIV risk, participants were also actively managing other STI risks. However, differing response rates between arms may have introduced some bias in comparisons based on questionnaire responses. Among participants in the nBT group who completed the 3-month survey, the proportion who had a HIV test between baseline and 3 months was twofold higher than the proportion who had a HIV test in the 3 months prior to enrolment. This suggests that participation in SELPHI even without an offer of a free self-test kit may have increased testing rates. One reason for this is that participants may have enrolled

in SELPHI because they were considering testing for HIV and when they were not randomised to receive a HIV self-test with the trial decided to test elsewhere.

Qualitative work with groups of MSM from SELPHI demonstrated that HIVST was highly acceptable for diverse groups of MSM, particularly marginalised groups that experience stigma and discrimination in traditional testing settings.[36]

Conclusion

Human immunodeficiency virus Self-testing Public Health Intervention demonstrated that it is feasible and acceptable to promote and deliver free HIV self-test kits to MSM. However, the provision of free HIV self-test kits did not reveal undiagnosed prevalent infection of HIV or decrease the interval between infection and diagnosis among incident infections. This may have been due to the rapid national decline in HIV infections in MSM in the UK, which occurred after the study was planned. HIVST has particular utility and potential for *trans* people and Asian, black and Latin American MSM who may not access HIV testing in more traditional settings. Very few harms arose from HIVST.

Workstream 3: modelling, cost analysis and economic evaluation to assess cost-effectiveness of strategies for human immunodeficiency virus prevention in men who have sex with men in the United Kingdom

Workstream 3: overview

The main objective of this workstream was to understand the contribution of different HIV prevention and testing uptake interventions in reducing the HIV incidence among MSM so far and to estimate the value (i.e. the maximum cost for an intervention to be cost-effective) of activities going forward (including self-testing) to support HIV elimination. To do this we adapted our existing individual-based simulation model, which simulates the population of MSM from the start of the HIV epidemic, tracking levels of CAS with long-term and casual partners and hence risk of HIV acquisition, according to ongoing HIV prevalence in men having condom-less sex (CLS). After infection, we use detailed information from cohort studies to model cluster of differentiation 4 (CD4) count, viral load, use of specific antiretroviral drugs, adherence, resistance, risk of AIDS and death. Areas of uncertainty for which definitive data were needed for the cost-effectiveness analysis were on longitudinal patterns of CLS around the time of infection and as a result of diagnosis. In order to collect this information, a prospective addition to an existing cross-sectional study [the Attitudes to and Understanding Risk of Acquisition of HIV (AURAH2) study (study 3A)] used frequent low-cost brief web-based questionnaires over a three-year period to assess recent sexual activity. In addition to providing information about longitudinal changes in risk behaviour, the AURAH2 study allowed us to investigate incidence and predictors of new HIV infections, and trends in HIV testing behaviour.

To ensure that the proposed economic evaluation would be relevant to the NHS, it was important that a carefully considered set of prevention activities were identified and evaluated, which we did through a systematic review of HIV-prevention interventions (study 3B). Estimates of the UK healthcare costs associated with different stages of infection were also calculated using electronic records from a single London-based HIV treatment centre, for incorporation into the cost-effectiveness model (study 3C).

In this workstream, we set out the overall scope in terms of interventions to be evaluated and conducted a number of studies to inform any necessary changes to the model in terms of structure as well as inform parameter values. This allowed us to estimate the value of HIV prevention and testing activities, including the potential role of self-testing in study 3D.

Workstream 3: introduction

There was a substantial national decline in new HIV diagnoses among MSM in the UK that was coincident with the SELPHI study, where new diagnoses nearly halved from a peak of 3214 in 2014 to

1700 in 2019.[42] The decline was attributed to a number of policies and interventions that limited the onward transmission of HIV, including the offer of immediate ART at diagnosis for PLHIV in 2015,[43] the availability of PrEP for HIV-negative people to prevent HIV acquisition,[44,45] which was initially only available through the PrEP Impact trial [capped at 26,000 people until 2019 when it became freely available on the National Health Service (NHS)][46] or through specific websites set-up to improve access to PrEP in 2015/6,[47,48] and ongoing HIV and STI screening offered by sexual health clinics and other healthcare settings. It was important to determine what policy investments might best support further progress towards HIV elimination and offer the most economically sound investment for the NHS.

Workstream 3: research aims and objectives

The aim of WS3 was to estimate the value of strategies, individually and in combination, to prevent HIV in MSM in the UK.

The specific objectives of WS3 were to:

1. provide prospectively collected data to inform parameters of the mathematical model through longitudinal assessment of:
    a. changes over time in the number of CLS partners
    b. number of CLS partners before, during and after the estimated period of primary HIV-infection, and time of HIV diagnosis.
2. assess the extent to which baseline demographic, socioeconomic, health and lifestyle factors and attitudes to HIV are predictive of subsequent levels of CLS, incident HIV infection and HIV testing behaviours.
3. conduct an updated systematic review and consult with key bodies to identify proposed HIV prevention strategies to include in the cost-effectiveness modelling analysis.
4. update estimates of HIV care costs through a resource linkage study.
5. determine the value (from an NHS perspective with outcomes expressed as quality-adjusted life-years) of strategies for preventing transmission of HIV in the UK among MSM, alone and in combination, including free self-testing provision after obtaining an estimate of the effect from our RCT in WS2.

Study 3A: human immunodeficiency virus incidence and risk behaviours in human immunodeficiency virus-negative men who have sex with men at the time of human immunodeficiency virus infection and after diagnosis through web-based longitudinal follow-up (to provide key parameters for the cost-effectiveness model): the Attitudes to and Understanding Risk of Acquisition of HIV study

The aims of the AURAH2 study were to estimate HIV incidence, to identify predictors of new HIV infections among originally HIV-negative MSM at risk of acquiring HIV, and to assess changes over time in sexual behaviour, recreational drug use, HIV testing practices and HIV incidence.[49] The AURAH2 study specifically provided data to meet objectives 1 and 2 of WS3.

Methods

The AURAH2 study was a prospective cohort study designed to collect longitudinal data on HIV-negative or undiagnosed MSM at risk of HIV infection. It used a combination of (one) paper-based questionnaire at the point of recruitment in sexual health clinics, and multiple (up to nine) online follow-up questionnaires over 3 years. HIV-negative (or presumed negative at enrolment) MSM adults (> 18) attending three sexual health clinics in Brighton and London were invited to participate.

Analysis

Records of all MSM enrolled in the AURAH2 were linked to national HIV surveillance data by the UKHSA, to ascertain the incidence of HIV diagnosis during follow-up. Person-years (PY) of follow-up

were calculated from the date of completing the baseline questionnaire until (1) the date of HIV diagnosis from UKHSA for men who seroconverted or (2) 3 months before the date of data linkage with UKHSA data sets was completed (30 June 2019) for men who did not seroconvert.

HIV incidence rates (IRs) were calculated as the number of new HIV infections divided by the number of PYs of follow-up. The associations of baseline factors and current calendar year with HIV incidence were analysed by calculating HIV IRs and using a two-level random-intercept proportional hazard model with sexual health clinic sites defining the second level, unadjusted and adjusted for age, country of birth and ethnicity, sexuality and education level. The second analysis examined associations of time-updated factors with HIV incidence using mixed-effect Poisson regression models. The use of hierarchical models was chosen to take into account clustering according to clinics (clustering within AURAH2 sites).

Key findings

Among all 1162 men enrolled in the AURAH2 study, 33 HIV seroconversions occurred over 4618.9 person years (PY) of follow-up: an overall HIV incidence rate of 0.71 (95% CI 0.51 to 1.00) per 100 PY. Incidence declined from 1.47 (95% CI 0.48 to 4.57) per 100 PY in 2013–4 to 0.25 (95% CI 0.08 to 0.78) per 100 PY in 2018–9; average annual decline was 0.85-fold ($p < 0.001$).

The investigation of within-person changes in sexual behaviour provided useful information that informed the model; the annual prevalence of CLS with two or more partners in the past 3 months increased somewhat during the study period of the AURAH (between 2013–4 and 2018), while group sex declined substantially, as did bacterial STI diagnoses. Past 12-month PrEP use increased significantly in the past year from 0% (none of 28 respondents) in 2013 to 43% (23 of 53) in 2018;[50] on the other hand, post-exposure prophylaxis (PEP) use peaked in 2016, then declined in 2018.

Limitations

Men in the AURAH2 study were recruited from sexual health clinics in urban areas of London and Brighton, were predominantly highly educated, employed, in a stable economic situation, and of white ethnicity, thus may not be representative of the broader MSM population in England and the UK.

Successes

The AURAH2 study was the largest observational cohort study of HIV-negative MSM in the UK at the time. The regular follow-up every 4 months allowed detailed data collection of sexual risk behaviour among a high-risk group of MSM, and linkage to national HIV surveillance data allowed complete ascertainment of HIV incidence. The study also captured unique data on PrEP use as it became more readily available in the UK.

Study 3B: identification of proposed prevention strategies to be modelled and estimates of effects

To address objective 3 of WS3, we conducted a literature review to identify and describe studies evaluating the efficacy or effectiveness of behavioural HIV-prevention interventions for reducing HIV incidence among MSM in high-income countries.

Methods

We undertook a systematic review to update a previous one which covered evidence to the end of 2012.[51] We searched nine electronic databases for RCTs up until the end of February 2021.

Key findings

The search process returned 10,539 records from all sources, reducing to 6645 after excluding duplicates, 298 after title and abstract screening and 49 after accessing the full text. The 49 studies

that were included underwent quality assessment and data extraction. Seven intervention types were identified: one-to-one counselling (16 studies),[52–67] group interventions (7 studies),[68–74] couples interventions (1 study),[75] online interventions (9 studies),[76–84] contingency management for substance abuse (3 studies)[85–87] and HIV PrEP (12 studies).[88–98] Outcomes considered were: HIV incidence; STI incidence; measures of CLS; partner numbers.

Overall, PrEP was the only intervention consistently found to be effective at reducing HIV incidence. One-to-one counselling, group interventions and online interventions were occasionally shown to be effective at reducing CAI, but the results suggested that implementing these would not necessarily lead to reduced HIV incidence.

Study 3C: estimating the hospital costs of people diagnosed with human immunodeficiency virus

Study 3C aimed to address objective 4 of WS3.

Methods

In this study, we used a routine clinical data set to estimate the clinic/hospital costs of treating HIV infection in England according to factors, such as viral load, CD4 count and history of virological failure. The analysis used the HIV electronic patient record (EPR) system from the North Middlesex University Hospital NHS Trust (NMUHT), a large North London-based hospital in England, serving an ethnically diverse population with higher-than-average levels of deprivation. The study included data recorded between January 2010 and December 2017 for all individuals who were aged 18 years or more at the time of HIV diagnosis.

Analysis

Resource use recorded in the database (e.g. inpatient episodes, day case and outpatient visits) was linked to 2018–9 NHS reference costs via generated Health Resource Grouping codes. We did not include antiretroviral drug costs as these are added separately in the modelling. A panel data set was constructed (with one panel representing a 3-month period), and cost data were analysed using general estimating equations.

Key findings

The final data set included 1768 people diagnosed with HIV, 36,850 quarterly periods and 69,917 clinic/hospital visits, 98% of which were outpatient appointments. The unadjusted mean cost per person living with HIV (PLWH) per quarter was £440 [standard deviation (SD) £606]. Outpatient visits accounted for 98% of hospital activity, and 88% of total costs. Inpatient stays were infrequent (once every 9 years on average), but relatively costly when they occurred, accounting for 6% of total costs. Multivariable analysis showed that the factors that increased quarterly costs the most were being a new patient to the Trust, having a low CD4 count category, followed by current viral non-suppression or previous virological failure. Demographic factors, such as ethnicity had a lesser impact on costs.

Limitations

The main limitations were that the analysis was based on records from a single HIV treatment centre and we were not able to incorporate socioeconomic or lifestyle factors (e.g. smoking), which are known to be key determinants of health outcomes in HIV-diagnosed populations. Thus, the independent contribution of such factors to total costs is unknown. In addition, the SARS-CoV-2 pandemic has unquestionably changed how most HIV and non-HIV NHS services are currently being delivered in the UK, with online or telephone outpatient consultations used to replace or reduce face-to-face attendances. The extent to which changes will remain permanent is unknown, meaning the relevance of our cost estimates for use in future studies is difficult to judge.

Study 3D: modelling the cost-effectiveness of human immunodeficiency virus prevention strategies, including human immunodeficiency virus testing interventions, using a simulation model to determine the cost-effectiveness (from a National Health Service perspective with outcomes as quality-adjusted life-years) of strategies for preventing human immunodeficiency virus transmission, alone and in combination

Study 3D had three main aims:

1. understand the contribution of different HIV prevention and testing uptake interventions in reducing the HIV incidence so far
2. estimate the impact on HIV incidence of continuation of current policies
3. estimate the value (i.e. the maximum cost for an intervention to be cost-effective) of activities going forward (including self-testing) to support HIV elimination.

Through addressing these aims, objective 5 of WS3 was completed.

Methods

We used a dynamic individual-based simulation model (the HIV Synthesis Model) that recreates the lifetime HIV risks and, for those acquiring HIV, HIV progression and treatment outcomes of the MSM population in the UK. In brief, we model age, CLS with primary (long-term) and short-term (e.g. casual) partners, presence of other STIs, HIV testing patterns, and then, in those infected with HIV, viral load, CD4 cell count, use of specific antiretroviral drugs, adherence, presence of specific resistance mutations, risk of AIDS and death, including death from non-AIDS conditions. The model was modified based on the findings of the study 3A and 3C.

The parameter values determining sexual behaviour, the transmission rate, testing patterns and the extent to which HIV diagnosis leads to a reduction in CLS are varied with each model simulation run by sampling from distributions and the model was calibrated to the most recent data available.[99]

Analysis

To address the first aim, having reconstructed the epidemic to date, we compared the HIV incidence in 2022 to that in counter-factual scenarios in which interventions from 2012 were either not introduced or introduced to a lower extent, to understand the role of the different interventions. The counter-factual scenarios considered were: (1) from 2012 CLS being high, at levels similar to those observed in 1980, (2) the HIV testing rate stopping increasing in 2012 and the policy of antiretroviral treatment (ART) at diagnosis (as opposed to when the CD4 count was below 350/mm^3) not being introduced in 2015, (3) a PrEP strategy not being introduced (through PROUD, self-sourcing, the Impact trial and lately general commissioning) with consequent lower levels of testing (as people on PrEP test every 3 months) and ART initiations, and (4) HIV testing rates stopping increasing in 2012, the policy of ART at diagnosis not being introduced in mid-2015 and PrEP not being introduced.

To address the second and third aims, starting from the 302 simulations to 2022 with the best fit, we projected forward from 2023 to 2103 to understand what is the maximum cost that it would be worth spending for activities enabling an increase in the uptake of evidence-based intervention to be cost-effective and the impact on HIV incidence of continuation of current policies. All costs and health outcomes are discounted at an annual rate of 3.5%. The following scenarios were considered to address the third aim:

1. no change in interventions – sexual behaviour, HIV testing behaviour, and the probability of being on ART, and of initiating and remaining on PrEP are fixed to the level reached in 2022
2. increase in the rate of HIV testing (around 30% increase, corresponding to around 400,000 men having tested in the past year)

3. increase in PrEP use (up to 140,000 at its peak, compared to the current 70,000)
4. decrease in CLS (from around 17% of MSM having five or more condom-less partners in the past year to 5%)
5. increase in HIV testing and PrEP use.

Key findings

Combination prevention, including a PrEP strategy (with its consequent repeat HIV testing in people at risk of contracting HIV, as people on PrEP are assumed to be testing every 3 months), increased HIV testing with ART initiation at diagnosis and condom use each played a major role in the reduction in HIV incidence observed so far in the UK among MSM. Without any one of them, the number of HIV infections in 2022 would have been roughly double.

Continuation of current activities should lead to a continued decline; however, this would not reach the target set by UKHSA in the 'Towards zero' action plan, which aims for < 50 HIV infections per year in MSM in the UK by 2030. Interventions leading to around a 30% increase in HIV testing or substantial increase in PrEP or decreases in CLS would further substantially reduce HIV incidence, by, respectively, 15%, 23% and 36%. A combined substantial increase in HIV testing and PrEP could avert 34% of infections. However, at the current cost-effectiveness threshold, a 16% reduction in the cost of delivery of testing and PrEP would be required for this scenario to offer value for money. Our modelling suggests that the introduction of PrEP may be cost-saving, but it would take 40 years for the incremental cost-effectiveness ratio to be below £13,000. Therefore, commissioners would have to sustain an additional cost for the first 20 years, unless drug prices substantially reduce.[100]

Limitations

Our estimates are obtained using a mathematical model, which is a simplification of the reality. Secondly, there is uncertainty over some parameter values used and we have incorporated this by sampling a number of parameters from distributions. Overall, we believe we have been conservative by choosing broad distributions, which may convey more uncertainty than there actually is. Third, the population simulated by the model, because of computer capacity, is 1/22 of the UK GBMSM population and this increases the stochastic variability of our results.

Work package 3: discussion

The results from the AURAH2 study provided a detailed observation of a cohort of HIV-negative MSM at risk of acquiring HIV over a 3-year period and provided key information for specific parameters of the model, particularly on sexual behaviour among MSM. The national decline in HIV diagnoses from 2016 onwards was reflected in the results of the AURAH2 study, indicating that while HIV prevention strategies are working, there remains a clear need to focus prevention efforts on potential transmission risk among a small group of HIV-negative MSM with risk behaviours. The HIV costing study highlighted the importance of timely diagnoses, as the strongest predictors of cost were having a very low CD4 count and being a new patient to the hospital trust. By compiling the information from studies 3A and 3C, the model-based cost-effective analysis demonstrated that multiple prevention strategies are necessary, and, in line with the systematic review on prevention interventions, PrEP offers clear potential benefits. Additionally, increasing HIV testing through modalities such as HIVST is necessary if HIV elimination is to be achieved in the UK. However, a reduction in the cost of delivery of HIV testing and PrEP is necessary in order to provide value for money.

Conclusion

The national decline in HIV incidence can be attributed to a combination of HIV prevention strategies, with PrEP being one of the major contributors, along with high testing rates, immediate HIV treatment initiation and good retention on ART for those diagnosed. The RCT did not demonstrate that self-testing increased HIV diagnoses. However, multiple prevention strategies such as increasing the uptake of HIV testing, PrEP and condom use are needed to achieve elimination of HIV in the UK.

Summary of the programme

The PANTHEON programme aimed to reduce HIV incidence by determining the most cost-effective HIV prevention and testing policies in MSM and *trans* people in the UK. Over the 6 years of our research programme, we undertook extensive and widely cited feasibility work (WS1), developed and implemented an innovative large-scale online RCT delivering HIVST to 10,135 MSM (WS1 and WS2) and conducted modelling work investigating cost-effectiveness (WS3).

During WS1 we worked in partnership with the WHO on systematic reviews used to update their normative guidelines on HIVST.[19] We led the key populations meta-analysis and the qualitative components of their values and preferences review,[16] producing crucial evidence on the potential for HIVST implementation globally.[18] The FGDs and interviews with stakeholders were instrumental in informing aspects of the trial in WS2,[20,28] as was the process evaluation that assessed the trial feasibility.[30,39] The extended process evaluation produced important social science research outputs throughout the trial.

Workstream 2 successfully implemented the RCT (SELPHI) that was used to address one of the main programme aims, investigating whether the provision of free HIVST increased rates of HIV diagnoses among MSM. While the results demonstrated that the intervention of a free HIVST did not lead to increased confirmed diagnosis of prevalent or incident HIV infections, the RCT remains the largest HIVST trial implemented in a high-income setting and has shown the potential of HIVST to increase HIV testing uptake without reducing STI testing or linkage to HIV care, particularly in more marginalised groups.[36] The primary results may reflect relatively low levels of undiagnosed infections due to falling incidence rates in the UK, also described in the longitudinal cohort study of HIV-negative MSM (Study 3A of WS3). The extended process evaluation to cover the whole RCT drew out unique narratives from marginalised groups of MSM and *trans* people who participated in the trial, elucidating the value that HIVST may have for these groups.

The substudies within WS3 were pivotal to informing the parameters of the model-based cost-effectiveness analysis for the PANTHEON programme and provided valuable contextual information within their own right.[101,102] The results from our modelling suggested that the introduction of a PrEP programme for MSM in the UK would be cost-effective and possibly cost-saving in the long term.[100] Furthermore a reduction in the cost of antiretroviral drugs (including the drugs used for PrEP) would substantially shorten the time for cost savings to be realised. This work directly influenced policy in Scotland (with provision of PrEP by NHS Scotland) and England (provision of PrEP through a large implementation study and the subsequent commissioning of PrEP by NHSE). A combination of prevention approaches will be necessary to contribute towards reductions in HIV incidence and progression towards the goal of HIV elimination in the UK.

Reflections on the successes and limitations of the programme

The impacts of the innovative research which emerged from PANTHEON have been substantial. WS1 had broad impact, leading to significant innovations in HIV testing in the UK and more widely. Our first acceptability study exploring HIVST values and preferences has become the most widely cited HIVST study in Europe.[20] The results from our RCT pilot and trial acceptability studies[20,32,38,39] have directly informed HIVST implementation through the voluntary sector in England, Wales and Scotland as well as the Republic of Ireland through organisations, such as the Terrence Higgins Trust, HIV Scotland and HIV Ireland. We have also sought to respond to critical questions pertaining to HIVST and health inequalities by optimising HIVST interventions for priority groups within the HIV response. In particular, our qualitative work with *trans* people has been met with substantial international acclaim. The results were

included in a NIHR alert and have filled an important evidence gap in expanding our understandings of the challenges *trans* people face when accessing gender-affirming care. Through this programme, we considered the cost-effectiveness of PrEP introduction in MSM in the UK, which directly influenced policy in Scotland (with provision of PrEP by NHS Scotland) and England (provision of PrEP through a large implementation study and subsequent commissioning of PrEP). This work was published in *Lancet ID*[100] and received significant media exposure including in the BBC, reflecting the importance and public impact of the work.

One of the original aims of PANTHEON was to ensure the adoption of cost-effective HIV-prevention interventions by directly working with policy-makers. The results of the RCT demonstrated that HIVST is highly acceptable, feasible to deliver and increases testing uptake; however, routine commissioning of HIVST has not yet occurred in England and Wales. Instead, commissioners have favoured the continued provision of HIVSS due in part to concerns about suboptimal linkage to care and issues of surveillance of those with reactive results. This is in spite of HIVSS performing less well than HIVST in terms of test completion, leading to significant unmet need.[32,103] A substantial potential role for HIVST exists, but clear, practical guidance facilitating scale-up is required to guide policy-makers, commissioners and voluntary-sector stakeholders to ensure roll-out occurs and meets the needs of a range of individuals. The WS1 team from PANTHEON have recently had follow-on funding from the NIHR programme development grants scheme (NIHR203298) to re-analyse existing data collected as part of this programme grant, and synthesise it with previous publications, leading to the development of an implementation action framework and toolkit. This research will promote and guide HIVST implementation in England and Wales.

Conclusions from the whole programme

Human immunodeficiency virus self-testing has the potential to increase uptake and frequency of testing among diverse groups of MSM, due to the privacy, utility and convenience ascribed to it. Through the PANTHEON programme of research, we demonstrated that HIVST is a highly acceptable form of testing that could complement and expand MSM testing strategies, is feasible to deliver at large scale and can increase testing uptake. Although the SELPHI RCT did not demonstrate that self-testing increased HIV diagnoses, the provision of free HIVST did increase testing rates and was found to have particular utility and potential for *trans* people and Asian, black and Latin American MSM who may face barriers to traditional HIV testing strategies.

A model-based cost-effectiveness analysis of HIV-prevention interventions suggested that, in the context of high levels of diagnosis of HIV and access to successful ART, PrEP could be a key intervention that is highly effective and cost-effective in further reducing incidence, but that commissioners would have to sustain additional costs for the first 20 years, unless drug prices substantially reduce. Activities to further increase the uptake of HIV testing, including HIVST, and condom use also remain important to achieve elimination of HIV in the UK.

Recommendations for future research

Over the course of this programme grant substantial progress has been made and the global evidence base surrounding HIVST has begun to mature. In several high-income settings, HIVST has been demonstrated to be feasible to deliver, and successful in improving uptake of HIV testing services and yield of positive results, especially among MSM.[104–106] The flexibility of the intervention provides policy-makers and commissioners with the ability to design HIVST interventions which respond to the specific needs of the populations with which they work.[19] Indeed, recent advances have focused on reaching individuals most likely to

have undiagnosed HIV and least likely to engage in services; approaches include using secondary HIVST distribution methods to access wider social networks of end-users as well as distribution in unconventional settings, such as sex-on-premise venues and through vending machines.[107–110] Nevertheless, some important evidence gaps remain especially critical to the UK context which must be addressed.

1. Substantial health inequalities among MSM related to ethnicity, migration status, educational attainment, social connectedness, gender and sexual identity exist. If HIV elimination is to be achieved in the UK, interventions, including HIVST, require careful planning to ensure they meet the needs of marginalised MSM. A better understanding of the role HIVST might play in the broader landscape of free HIV service provision and how the scale-up of HIVST could reduce rather than exacerbate inequalities is needed. As such, there is a need to better understand the personal contexts of HIVST use, as well as the place HIVST might take in the wider context of clinical services alongside the role of social and sexual networks in testing decision-making. An analysis exploring this is the focus of the PANTHEON 2 follow-on programme development grant.
2. There has been a recent shift to online models of testing to reduce the burden on bricks-and-mortar sexual health services, but also in response to the COVID-19 crisis.[103,111] While HIVST supports this shift and broadens the opportunity to test outside of a conventional setting, more work needs to be done to inform the scale-up of HIVST so that it can be commissioned at a national level. Furthermore, there remain unanswered social science questions critical to developing and targeting new health promotion interventions, which can contribute to improving well-being and to progress towards HIV elimination. Some of these analyses are the focus of the PANTHEON 2 follow-on programme development grant.
3. RCT evidence to date suggested that among key populations, HIVST compared to standard testing can reduce linkage to care. It is critical that innovative approaches to linking those with reactive HIV self-tests to care are developed.[16] In addition, further research on the potential of HIVST to link those disengaged from services to HIV-prevention interventions are a priority.[112]

Implications for practice

Prior to this programme of research, the role of self-testing for HIV among MSM had not been explored in the UK. Evidence was lacking on the potential impact of HIVST on diagnosis rates and on linkage to HIV treatment and care. Our results demonstrate that HIVST is widely acceptable and feasible for MSM and can increase the frequency of testing, including in those who do not test regularly and those at additional risk. Further, a HIV-prevention intervention such as self-testing may respond to specific health inequalities in marginalised groups of MSM more vulnerable to HIV but who have been left behind in HIV-prevention intervention strategies, as demonstrated in our research with Asian, black and Latin American MSM.

The successful dissemination of our findings on the cost-effectiveness of PrEP introduction in MSM in the UK has had and continues to have large implications for clinical practice. PrEP is now provided by NHS Scotland and NHS England and has played a substantial role in the reduction in HIV incidence among MSM.

Additional information

Contributions of authors

Janey Sewell (https://orcid.org/0000-0001-7148-2391) PhD Student. Coordinated the AURAH2 study in WS3.

Charlie Witzel (https://orcid.org/0000-0003-4262-261X) Assistant Professor. Took a lead role in the feasibility work and the qualitative analysis and PE (WSs 1 and 2).

David Dunn (https://orcid.org/0000-0003-1836-4446) Professor, Medical Statistics. Was a co-applicant on the research programme grant and led and contributed to the design and analysis of data in WS2. He was a member of the Core Management Group.

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Nadia Hanum (https://orcid.org/0000-0002-9648-5115) PhD Student. Analysed data from the AURAH2 study in WS3 and contributed to the dissemination of findings.

Andrew Phillips (https://orcid.org/0000-0003-2384-4807) Professor, Epidemiology and Biostatistics. Was a co-PI on the programme grant and contributed to the set-up, design and analysis of component studies in WS2 and led the modelling work in WS3. He was a member of the Core Management Group.

Alison Rodger (**https://orcid.org/0000-0001-8817-4651**) Professor, Infectious Diseases. Was the programme grant holder and chief investigator for the research programme, oversaw the design and running of all component studies, in particular the feasibility work and the SELPHI RCT, and led the Programme Management Group. She co-led the Trial Management Group.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

Registration, approval and ethics: SELPHI was prospectively registered with the ISRCTN (ref: ISRCTN20312003). Ethical approval for SELPHI was sought from and granted by the University College London (ref: 11,945) and the London School of Hygiene and Tropical Medicine (LSHTM) (ref: 9233/001). Ethical approval for the AURAH2 study was granted by NRES Committee London-Hampstead (REC ref: 14/LO/1881).

Information governance statement

University College London is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, UCL is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (https://www.ucl.ac.uk/data-protection/).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/AYHE4598.

Primary conflicts of interest: Charles Witzel reports grant funding from Wellcome Trust, HIV Ireland, and The Health Service Executive (Ireland) and consultancy fees from Four Health International and Gilead. Fiona Burns reports grants from the National Institute for Health Research (NIHR) Health Protection Research Unit in Blood Borne and Sexually Transmitted Infections, the Terrence Higgins Trust and Public Health England. Sheena McCormack reports a grant from the EU to fund the European HIV Alliance, an EDCTP and Gilead grant to fund the PrEPVacc programme, and a grant from Imperial College London to fund the COVAC1 vaccine trial, payment from Queens' university of Belfast and University of Bern for talks, support from the Japanese AIDS society and ECDC for travel to meetings, and is the Chair of DSMB overseeing DoxyPeP and D-PEP trials. Alec Miners reports a grant from Gilead for non-HIV-related research. Valentina Cambiano reports grants from the Medical Research Council and UNITAID and consulting fees from the World Health Organisation.

Publications and presentations list

Publications in peer-reviewed journals

WS1:

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WS1:

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- Witzel TC, Weatherburn P, Burns FM, Rodger AJ, Rhodes T. *What Role Does HIV Self-testing Have for Men Who Have Sex with Men in the UK? Testing Needs, Social Norms and Biological Citizenship*. In: 21st International AIDS Conference. Durban, South Africa; 2016.
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- Witzel TC, Guise A, Parkes L, Weatherburn P, Burns FM, Mandal S, *et al.* Working across epidemics: comparing the acceptability of self-led testing options for HIV and hepatitis C virus (HCV) among men who have sex with men (MSM) and people who use drugs (PWUD). *HIV Med* 2018;**19**:S66. BHIVA/BASHH Joint Annual Conference (poster presentation).
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- Witzel TC, Burns FM, Roger AJ, Bonell C, Lampe F, Speakman A, *et al. Using Social Science Methods to Understand Pathways to Impact: A National HIV Self-testing Intervention Targeting Men Who Have Sex with Men and Trans People in England and Wales*. In Symposia Session: Innovations in Social and Behavioral Science: Frameworks, Methods and Measures. AIDS 2018 (invited speaker presentation).
- Witzel TC, Bourne A, Burns FM, Rodger AJ, McCabe L, Gabriel MM, *et al. HIV Self-testing Intervention Experiences and Kit Usability: Results from a Qualitative Study Among Cisgender Men Who Have Sex with Men (MSM) in the SELPHI RCT in England and Wales*. AIDS Impact (oral presentation).
- Witzel TC, Burns FM, Bonell C, Rodger AJ, Weatherburn P. W*hat Are the Perspectives on Key Informants on the Implementation of HIV Self-testing in England? A Qualitative Study of Barriers, Facilitators and Anticipated Impacts*. BASHH conference 2017; 93:A42.

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- *The Present and Future of HIV Epidemiology*. 9th German Hepatitis/HIV Workshop, 17–18 April, Cologne, Germany.

WS3:

- Cambiano, V *Is PrEP for HIV Prevention Cost-effective in MSM in the UK?* Imperial College London, 15 June 2015.
- Cambiano V. *Is Pre-exposure Prophylaxis for HIV Prevention Cost-effective?* Seminar in the series 'Global Health and Development' at London School of Hygiene and Tropical Medicine, 17 June 2015 on 18 September 2015 in a webinar organized by EATG.
- Cambiano V. *Is PrEP for HIV Prevention Cost-effective in MSM?*'15th European AIDS Conference, 21–24 October 2015, Barcelona, Spain.
- *Cost-effectiveness of ART as Prevention*. Plenary Lecture, 22nd Annual Conference of BHIVA, 19–22 April 2016, Manchester, UK.
- Cambiano V. *Overview on Cost-effectiveness of PrEP: What Evidence is Available?* 27 April 2016, 'Pre-exposure prophylaxis in the EU/EEA setting: challenges and opportunities meeting' organized by the European Centre for Disease Prevention and Control, Stockholm, Sweden.
- Cambiano V. *Evaluation of the Cost-effectiveness of Pre-exposure Prophylaxis for HIV Prevention Among Men Who Have Sex with Men in the UK*. 15 July 2016, 10th European Conference on Mathematical and Theoretical Biology, Nottingham, UK.
- Cambiano V. *Brief Overview of Cost-effectiveness of PrEP*. 26 October 2016, 13th International Congress on Drug Therapy in HIV infection, Glasgow, UK.
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