Monitoring the treatment and health of patients accessing HIV care in low and middle-income countries

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by

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

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ABSTRACT

Monitoring patient health in low and middle-income country HIV care programmes is challenging, as, without evidence, measurement tools derived from high-income country studies have been adapted and paper-based monitoring systems quickly developed. An accurate understanding of the population in care may be compromised. This thesis examines aspects of HIV care: access to Cotrimoxazole preventive therapy (CPT), prevalence of common mental disorders (CMD), and tools used to measure outcomes on antiretroviral therapy (ART).

CPT access is frequently cited as being as low as 4% with few studies estimating long-term access. Estimated prevalence of CMD varies widely as little standardisation in measurement tools exists. And, while international ART programme monitoring recommendations exist, no study has compared the concordance, or otherwise, between information collected in different countries.

The first study in this thesis, in Ugandan and Tanzanian patients, estimates time from HIV diagnosis to CPT initiation, time spent on CPT and associated factors. These estimates are compared to reported data. CPT coverage and time on CPT were poor. The absence of unique patient identifiers means monitoring data cannot distinguish patients who were diagnosed and initiate CPT in different reporting periods. Furthermore, no long-term data are officially reported.

The second study estimates CMD prevalence and associated factors among HIV-positive Ugandans, and validates measurement tools for this. Prevalence was around 10% but no routinely-collected data identified at-risk patients.

Measurement tool validity was poor, and their use substantially overestimates prevalence.

The third study compares ART programme monitoring systems in Malawi, Uganda, Ukraine and Tanzania. There was little concordance with international recommendations, and discordance in additional data-items and paediatric age-groupings. This signalled a lack of understanding of how best to monitor the health of treated populations.

Finally, a fourth study is proposed with the aim of assessing the validity and predictive value of existing programmatic monitoring systems.

CONTRIBUTIONS AND PUBLICATIONS

My thesis is based on work conducted while working at the Medical Research Council Clinical Trials Unit at University College London (MRC CTU at UCL), with partners from the Evidence for Action Research Programme Consortium (EfA). EfA was a consortium led by the London School of Hygiene and Tropical Medicine (LSHTM), conducting research into issues relating to HIV treatment and care programmes in low and middle-income countries (LMIC). The consortium was funded by the UK Department for International Development from 2006 – 2012. Primary southern partners in the consortium were the National AIDS Research Institute, India, the Lighthouse Trust, Malawi, the Medical Research Council/Uganda Virus Research Institute (MRC UVRI), Uganda and Zambia AIDS related TB Project (ZAMBART), Zambia. Secondary southern partners included Mwanza Interventions Trials Unit (MITU), Tanzania and Perinatal Prevention of AIDS Initiative, Ukraine (PPAI). Northern partners included the LSHTM, International HIV/AIDS Alliance (IHAA), University College London (UCL), and the Medical Research Council Clinical Trials Unit (MRC CTU).

Chapter 1 of this thesis presents the background to my work. I am responsible for this complete write-up. Chapter 2 presents a review of the literature relating to the health of treated populations in LMIC. I am responsible for the complete review and write-up.

Chapters 3 and 4 describe a study assessing access to Cotrimoxazole Preventive Therapy (CPT). The study forms part of a wider study I designed with colleagues at the LSHTM (Justin Parkhurst, (JP)) and MRC CTU (Diana M Gibb, (DMG)). The aim

of the wider study was to examine how research results on CPT progressed from evidence to policy and practice. I wrote the grant application for the full study and secured funding from a Small Initiative Grant from EfA. The research to policy component was developed by JP and conducted in Malawi, Uganda and Zambia by Eleanor Hutchinson (EH), LSHTM. Briefly, this component demonstrated wide differences in the timing of national CPT policy development in the three African countries and found that ensuring the uptake of CPT evidence into policy was influenced by the following: the degree to which the local context and national health priorities within which the CPT research findings were based was understood; the degree to which the strength of the evidence and its relevance in-country was perceived; and having a powerful policy advocate to facilitate getting CPT onto the policy agenda [2, 3]. These results have been published and can be found in Appendix 1.1. EH wrote the first draft of these publications and I contributed substantially to their revisions.

The study included in my thesis describes how well, following national CPT policy formulation, CPT is accessed by patients newly diagnosed with HIV in Uganda and Tanzania. I was responsible for designing the study and for applying for and obtaining ethical clearance in Uganda, from the MRC UVRI Science and Ethics Committee (MRC UVRI SEC) and the Ugandan National Council for Science and Technology (UNCST), and in Tanzania from the National Institute for Medical Research. Copies of these approval letters can be found in Appendix 1.2. I trained the study research assistants Kate Coughlin (MRC CTU at UCL), Deus Wasswa (MRC UVRI) and Joseph Chilongani (MITU). I collected the data with the research assistants in Uganda and collected the initial data in Tanzania, the remainder were collected by the local research assistant. Data management was carried out by a

designated data manager (Gertrude Mutonyi, (GM)) in the Statistics section of MRC UVRI. I was responsible for undertaking the data analyses relevant to this thesis. The study was facilitated in country by the MRC UVRI, Uganda (Paula Munderi, Yunia Myanja) and MITU, Tanzania (Saidi Kapiga).

Chapter 5 presents the results of a cross-sectional study to assess prevalence and clinical risk factors for common mental disorders, and to validate tools used to measure this. I undertook the study in collaboration with a Ugandan Research Psychiatrist at the MRC UVRI (Dr Eugene Kinyanda, (EK)). I was responsible for designing the study in collaboration with EK with advice from Vikram Patel (LSHTM): I designed the sample size and sampling frame, the inclusion and exclusion criteria, the procedure flow from study recruitment, psychiatric assessment interview to screening tool validation interview. Having received copies of the international psychiatric tools from EK, I designed the interviews, working with the Ugandan database manager to ensure easy data-entry. My further responsibilities involved applying for and securing ethical clearance in the UK from the LSHTM and in Uganda, from the MRC UVRI SEC and from UNCST. The approval letters can be found in Appendix 1.3. I wrote the grant application and secured funding from a Small Initiative Grant from EfA. The study was facilitated in-country by the MRC UVRI, (EK). Discussions with the Head of Entebbe Hospital regarding logistics of the study were conducted by EK. A local psychiatrist was employed as Study Manager to supervise the day-to-day coordination of the study (Juliette Nakku) and psychiatric research nurses were employed to undertake the interviews. I was responsible for training the study manager and psychiatric research nurses in the use of the interview tools. HIV counsellors who conducted the screening tool assessments were trained by the study manager who led a period of pilot testing. I

maintained oversight of the study from the UK, receiving fortnightly feedback on the progress from the study manager. I was jointly responsible with EK for ensuring that solutions to day-to-day challenges were found in a timely manner. I was responsible for undertaking the data analyses relevant to this thesis. Information was also gathered during the interviews on a range of psychosocial factors (e.g. employment status, educational level attained, household income-level, use of positive or negative coping mechanisms, previous psychiatric history in the family) to understand the psycho-social aetiology of specific mental disorders in this African setting. The analyses of these factors was led by EK separately from this thesis and three papers on this work have been published. EK wrote the first drafts of these manuscripts and I contributed to their revisions. Copies of these publications can be found in Appendix 1.4.

Chapter 6 presents the results of a cross-sectional study to compare ART programme monitoring tools used in Malawi, Uganda, the Ukraine and Tanzania in 2008 and 2010. I was responsible for designing the study after discussions with EfA colleague Andreas Jahn, about how to interpret reported data from different EfA colleagues on retention in care in ART programmes without understanding what data on deaths, transfers-out and losses to follow-up were collected in each country. I was responsible for applying and securing funding for country visits to meet representatives from the Ministry of Health from a Small Initiatives Grant from the EfA consortium. The study was facilitated in each country by a member of staff in the EfA partner: Sam Phiri (Lighthouse, Malawi), Heiner Grosskurth and Saidi Kapiga (MITU, Tanzania), Pontiano Kaleebu (MRC UVRI, Uganda) and Ruslan Malyuta and Igor Semenenko (PPAI, Ukraine). I presented the 2008 comparison as an oral presentation at the International AIDS Conference, Mexico 2008 and I have

since published two papers on this study. The first paper compared the use of country monitoring tools, and the second paper described challenges associated with monitoring the health of the population in this way. I was responsible for the first and final drafts of these papers, having incorporated comments from co-authors. Copies of the IAS abstract and these papers can be found in Appendix 1.5.

Chapter 7 presents the design of a study to assess the predictive value and validity of ART programme monitoring indicators. I was responsible for designing this study. I submitted a funding application to the Wellcome Trust for this work but it was unsuccessful on the grounds that they do not fund operational research. I continue to look for avenues to fund this work.

ACKNOWLEDGEMENTS

This work was undertaken while I was employed at the MRC CTU at UCL as Epidemiologist for the Evidence for Action Research Programme Consortium (EfA). This work was only feasible with support from friends and colleagues in the UK and overseas.

I would especially like to thank Professor Kholoud Porter and Professor Ian Weller whom I have been privileged to have as my supervisors. I am extremely grateful to them for always finding time in their busy schedules to give guidance, encouragement and endless support. I am especially thankful to Professor Porter for her trust in my abilities, even when life threw in its surprises.

I am most grateful to Professor Diana Gibb for her support and advice. I am indebted to Dr Andreas Jahn for his generosity of time, despite a busy schedule at the Ministry of Health, Malawi, in assisting me to comprehend the complex area of monitoring of HIV care in low income countries. I am especially thankful for his approachable manner.

I am most grateful to Professor David Ross at the London School of Hygiene and Tropical Medicine for enabling EfA's funding of this doctorate and to Professor Vikram Patel, for his time to clarify many issues relating to mental health disorders.

Many colleagues at MRC Uganda Virus Research Institute (MRC UVRI), Mwanza Interventions Trial Unit (MITU), Peri-natal Prevention AIDS Initiative Ukraine (PPAI), national Ministry of Health Malawi, Uganda, Tanzania and the Ukraine, University

College London (UCL), the London School of Hygiene and Tropical Medicine (LSHTM), and the MRC CTU have helped make my job more manageable and the goals more achievable. I would like to express my gratitude to them all and in particular: MRC UVRI: Professor Pontiano Kaleebu, Professor Heiner Grosskurth, Dr Paula Munderi, Dr Yunia Mayanja, Dr Eugene Kinyanda, Dr Juliette Nakku, Gertrude Mutonyi and Deus Wasswa. MITU: Dr Saidi Kapiga and Dr Joseph Chilongani. PPAI: Dr Ruslan Malyuta and Dr Igor Semenenko. MoH Malawi: Dr Erik Schouten. MoH Uganda: Dr Wilford Kirungi and Dr Norah Namuwenge. MoH Tanzania: Dr Geoffrey Somi. UCL: Professor Deenan Pillay. LSHTM: Dr Justin Parkhurst. MRC CTU: David Dolling, Dr Andrew Copas.

This work would not have been possible without the help of patients, clinicians, nurses and clinic staff in a number of health centres in Malawi, Uganda, the Ukraine and Tanzania. I am very grateful to each of them for their help and support.

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AIDS – acquired immunodeficiency syndrome
ADI – AIDS defining illness
AE – adverse event
aHR – adjusted hazard ratio
aOR – adjusted odds ratio
AR – art register
aIRR – adjusted incidence rate ratio
ART – antiretroviral therapy
ART-LINC – antiretroviral therapy in low-income countries collaboration
AUD – alcohol use disorders
AUDIT - alcohol use disorders identification test
AUROC – area under receiver operating characteristic curve
CD4 – CD4-lymphocyte count
CI – 95% confidence interval
CES-D – centre for epidemiological studies depression scale
CMD – common mental disorders
CPT - Cotrimoxazole Preventive Therapy
CR – cohort report
CS – cross-sectional report
CTX - Cotrimoxazole
DBS – dry blood spots
DSM- diagnostic statistical manual of mental disorders
EfA – evidence for action research programme consortium
EPDS- Edinburgh post-natal depression survey
GAD – generalised anxiety disorder
GFATM – global fund to fight AIDS, tuberculosis and malaria
GPD – global psychological distress
HIV – human immunodeficiency virus
HIVDR – HIV drug resistance
HR – hazard ratio
HSCL – Hopkins Symptoms Check List

HTQ- Harvard trauma questionnaire

ICD – international classification of diseases

IDU – injecting drug user

IQR – inter quartile range

IRIS – immune reconstitution inflammatory syndrome

IRR – incidence rate ratio

K10 - Kessler's psychological distress scale (10-item version)

K6 – Kessler's psychological distress scale (6-item version)

KS – Kaposi's sarcoma

LMIC – low and middle-income countries

LSHTM – London school of hygiene and tropical Medicine

LTFU – loss to follow-up

MC – patient master card

MDD – major depressive disorder

MINI- mini international neuropsychiatric interview

MoH – ministry/ministries of health

MITU – Mwanza interventions trials unit

MRC UVRI – medical research council/Uganda virus research institute

MI – mental illness

NGO – non-governmental organisation

NPV – negative predictive value

OI – opportunistic infections

OR – odds ratio

PCP – pneumocystis carinii pneumonia/now classified as pneumocystis jeroveci

PEPFAR – president's emergency fund for AIDS relief

PHQ-9 – patient health questionnaire

PMTCT – prevention of mother to child transmission

PPAI- perinatal prevention of AIDS Initiative

PPV- positive predictive value

PTSD – post-traumatic stress disorder

py – person years

TB - tuberculosis

TDR – transmitted drug resistance

T/I – transfers-in

T/O- transfers-out

TMP-SMZ – Trimethoprim-Sulphamethoxazole

UK DfID – United Kingdom department for international development

UNAIDS – united nations department for AIDS

UNAIDS MERG – UNAIDS monitoring and evaluations reference group

UNGASS – united nations general assembly special session on AIDS

VL – viral load

WHO – world health organisation

WHO EWI HIVDR – world health organisation early warning indicators of HIV drug resistance

Chapter 1 Introduction

This chapter presents an overview of my thesis describing the rationale, aim and objectives and context of my work. In more detail I present a background to this thesis and I provide a summary of the work I undertook.

1.1 Overview

The Human Immunodeficiency Virus (HIV) is the cause of one of the most destructive disease pandemics in recorded history having killed over 25 million people in less than 30 years. Globally, an estimated 33 million people were living with HIV at the end of 2008 when I embarked upon the work included in this thesis [4]. The greatest burden of HIV is experienced in low and middle-income countries (LMIC), particularly in sub-Saharan Africa, which is home to more than two-thirds of all people living with HIV worldwide [4].

As HIV treatment becomes more accessible in LMIC and patient life-expectancy is increased, the number of patients requiring long-term management in care and treatment programmes increases exponentially. Having accurate epidemiological data on patients accessing HIV care and treatment programmes in LMIC is crucial to monitoring and controlling HIV. Furthermore, if reported data lack validity, their use to inform patient and programme management is limited. However, in LMIC, in the rush to keep pace with expanding access to HIV care, in the absence of scientific evidence, many measurement tools have been translated from versions developed based on high-income country studies and monitoring systems have been quickly developed which rely, for the most part, on paper-based records. Generating

accurate HIV-related data from resource-limited care programmes is challenging. Our resultant understanding of the treatment and health of populations in HIV care in LMIC may be compromised.

The overarching theme of this thesis is to examine how the treatment and health outcomes of people accessing HIV care are being measured in Low and Middle Income Countries (LMIC), and to provide recommendations for evaluating such measurements. Chapter 2 contributes to this theme by reviewing published literature primarily to identify which measures are used, and at which common time-points, to report on the health of populations in care, and to summarise retention and attrition in care, and immunological and virological response to therapy. Chapters 3 - 5 focus on two specific aspects of care: use of Cotrimoxazole Preventive Therapy (CPT) and screening for Common Mental Disorders (CMD). Access and retention on CPT, an intervention identified by the WHO as a key element of HIV care, by individuals newly diagnosed with HIV in Uganda and Tanzania is assessed, and compared to data reported in monitoring and evaluation reports. The prevalence and risk factors of CMD of patients attending HIV clinics in Uganda, an area identified by the WHO as under-researched, is estimated and simple screening tools, which are often used to measure and report prevalence of CMD among HIV-infected populations, are validated. Chapter 6 compares monitoring indicators used to assess the treatment and health outcomes of people accessing ART programmes collected by the Ministries of Health in four LMIC and discusses epidemiological challenges associated with the use of such indicators to measure the health of populations in care. Chapter 7 highlights the lack of evidence for current monitoring indicators used to assess the treatment and health outcomes

of people accessing HIV care and proposes a study to validate such indicators against longer-term outcomes.

The aim of my thesis is to contribute to our understanding of key aspects of the treatment and health of patients accessing HIV-care programmes in LMIC, to evaluate the ways in which this is measured, and to identify ways in which the health of populations in HIV care can be better monitored. The objectives are:

i) to review the health of the adult HIV-treated population in LMIC in published literature based on the most commonly reported outcome measures used to assess the health of treated populations,

ii) to examine two specific aspects of HIV care:
   a. use of Cotrimoxazole Preventive Therapy (CPT) as prophylaxis against opportunistic infections in Uganda and Tanzania, and compare clinic data with reported monitoring data,
   b. the burden of, and risk factors for, mental health disorders among patients accessing HIV care in Uganda, and to validate simple tools for their diagnosis,

iii) to compare tools and indicators used to monitor the health of populations on HIV treatment in Malawi, Tanzania, Uganda and Ukraine, to discuss challenges arising from monitoring the health of treated populations in the current way, and

iv) to design a study to evaluate the validity and predictive value of indicators used to monitor outcomes in HIV treatment and care programmes in LMIC.

1.2 Background

1.2.1 HIV and its pathogenesis

Acquired Immune Deficiency Syndrome, and its causative agent, HIV, were relatively recently discovered. In 1981, cases of an aggressive form of the usually benign skin cancer, Kaposi's Sarcoma (KS) and *Pneumocystis Carinii Pneumonia /pneumocystis jeroveci* (henceforth referred in this thesis as PCP) were documented in the United States [5, 6]. Around the same time in Zambia and the Democratic Republic of Congo (DRC, Zaire at the time), cases were emerging of aggressive KS which responded poorly to treatment, and in Uganda, cases of a new fatal disease called locally 'Slim', marked by severe diarrhoea and weight loss, were being documented [7-9]. By 1982, an apparently common immunologic deficit, linked to an alteration in the ratio of helper T lymphocyte cells to suppressor T cells, had been reported in gay men, injecting drug users, heterosexuals and haemophiliacs in high and low-income countries [10-12]. The name Acquired Immune Deficiency Syndrome (AIDS) was proposed [13, 14]. In 1983, researchers at the Institute Pasteur, France isolated a novel retrovirus, similar to the human T-cell leukemia virus (HTLV) and apparently belonging to a family of T-lymphotropic retroviruses [15, 16]. One year later, researchers at the National Cancer Institute named an association between a further member of the HTLV family, HTLV-III, and AIDS [17]. At the time, Slim disease in Africa was found to be associated with HTLV-III infection and the symptoms were known to be similar to AIDS symptoms seen in the neighbouring DRC [9]. In 1986, the International Committee on the Taxonomy of viruses proposed to name the commonly seen virus the Human Immunodeficiency Virus (HIV) [18].

HIV causes systemic disease. HIV infects the cells in the body normally responsible for mediating immunity. The HIV virus breaks down the T cells of the white blood cells that bear the CD4 receptor (CD4+). As the amount of virus in the host increases, the level of healthy CD4 T-cells, the body's natural defence against disease and infection, is depleted. This loss of cell-mediated immunity increases the infected individual's vulnerability to life-threatening illness [19]. In the absence of treatment, life expectancy with HIV is severely reduced. Untreated, it is estimated that the median survival time after HIV infection for adults in LMIC is 11 years [20-22]. For untreated infants in LMIC, disease progression is particularly rapid: the risk of dying in the first two to six months of life is particularly high and one third of HIV-infected infants are estimated to die before their first birthday with 30% - 50% dying before the age of two [23-26]. For untreated HIV-infected children in Africa, median life expectancy is two years and most are estimated to die before their fifth birthday [27, 28].

HIV-related immune suppression increases the opportunity for microbes and pathogens in the environment to find a host, resulting in so-called 'opportunistic infections' (OI) and malignancies developing in HIV-positive individuals. HIV-related OI have multiple patterns through which they affect the immune system including bacterial (e.g. *Mycobacterium tuberculosis*), protozoal (e.g. PCP), viral (e.g. cytomegalovirus), and fungal (e.g. cryptococcosis), together with HIV-related malignancies (e.g. KS, non-Hodgkin's lymphoma) [29] [30] [31]. Potentially preventable OI are the cause of more than half of all HIV-related infections and deaths in sub-Saharan Africa [32]. In adults in LMIC, tuberculosis (TB) is the most common OI and is among the leading causes of HIV-related mortality [33]. In 2012, the estimated global incidence rate ratio of TB disease for an HIV-infected

person was 29.6 (interval 27.1 – 32.1) greater than for a non-HIV-infected person [34]. . After TB, other bacterial pathogens account for considerable amounts of HIV-related disease in Africa [31]. In adults, preventing and treating bacterial-related OI is vital to improving survival. For HIV-infected children in Africa, lung infections (e.g. pneumonia) and blood infections (e.g. septicaemia) caused by bacteria (e.g. *Pneumococcus, Haemophilus influenzae, Staphylococcus aureus*) are the most common OI leading to HIV-related mortality [35]. In early infancy, PCP is the most common OI and is highly associated with mortality [36] [37]. Preventing PCP in infants could eliminate one third to one half of all HIV-related deaths in African infants [38].

Further clinical features of HIV include depression, anxiety and issues of quality of life which arise as individuals adjust to being diagnosed with a chronic life-threatening illness [39]. As early as 1983, soon after HIV had been identified, observations were reported among individuals diagnosed with AIDS of mental disorders including depression, a perception of isolation and anxiety about transmitting HIV to intimate contacts [40]. For individuals living with HIV, consequences of untreated mental disorders have been reported to include impaired quality of life, increased rates of HIV transmission, increased need and use of health services, poor adherence to treatment regimens, weakened immune function, and faster disease progression and mortality [41-53]. Some mental disorders are recognised as indicating late stage 3 or stage 4 HIV disease (new onset psychosis and mania) and signal the need to start anti HIV medication even if other clinical features are above the threshold for treatment initiation [54]. Identifying and addressing the needs of patients with mental disorders at an early stage is thus important.

1.2.2 The growing burden of HIV in low and middle income countries

By 2008, HIV had become a pandemic and an important cause of global mortality. An estimated 33.2 (30.6 – 36.1) million adults and children were living with HIV, and in 2007 alone, 2.7 (2.2 - 3.2) million people were newly infected and an estimated 2.0 (1.8 -2.3) million HIV-infected persons died [4]. Global adult (age 15 - 49 years) prevalence in 2007 was estimated at 0.8 (0.7 - 0.9)%. However, HIV disproportionately affects individuals in LMIC. In 2007, 67% of all people and 90% of the estimated 2.0 (1.9 – 2.3) million children living with HIV lived in sub-Saharan Africa. Adult prevalence in sub-Saharan Africa was estimated to be 5 (4.6 - 5.4)% [4]. The continent accounted for an estimated 75% (1.5 million) of all AIDS deaths. Table 1.1 shows the global burden of HIV disease by WHO-defined geographical region as estimated at the end of 2007, by descending order of adult prevalence [4, 20]. Malawi, Tanzania and Uganda have an estimated adult prevalence above the average of sub-Saharan Africa (nearly 12%, >6% and >5%, respectively) and are classified as LMIC with generalised HIV epidemics [4] [20]. In Eastern Europe and Central Asia, 1.5 million persons were living with HIV in 2007, 90% of whom were living in the Russian Federation (69%) or the Ukraine (29%). In the Ukraine, adult prevalence is 1.6%, double the global adult prevalence of HIV [20]. Data from Malawi, Uganda, the Ukraine and Tanzania form the basis of the work in my thesis. They provide examples of countries with limited resources facing the challenge of responding to a high burden of HIV.

1.2.3 HIV care and healthcare systems in low and middle income countries

The introduction of potent anti-HIV treatment, also known as Highly Active Antiretroviral Therapy (HAART), has led to a greatly reduced rate of HIV disease

Table 1.1 Regional HIV burden, 2007: number living with HIV, adult prevalence (15 - 49 years), and number of AIDS deaths (in descending order of prevalence)

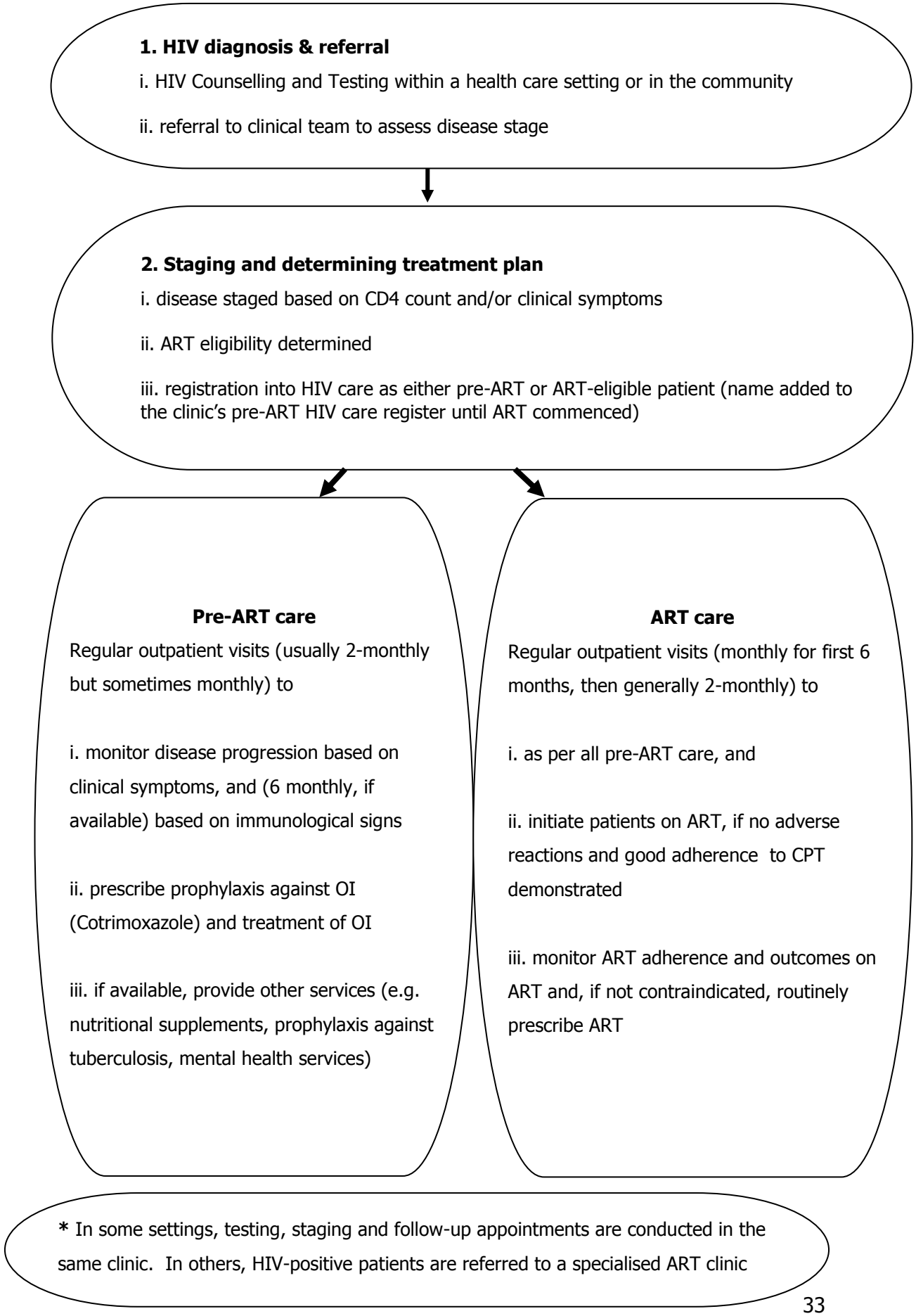
Region	**Adults and children living with HIV in (1000s) (range)**	**Adult (15 - 49 years) prevalence %**	**AIDS deaths in adults and children in (1000s) (range)**
Sub-Saharan Africa	22,000 (20,500– 23,600)	5.0 (4.6 - 5.4)	1,500 (1,300 – 1,700)
Malawi	**930 (860-1,000)**	**11.9 (11.0 - 12.9)**	**68 (59– 77)**
Tanzania	**1,400 (1,300– 1,500)**	**6.2 (5.8 - 6.6)**	**96 (86– 110)**
Uganda	**940 (870-1,000)**	**5.4 (5.0 - 6.1)**	**77 (68– 89)**
Ukraine	**440 (340– 540)**	**1.6 (1.2 - 2.0)**	**19 (14– 25)**
Caribbean	230 (210– 270)	1.1 (1.0 – 1.2)	14 (11 – 16)
Eastern Europe & central Asia	1,500 (1,100 – 1,900)	0.8 (0.6% - 1.1)	58 (41– 88)
North America	1,200 (760– 2,000)	0.6 (0.4 – 1.0)	23 (9.1 -55)
Latin America	1,700 (1,500– 2,100)	0.5 (0.4 – 0.6)	63 (49– 98)
Oceania	74 (66– 93)	0.4 (0.3 – 0.5)	1 (<1– 1.4)
South & South East Asia	4,200 (3,500-5,300)	0.3 (0.2 – 0.4)	340 (230- 450)
Western & central Europe	730 (580– 1,000)	0.3 (0.2 – 0.4)	8 (4.8 – 17)
North Africa & middle east	380 (280– 510)	0.3 (0.2 – 0.4)	27 (20– 35)
East Asia	740 (480– 1,100)	0.1 (<0.1 – 0.2)	40 (24– 63)
Global Total	33,000 (30,000– 36,000)	0.8 (0.7 - 0.9)	2,000 (1,800– 2,300)

progression, changes in the clinical course of HIV infection and increases in life expectancy [55-57]. From this point in my thesis, I use the term Antiretroviral Therapy (ART) when referring to current HIV treatment. For individuals accessing care, HIV can be managed as a chronic disease requiring life-long health-status monitoring and appropriate disease management.

The scale-up of providing access to ART in LMIC has been unprecedented. While, globally, sub-Saharan Africa has the highest HIV burden, in 2004 it was estimated that in the sub-continent, just over 1% of people in need had access to life-saving ART [4]. Since then, significant political and financial commitments have been made to make life-saving ART accessible to those most affected by HIV. These commitments resulted in over four million people accessing ART in 2007, a ten-fold increase over a 5-year period, with access growing by 42% in 2007 alone [20]. Within sub-Saharan Africa, during the four years from 2004 to 2008, ART coverage increased from an estimated 1% to 44% [4]. Multinational HIV treatment programmes have been hailed among the greatest public health successes of the twenty-first century [58].

The pathway to accessing HIV care in many LMIC is similar (Figure 1.1). Patients receive an HIV test at, for example, an HIV specialist care centre, a TB or antenatal care clinic or by health-care teams visiting communities throughout a country. If the test is positive, the patient is assessed to determine the stage of disease progression, on which the decision is made on whether they should be commenced on ART or they enter pre-ART care. This decision is based on an immunological or clinical assessment, depending on resources available. All HIV-infected patients are invited to attend follow-up appointments.

Figure 1.1 HIV diagnosis, treatment and care pathway in low and middle-income countries



If a patient is not yet eligible for ART, at the follow-up appointments they will receive prophylaxis against OI and disease monitoring to assess when treatment initiation becomes necessary. Prophylaxis against OI is given as a fixed dose combination of the generic drugs Trimethoprim and Sulphamethoxazole (TMP-SMZ). TMP-SMZ is produced under brand names including Bactrim, Bactrim DS, Bethaprim, Cotrimoxazole, Cotrim, Cotrim DS, Septra, Septra DS and Sulfatrim and is available in high quality generics. I refer throughout this thesis to TMP-SMZ as Cotrimoxazole (CTX). Given as a daily preventive therapy, it is referred to as Cotrimoxazole Preventive Therapy, Cotrimoxazole Preventative Treatment or Cotrimoxazole Prophylaxis. In my thesis, I use the term Cotrimoxazole Preventive Therapy (CPT). Providing prophylaxis against OI is vital for patients who are not yet eligible to initiate ART and the WHO recommends that it should be provided as key element of the chronic care package [59]. Various other services form part of the HIV-chronic care package. These may include, if available, advice on how to reduce the onward transmission of HIV, the provision of Isoniazid Preventive Therapy as prophylaxis against tuberculosis, the treatment of tuberculosis and other OI, nutritional support, and mental health services.

ART-eligible patients are initiated on ART and their response to ART is monitored continuously throughout their time in care. In 2008, the recommended first-line regimen combinations for adults were: Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP) (in one tablet called "Triomune") in Malawi; Zidovudine (known as AZT or ZDV), 3TC and Efavirenz (EFV) in Tanzania; ZDV and 3TC and either NVP or EFV in Uganda; and ZDV, 3TC and either EFV/NVP or Nelfinavir in the Ukraine [60-63]. For patients receiving and responding to ART, although the rates of disease

caused by major opportunistic pathogens decrease enormously, preventing OI is still important [64]. Therefore, in addition to receiving ART, patients receive the same care as that provided to pre-ART patients, including the provision of CPT.

At routine HIV care appointments, disease monitoring for patients accessing and not accessing ART includes assessing adherence to CPT and to ART regimens (if appropriate), monitoring the incidence of OI, the presence of drug toxicities, changes in weight and other clinical symptoms, as determined by the national MoH.

In LMIC, HIV care is coordinated by the national MoH, though care is often provided through a combination of the national health services, non-governmental organisations (NGOs) and private sector foundations. Because health centres vary in size and resources, there are often patient transfers between health centres, depending on individual requirements. Small clinics, health posts and outreach teams provide general care to patients with HIV, but often there are no specialist doctors in the care teams. In some small health clinics, HIV testing is provided but follow-up care has to be accessed in a health centre with more resources. More specialised care can be provided within peri-urban health centres and district hospitals, which are more likely to have specialist doctors. Regional and national hospitals can provide highly specialised care. Cases which cannot be managed in the original health centre will be referred up to the next appropriate level of care. Patients may also elect to transfer between health centres for logistical reasons (e.g. walking time to clinic) or reasons of stigma.

Our understanding of the health of populations accessing ART in LMIC is based largely on chronic disease monitoring systems that have been quickly adapted to

match the pace of expanding ART roll-out. Staff in health care centres aggregate data on individual patients in their care into summary reports for donors and the MoH. However, the accuracy of these monitoring systems, and in turn, our knowledge about the health of patient populations accessing HIV and ART care in LMIC, may be questioned.

1.3 Overview of chapters

My thesis evaluates key aspects of the treatment and health of HIV-infected patients accessing HIV care in Malawi, Uganda, the Ukraine and Tanzania and evaluates methods used to monitor this.

In Chapter 2, I present the results of a literature review on the health of adult patients treated within ART programmes in LMIC. The primary objective of the review was to synthesis evidence from cohort reports relating to i) survival and retention in care, ii) virological, iii) immunological and iv) other clinical outcomes of adult patients in HIV care. A secondary objective was to compare the outcome measures used to assess the health of treated populations.

In Chapters 3 and 4, I present a study I undertook to assess access to Cotrimoxazole Preventive Therapy (CPT) in Uganda and Tanzania. The aim of the study was to examine the extent to which the provision of CPT was being implemented in health centres on the ground. I estimated the probability of initiating CPT after HIV diagnosis among newly diagnosed patients or birth to an HIV-positive mother, examined time from HIV diagnosis/birth to CPT initiation and differences by age, sex and diagnostic clinic type. I also examined access to CPT for patients during their time in care and compared clinic data with reported CPT monitoring data.

In Chapter 5, I present a cross-sectional study I undertook to assess the burden of mental health disorders among patients in HIV clinics in Uganda, to identify whether routinely collected HIV-care data can identify at-risk patients, and to assess the validity of simple assessment tools which can be used by HIV health care workers to screen patients in care for mental health disorders.

In Chapter 6, I present a cross-sectional study I undertook to compare the degree to which internationally-recommended tools and indicators used to assess the health of populations in ART care have been incorporated into national monitoring systems in Malawi, Tanzania, Uganda and the Ukraine. The chapter also reviews challenges associated with using the current monitoring systems to assess the health of populations treated within ART programmes in LMIC.

In Chapter 7, I present the main recommendation from my thesis, that further work is necessary to determine how the health of populations treated within ART programmes can be better monitored. I describe the aim and design of a study to evaluate the ability of currently-used ART programme monitoring indicators to represent the health of the treated population by assessing the validity and predictive value of population-level monitoring indicators.

Chapter 8 discusses the contribution of this thesis to the wider context of the health of patients treated within HIV treatment and care programmes in LMIC. This final chapter outlines my recommendations and suggests further work that is needed to improve our understanding of the health of patients accessing HIV care in LMIC.

Chapter 2 Literature Review

2.1 Background

Programme managers and health professionals, entrusted with the care of the HIV-affected population, and donors accountable for their funds, have a responsibility to monitor and understand the health of the patient population within HIV programmes. HIV care can be viewed along a continuum, starting with prevention, HIV counselling, testing and diagnosis, disease staging/ART eligibility assessments, pre-ART care and ART care. Losses from HIV care along the continuum have been documented in two systematic reviews among adults and one among children [65] [66, 67]. This chapter focuses on outcomes of patients in ART care. With the advent of ART and the extensions to life-expectancy afforded by it, it has become possible to consider HIV a chronic disease [68]. Good chronic disease management is based on reliable information systems and a longitudinal record tracking a patient's clinically-relevant data and health outcomes [69] [53] [70]. Aggregated data from such systems can be used to monitor the welfare of groups of patients in care programmes and to measure and benchmark the performance of a programme [71] [72].

There is a growing body of literature on the welfare of ART-treated patients in LMIC. Systematic reviews to date have summarised information published before the end of 2009 relating to retention in ART programmes, immunological and virological outcomes on ART and rates of IRIS among patients in care in sub-Saharan Africa [73-77]. However, little is known about the health of patients treated within other LMIC geographical regions. Furthermore, most studies

included in reviews to date have presented information on short-term outcomes of ART programmes with the median duration of time on ART in one review being 10 months [75]. As HIV is now managed as a chronic condition and ART programmes expand globally, there is a need to understand the longer-term health of patients treated within ART programmes in LMIC. Moreover, as tracking the health status of patients in chronic care programmes over the long-term can be challenging, with few long-term outcome data reported, it would be useful to know if any early reported outcomes can predict later retention in ART programmes.

The aim of this chapter, therefore, is to review literature relating to the health of the adult population treated within ART programmes in LMIC and to explore whether any outcome reported at an intermediate time-point is related to later reported retention in care.

2.2 Methods

2.2.1 Search strategy

My search strategy involved multiple stages. Firstly, I used broad search criteria to identify studies published since the advent of ART in 1996 which reported on the outcome of patients treated within ART programmes in LMIC. I searched Medline through PubMed. The search was last updated on 22nd July 2013. I used the following search terms (MeSH and Text) resulting in the respective number of references:

i) HIV or AIDS or HIV/AIDS (290,763 references)

ii) combined with antiretroviral therapy (15,027 references)

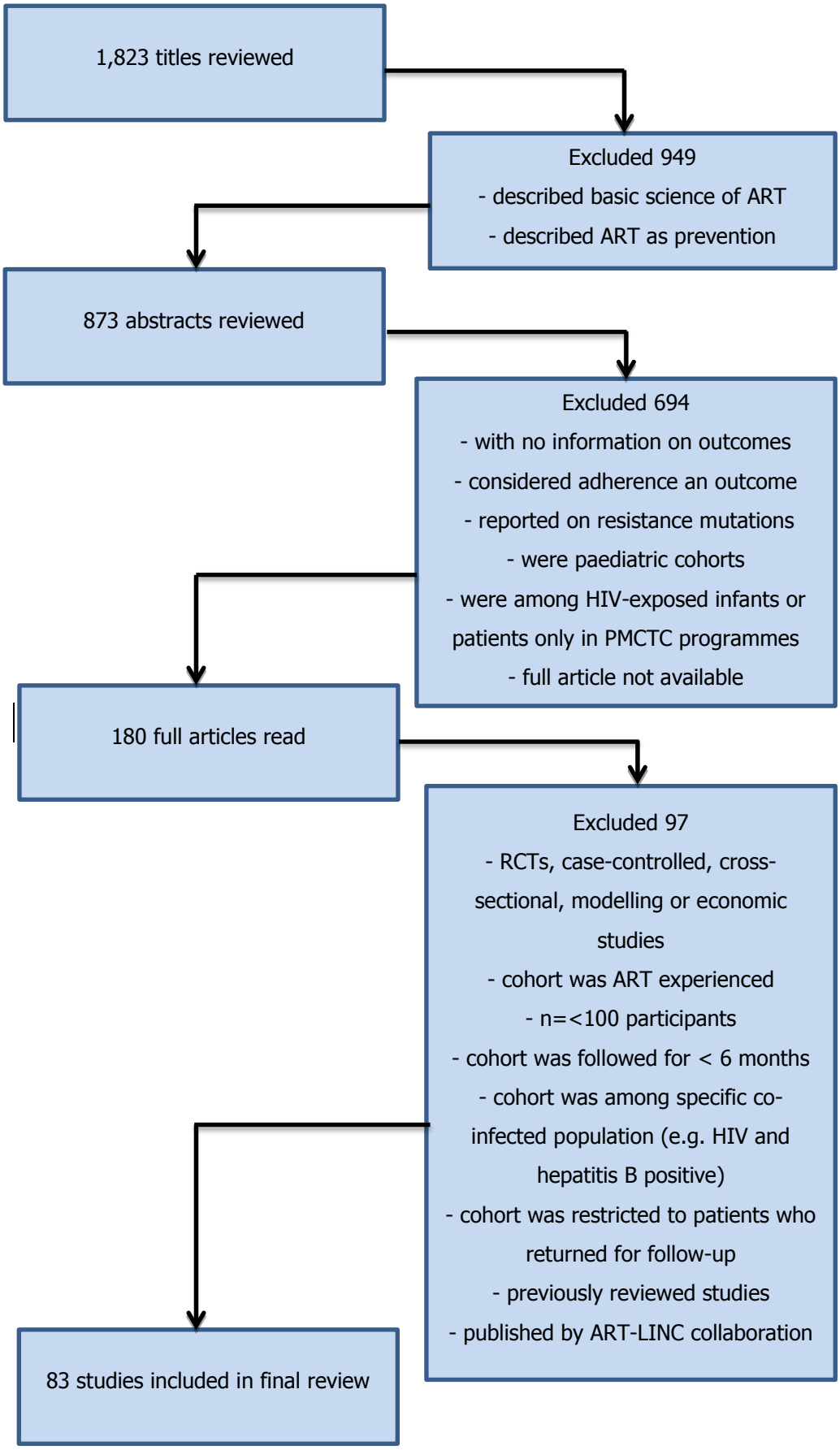
iii) combined with LMIC regional names: developing countries or low-income countries or Africa, Asia, Pacific Islands, Europe Eastern, Russia, Latin America, Central America, Caribbean Region (1,914 references)

iv) were English language and reported the outcomes of humans (1,823 references)

Secondly, having read 1,823 titles, I excluded titles that described the basic science of ART or referred to the use of ART as a method for the prevention of HIV transmission (Figure 2.1). Thirdly, therefore, I reviewed 874 abstracts and excluded studies which: did not report information on outcomes of ART, considered adherence an outcome of ART, only reported on resistance mutations, only reported on paediatric cohorts, or described outcomes for participants who were HIV-exposed or treated within PMTCT programmes. After these exclusions, 180 articles remained. Fourthly, as not all abstracts contained adequate information on study design or cohort inclusion criteria, I read the full manuscripts of these 180 articles and excluded studies that did not meet all of the following criteria:

a. prospective or retrospective observational cohorts (not randomised-control-trials, case-controlled-studies, cross-sectional, modelling studies or economic evaluations)
b. cohort patients were adults
c. patients were ART naïve at entry into the cohort
d. outcomes of more than 100 patients on ART were reported
e. cohort was followed-up for at least 6 months after ART initiation
f. cohort was not set up to study outcomes of a specifically co-infected population
g. cohort was derived at ART initiation and was not restricted to individuals who returned for follow-up visits

Figure 2.1 Flowchart depicting articles included in final literature review



I was unable to access the journals and retrieve the full manuscripts of three abstracts and I therefore did not include these data in this review.
In addition to the above inclusion and exclusion criteria, I excluded articles published by the Antiretroviral Therapy in Low Income Countries (ART-LINC) collaboration. ART-LINC was an international collaborative network of ART cohorts, some of whom participate in regional International Epidemiological Databases to Evaluate AIDS (IeDEA), TREAT Asia or CCASANet (Caribbean, Central and South America) collaborations. Some of these cohorts may have reported information independently and may already be included in my review. To avoid duplication, therefore, findings from ART-LINC cohorts, which met the above criteria, are summarised separately.

Finally, I excluded individual studies which had been reviewed in previous systematic reviews or meta-analyses, unless the study provided additional information not already reviewed (e.g. retention reviewed but immunological response not previously reviewed). I discuss the outcomes of my current review in the context of these reviews.

In addition to the above search strategy, I reviewed the latest global report published by UNAIDS which reports on the outcomes of country cohorts treated worldwide.

2.2.2 Data-extraction and summarising

I extracted and summarised information from the included articles relating to health status at ART-initiation and throughout follow-up using separate tables created in Microsoft Excel. I summarise the health status of patients initiating ART and throughout time in care using the most frequently reported outcomes. I summarise

the proportion of the treated patient cohorts retained in care as this is the closest proxy to survival on ART reported in most LMIC ART programmes. If outcomes were reported on the same cohort at different follow-up times in different manuscripts, data were combined. I do not summarise outcomes for sub-groups (e.g. sex, age groups, CD4 counts). When exploring the links between outcomes reported at intermediate time-points and retention in care at later dates, I did not include attrition outcomes (reasons for losses from care) as they directly influence retention.

2.3 Results

Eighty-three studies were included in this review (Table 2.1). The studies were from the following regions and countries:

Africa (61) : Botswana, Burkina Faso, Côte d'Ivoire, Democratic Republic of Congo, Ethiopia, Lesotho, Malawi, Mozambique, Nigeria, Rwanda, Senegal, South Africa, Tanzania, Uganda, Zambia and Zimbabwe

Asia (11): Burma, Cambodia, China, India, Indonesia, Lao

Eastern and Central Europe (3): Poland, Serbia

Latin America and Caribbean (3): Barbados, Jamaica, Curacao

Multi-country combined cohorts (5): including 2 from sub-Saharan Africa, 1 from Latin America and the Caribbean, 1 from Cambodia, Thailand, Kenya, Malawi and Cameroon, and 1 from 2 countries in Asia, 2 in Africa and Brazil.

The median number of patients included per cohort was 1,672 (range 100 – 829,640). Data were available from 5 systematic reviews and 16 studies from the ART-LINC collaboration [73-94]. Data on outcomes on ART from the latest UNAIDS report were available on 92 cohorts in LMIC [95]. UNAIDS data were provided for the following number of regional country cohorts: the Caribbean (10), Latin America

Table 2.1 Cohort characteristics at ART initiation, length of cohort follow-up, median length of time on ART, and retention in care (studies are ordered by publication date, with the most recent data first)

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
Uganda [96]	2004-2011	peri-urban hospital	6970	66%	36	-	82% <250	-	-	36	86%	36
Mozambique [97]	2004-2007	30 clinics	2596	62%	34	153	-	63%	-	18	-	-
Lao [98]	2003-2009	provincial hospital	913	44%	32	49	86%	87%	-	22	73%	24
Zimbabwe [99]	2005-2008	25 rural clinics	898	71%	-	119	66%	-	36	15	81%	36
Malawi [100]	2010	2 district hospitals	370	58%	-	-	-	-	6	6	76%	6
South Africa [101]	2006-2007	2 urban clinics	498	75%	35	106		69%	6	5	95%	6
Uganda [102]	2005-2007	ART programme in mental	773	64%	35	118	-	-	15	-	65%, 47% (mentally well, ill)	12

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
		hospital										
Nigeria [103]	2007	10 hospitals	4785	59%	34	152	-	45%	36	28	57%	36
Democratic Republic of Congo [104]	2005-2009	6 ambulatory treatment centres	1450	66%	40	150	24%	67%		19	57%	36
South Africa [105]	2004-2009	urban clinic	5996	-	-	-	-	-	-	28	-	-
Zambia [106, 107]	2006-2007	urban clinic	142	61%	32	34	-	-	3	3	59%	3
Ethiopia [108]	2005-2009	urban hospital	4210	59%	35	113	87%	75%	60	31	76%	60
Burma [109]	2003-2007	10 country-wide clinics	5963	61%	33	71	85%	94%	85	36	76%	60
Cambodia [110]	2003-2010	urban hospital	2581	52%	35	87	-	80%	-	-	-	-
Tanzania [111]	2005-2010	101 clinics with electronic data	88875	66%	(36-37)	-	-	-	54	10	56% (m) 60% (f)	60

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
Tanzania [112]	2007-2010	2 urban hospitals	486	-	-	-	100%	5% stage IV	11	-	63% (ART) 55%(&TB treatment)	12
South Africa [113]	2002-2009	peri-urban clinics	818	87%	(20-28)	116	-	-	-	31	-	-
Tanzania[114]	2004-2009	urban clinics	18965	67%	36	124	55%	85%	-	-	-	-
Burkina Faso [115]	2003-2009	24 country-wide clinics	5608	70%	35	124	83%	82%	-	23	77%	24
Rwanda [116]	-	urban women's clinic	490	-	36	185		most stage IV	15	-	79%	12
Uganda [117]	2004-2010	11 regional & 35 rural clinics	22315	69%	-	-	84% <250	42%	-	-	-	-
South Africa [118]	2004-2007	urban hospital	9040	66%	-	81	-	-	-	19	71%	24
South Africa [119]	2003-2008	279 community &	15060	36%	38	127	-	61%	-	22	40%	24

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
		workplace-clinics										
China [120]	2006	multiple clinics in 31 provinces	3457	41%	38	109	78%	-	24	21	84%	24
Tanzania [121]	2004-2009	urban clinic	18271	65%	36	112	78%	85%	36	12	-	-
India[122]	2002-2004	urban hospitals & non-hospitals	141	-	-	218	-	-	-	15	-	-
Jamaica[123]	2004-2009	urban hospital	165	56%	37	186	-	-	-	-	-	-
Nigeria [124]	-	urban clinic	130	69%	-	-	-	-	12	-	-	-
Uganda [125]	2004-2005	urban clinic	559	69%	38	98	-	88%	36	-	71%	36
Uganda [126]	-	urban clinic	219	70%	36	130	-	49%	-	-	83%	12
Lesotho [127]	2008	decentralised clinics	1124	68%	39	-	-	-	24	16	-	-

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
Curacao [128]	2005-2008	urban hospital	123	38%	44	141	63%	-	12	-	80%	12
South Africa [129]	-	multi-site workplace programme	3270	7%	45	155	_	45%	12	_	-	_
South Africa [130]	2002-2008	peri-urban clinics	3162	67%	34	_	89%	75%	84	29	63%	60
Lesotho [131]	2006-2010	14 clinics, 1 hospital	1177	67%	38	212	46%	_	_	17	-	_
South Africa [132]	2004-2008	urban hospital	7536	67%	36	_	88%	_	_	21	79%	24
Uganda [133]	2004-2005	urban clinic	559	70%	38	98	_	_	36	33	74%	36
South Africa [134]	2004-2009	peri-urban clinic	1154	65%	32	122	-	76%	-	17	-	-
South Africa [135]	2004-2006	32 clinics	28835	67%	34	-	-	-	-	22	78%	24
Senegal [136]	1998-2002	urban clinic	404	55%	37	128	-	56%	-	-	73%	42

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
Nigeria [137]	2005-2006	5 hospitals	5760	59%	35	121	76%	-	-	7	-	-
South Africa [138]	2004-2006	urban hospital	1719	82%	38	79	-	-	-	-	-	-
Uganda [139]	2003-2009	urban clinic	5982	66%	37	117	-	-	-	20	69%	24
Malawi [140]	2005	urban hospital	300	61%	36	157	-	29%	12	-	72%	12
Indonesia [141]	1996-2008	urban hospital	626	-	-	99	-	-	-	12 (IDU) 8 (non IDU)	67%	6
South Africa [142]	2001-2006	3 rural clinics	7322	68%	31 (f), 36 (m)	43	-	-	60	-	65%	60
Serbia [143]	1998-2007	urban clinic	563	31%	-	-	78%	-	-	72	-	-
China [144]	2001-2007	multiple-clinics 1 province	512	-	-	123	-	-	-	27	81%	60
Uganda [145]	2004-2007	peri-urban clinic	3628	61%	35	95	-	-	45	-	-	-
China [146]	2002 - 2008	multiple clinics	48785	42%	38	118	-	-	60	17	76%	60

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
Côte d'Ivoire [147]	-	urban hospital	303	75%	35	150	70%	21%	-	-	95%	6
Rwanda [148]	2004-2005	71 clinics	3194	65%	37	141	-	-	-	-	-	-
South Africa [149]	-	multiple clinics	1480	70%	34	97	73% <150	80%	-	25	72%	54
Latin America & Caribbean [150]	1996-2007	7 urban clinics	5152	35%	37	107	63-85%	-	-	-	86%	12
sub-Saharan Africa [151]	2001-2006	workplace programme	249	41%	39	170	-	24%	67	32	89%	48
Malawi [152]	2006-2007	1 hospital & 9 clinics	4074	61%-72%	32	-	-	96%	-	5	83%	12
South Africa [153]	2004-2007	urban clinic	7512	66%	35	58(TB) 94(no TB)	88%	10%	-	14	-	-
Ethiopia [154]	2004-2006	rural hospital	1002	57%	34	89	-	-	-	-	-	-

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
Botswana [155]	2002	urban hospital	349	59%	35	22	-	90%	-	14	78%	12
Uganda [156]		peri-urban hospital & home-based care	1625	72%	39	157	68%	-	-	13	-	-
India [157]	2005	urban hospital	142	36%	38	-	-	-	6		69%	6
Botswana [158]	2002	32 clinics	633	60%	35	67	-	81%	-	42	-	-
South Africa [159]	2001-2006	3 rural clinics	3970	68%	31 (f), 36 (m)	-	-	-	72	-	-	-
South Africa [160]	2003-2006	rural clinic	609	71%	35	67	-	-	12	-	67%	12
South Africa [80]	since 2001	10 clinics	2348	71%	33	80	-	91%	24	11	-	-
Côte d'Ivoire [161]	2004-2007	19 clinics	10211	70%	36	123	-	81%	-	18	-	-

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
Mozambique, Tanzania, Malawi [162]	2003-2005	12 clinics	3456	60%	37	166	62%	72%	12	-	-	-
Senegal [163]	1998-2002	multiple clinics	404	55%	37	128	-	56%	-	46	-	-
Abidjan [164]	1998-2003	urban clinic	187	69%	-	174	-	-	-	19	89%	24
South Africa [165]	2004-2005	urban hospital	1735	63%	-	-	-	-	48	-	-	-
Cambodia [166]	2001-2005	urban hospital	1735	42%	32 (f), 35 (m)	20	99%	-	24	13	87%	24
Zambia [167]	2004-2005	18 clinics	16198	61%	35	143	-	73%	-	-	-	-
Cambodia, Thailand, Keyna, Malawi, Cameroon [168]	2001-2003	5 multi-site programmes	3151	57%	33-35	-	90%	13% - 47%	-	7	-	-
Barbados [169]	2002-2003	urban clinic	158	42%	39	74	82%	-	12	-	94%	12
Côte d'Ivoire	1996-		129	63%	32	125	-	87%	-	26	88%	2

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
[170]	2003	multiple clinics										
South Africa [171]	2005-2009	multiple clinics	829640	-	-	-	-	-	-	-	76%	51
Studies reviewed with no aggregated baseline or retention data												
Poland [172]	2000 - 2002	10 clinics	-	-	-	-	-	-	-	-	-	-
India [173]	2006-2007	urban hospital	100	-	-	-	-	-	-	-	-	-
6 African, 2 Caribbean countries [174]	2004-2005	27 clinics	13391	-	-	-	-	-	12	-	-	-
Malawi [175]	2008-2009	rural hospital	555	-	-	-	-	-	-	6	90%	6
Zambia [176]	2007-2009	multiple urban	10485	-	-	-	-	-	-	8	-	-

Country	Year of ART initiation	Sample	Cohort size	Proportion female	Median age (years)	CD4 cells/mm³ (median)	CD4 <200 cells/mm³ (%)	WHO stage III/IV or CDC C/D (%)	Length of cohort follow-up (mths)	Median Time on ART (mths)	Retained in care (%)	Retention reporting time (mths)
		clinics										
Serbia & Montenegro [177]	1998 - 2005	urban clinic	481	-	-	-	-	-	-	72	-	-
Malawi [178]	2005	-	4347	-	-	-	-	-	12	-	65%	12

(15), East Asia (2), South and South East Asia (12), Eastern Europe and Central Asia (10), Middle East and North Africa (12) and sub-Saharan Africa (31). The median size of the cohorts was 714 patients (range 5 – 144,854).

Studies reviewed were of heterogeneous study design (including retrospective reviews of routinely-collected records, prospective studies and research-specific data gathering), size and geographical origin which may influence the ability to compare cohort outcomes. The results from studies whose cohorts form part of existing research groups or which were set-up to ask a specific research question may be biased towards higher retention rates as the quality of care in such sites may be better as a result of additional resources. Furthermore, key outcomes such as deaths, losses to follow-up (LTFU) and transfers-out may have been better captured in prospective studies if staff understood the importance of accurately capturing these outcomes compared to retrospective data-collection. Conversely, data-completeness on key outcomes for cohorts with larger number of patients may have been less accurate than for smaller cohorts, due to overburdened staff in large health centres. Although I do not show these data, the age-definitions used for adults varied between studies, with some cohorts including patients as young as 14 years while others only included adults aged ≥18 years. Adolescents experience lower rates of virological suppression and immune recovery and higher rates of rebound, therefore, comparing aggregated results from cohorts with varying proportions of adolescents must be done with caution [179].

Previous systematic reviews and meta-analyses of the health of the treated adult population in LMIC have focused on sub-Saharan Africa [73-76]. This review adds to our knowledge by expanding to countries in Latin America, Asia and Eastern

Europe. Nevertheless, the majority (63, 76%) of included studies were based in sub-Saharan Africa. In fact, of the single-country African studies, nearly half (29, 48%) were based on cohorts in South Africa or Uganda. This distribution of literature somewhat reflects the global HIV disease burden at the time of the literature search in 2013, as sub-Saharan Africa continues to have the highest adult prevalence of HIV (4.7%, CI 4.4 – 5.0%) compared to Latin America (0.4%, 0.3 – 0.5%), the Caribbean (1.0%, 0.9 – 1.1%), East Asia (0.1%, 0.1 – 0.1%), South and South East Asia (0.4%, 0.2 – 0.4%) or Eastern Europe and Central Asia (0.7% (0.6 – 0.9%) [95]. If HIV prevalence were an explanation for the dominance of literature from Africa, countries with high prevalence should be represented here. However, some countries with extremely high prevalence (e.g. Swaziland at 26.5% (24.6 – 28.3%), Botswana 23% (21.8 – 24.4%) or Lesotho 23.1% (21.7 – 24.7%)) are either poorly represented here, or not represented at all [95]. It is possible that researchers from such countries elect not, or do not have resources, to publish in international journals, despite information most likely being available in unpublished government documents. However, it is also possible that international journals prioritise data from certain geographical regions, resulting in a lack of published literature from studies assessing the health of the treated population in areas other than sub-Saharan Africa.

In LMIC geographical regions outside of sub-Saharan Africa, the number of patients living with HIV and accessing ART programmes continues to grow [95]. Most ART programmes, globally, are required by programme funders and MoH to collate data and compile reports to monitor the health of patients in their care. Given the availability of these pre-generated data, it is surprising that more ART programmes do not publish articles using these data. There is an obligation to monitor, publish

and understand the outcomes of patients treated in ART programmes throughout the world.

2.3.1 Health of patients at ART initiation

The most commonly reported cohort characteristics were proportion female, median age, median CD4 cell count, proportion with CD4 <200 cells/mm^3, and proportion in WHO stage III or IV or CDC stage C or D (i.e. those with more advanced clinical disease). Less commonly reported characteristics at ART initiation included viral load (VL), Body Mass Index (BMI), and proportion with tuberculosis (TB).

Patients initiated ART at a median age of 36 (range 32 – 45) years. The majority (median 65%, range 7 – 87%) of patients were female. The median weight was 51 (range 46 – 57) kg (n=7) and the median BMI was 19.9 kg/m^2 (IQR 19 – 22.3) (n=18), higher than the BMI used to classify patients as underweight (18.5kg/m^2). The majority of patients (median 75%, range 10 - 96%) initiated ART at late stage HIV (WHO stage III/IV or CDC stage C/D) with the median CD4 count being 119 (IQR 95 – 143) cells/mm^3. A median of 80% (range 24 – 100%) of participants initiated ART with a CD4 < 200 cells/mm^3 and the median viral load was 5.1 (IQR 4.9 – 5.3) log copies/mL (n=18). The median proportion with TB was 16% (range 2 – 54%) (n=15).

This demographic and clinical profile of patients initiating ART in LMIC is similar to that described in earlier systematic reviews of ART-treated patients in sub-Saharan Africa [75] [76]. This emphasises the need for continued efforts to encourage males and older adults into care and to encourage all to seek HIV testing and to initiate ART at lower levels of immune suppression.

2.3.2 Health of patients over time on ART

The median length of cohort follow-up was 24 (range 3 – 85) months and the median length of time on ART was 19 (range 3 – 72) months. Such short median times on ART before stopping have huge implications for universal access to ART. If patients, on average, spend less than two years on ART, consequences for their own health (in terms of viral rebound) and for the health of others (in terms of onward transmission of HIV when viraemia is not controlled) are vast.

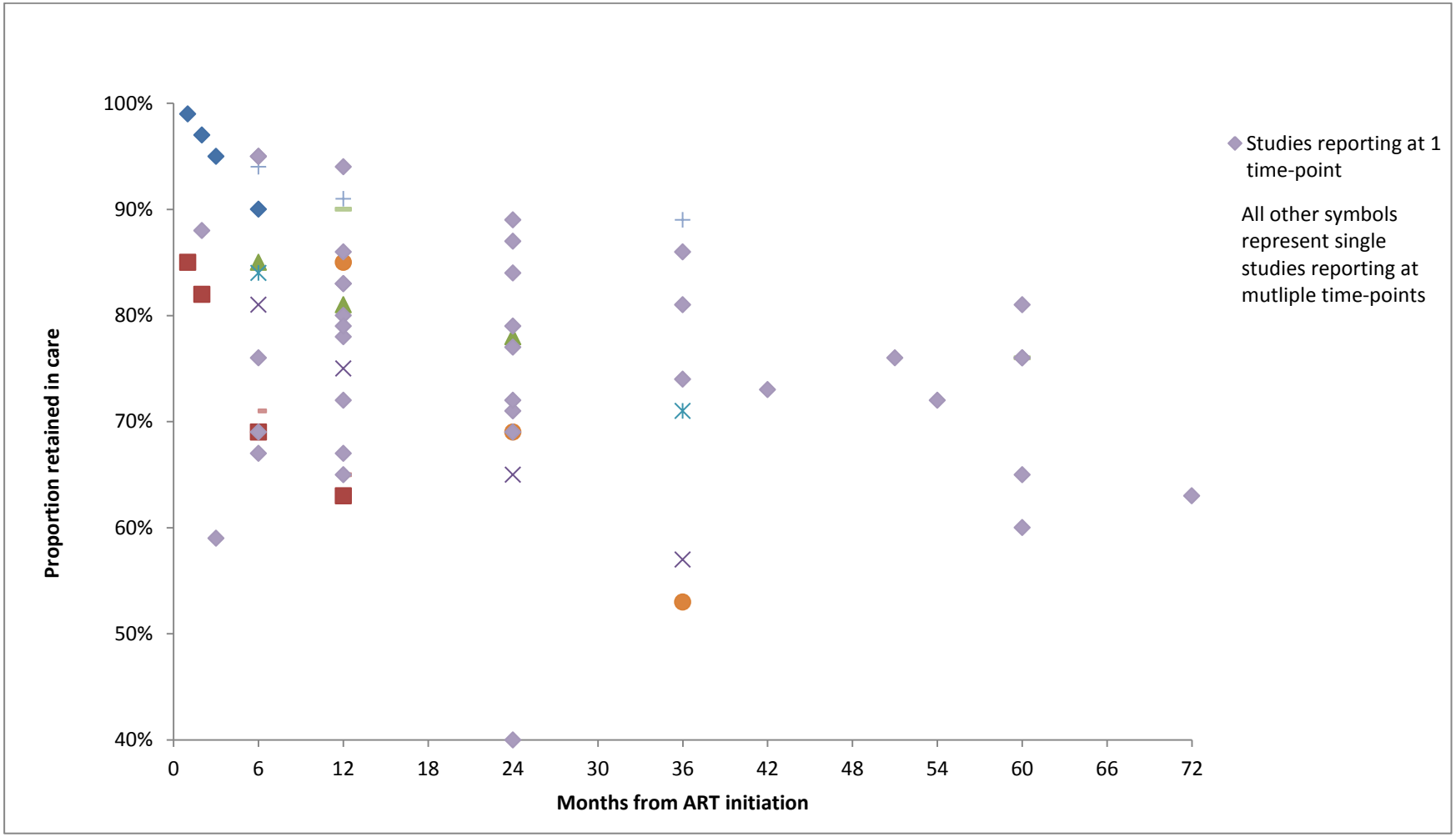
The most commonly reported outcomes were retention in care, attrition from care (deaths, losses to follow-up, transfers-out, stopping ART), immunological response, virological response, and other important clinical outcomes (TB, Immune Reconstitution Inflamatory Syndrome (IRIS), AIDS defining illnesses (ADI) and hospitalisations). Other less commonly reported outcomes were virological failure, weight changes, adherence, haemoglobin changes and total lymphocyte (TLC) changes.

2.3.3 Retention in care and losses from ART programmes

Of the 83 studies included in this review, 47 (57%) reported information on retention in care, at between 1 - 72 months of cohort follow-up (Figure 2.2). The majority (33, 70%) of these 47 studies reported retention in care at ≤ 24 months, while few (7 at 36 months, 7 at ≥ 48months) reported longer-term retention of patients in care. The change in retention in care was greatest early after ART initiation. The median proportion retained in care at 6, 12, 24, 36 and ≥ 48 months was 81% (range 67 – 95%), 80% (63 – 94%), 77% (40 – 89%), 74% (53 – 89%), and 76% (60 – 81%).

For patients treated within ART-LINC programme cohorts, between 4 - 6% never

Figure 2.2 Proportion retained in care from time since ART initiation, as reported by 47 studies



returned for a single follow-up appointment [84] [82]. Retention at 12 months was 80% and dropped to 64% by 36 months after ART initiation [84] [82]. For cohorts reporting to UNAIDS, the median proportion known to be alive and on ART 12 months after initiation was 82% (range 33 – 100%) [95].

The wide range in proportions retained in care at each time-point can partly be explained by the different geographical origins of the cohorts. Of the 10 cohorts reporting the highest proportion retained in care at 6, 12, 24, 36, and 48 months (highest 2 cohorts per time-point), 40% were based in Africa, compared to 90% of the 10 cohorts reporting the lowest proportion retained. No other cohort characteristics at ART initiation (cohort size, date of ART initiation, proportion female, age, WHO stage, CD4 cell count) appeared to account for the differences in proportions retained in care. This geographical explanation, however, should be interpreted with caution as the number of non-African cohorts in this review was small. Yet, this explanation also seems to account for the variation in retention in care reported by cohorts reporting to UNAIDS. UNAIDS reported retention in care at 12 months varying by nearly 10% depending on geographical origin of the cohort, with cohorts in sub-Saharan African reporting amongst the lowest: Caribbean 78%, sub-Saharan Africa 79%, Latin America 82%, Eastern Europe and Central Asia 82%, South and South East Asia 86%, East Asia 87% and the Middle East and North Africa 87% [95].

The difference in proportions retained in care may also be explained by differences in methods of defining the original cohort. Failure to distinguish between patients newly initiating ART and entering a reporting cohort and experienced-patients transferring in for care will mean that data in the reporting cohort are included on

patients who have already survived past the first few months of treatment. This will bias all outcome data in favour of a healthier population and increased retention in care. It is likely that some reporting cohorts include transfers-in (and thus healthier patients) while others do not, thus making comparisons between programmes problematic. Whether there is any geographical propensity to account for transfer-ins, originating perhaps from some governments but not all requiring nationally reported data to be disaggregated in such a way, should be examined.

Twelve-month (80%) and 24-month (77%) retention is higher than retention estimates from earlier systematic reviews which suggested that 75% - 77% of patients remained in care at 12 months, and 62% - 75% at 24 months, the lower proportions being reported in the earlier reviews [75] [76]. This suggests a calendar time effect, with newer ART programmes retaining more patients in care. Such an accomplishment should be commended, however, more information on longer-term retention is urgently needed as the available data, though few, suggest that retention dramatically decreases as length of time on ART increases. Furthermore, as fewer studies report over the longer-term, this may represent a reporting bias with studies with worse longer-term retention only electing to report over the short-term, or not reporting at all.

Although the included studies had different durations of reporting, I did not attempt to account for missing data if not reported at certain time-points through measures such as imputation, or scenario projections. This meant that the number of studies reporting retention in care and other outcomes at the same time-points, particularly after 24 months, was small and interpretation of the summary estimates should be done with caution. Both previously published systematic reviews on retention in

care attempted to account for missing data. The first review projected retention to 24 months for studies reporting short follow-up periods and assumed best (no further attrition) and worse (linear continuation of attrition) scenarios. This resulted in a mid-point retention estimate of 50% (range 24% - 77%) retention in care at 24-months [75]. The second review, projected retention over time using the same methods as the first study and, additionally, interpolated missing retention rates using later reported data and used a pooled-random-effects-meta-analysis. Using the first method, retention was 70% and 65% at 24 and 36 months and, using the second method, was 86%, 80%, 77% and 72% at 6, 12, 24 and 36 months [76]. These data, which estimate 24-month retention at 50, 70% or a maximum of 77%, compared to a median of 77% in the individual studies included in this review, suggest that summarising the proportion retained in care from only the few studies with available long-term data may considerably overestimate retention in care. True retention of patients in ART care, where data are few, may actually be lower than that summarised here.

Even assuming that the consistent reports of 80% retained in care at 12 months are not overestimates, this represents, in routine care in LMIC, that every fifth patient initiated on ART is lost from care within the first year of therapy. In ART-Cohort Collaboration (ART-CC) cohorts in HIC, after nearly 12 months on ART, a higher proportion of ART initiators (up to 88%) remained alive and in care [180]. Retaining greater numbers of patients in ART care is feasible in LMIC settings, when adequate resources are available. Within the DART randomised clinical trial, which compared patient monitoring in ART programmes in Uganda and Zimbabwe using routine laboratory tests versus clinical monitoring alone, survival on ART in routine health centres was 90% and 87%, respectively, after 5 years [181]. Establishing

and addressing reasons for losses from care in routine ART programmes in LMIC is essential if improvements in retention are to be made.

2.3.4 Attrition from care

While retention in care was reported in 47 studies, 33 studies reported reasons for patients leaving the original treatment cohort, while the remainder (30%) did not (Table 2.2). Reasons for leaving the original ART cohort can include deaths, electing to stop ART, transferring officially to another ART clinic, or leaving ART care and providing no further information on vital status to the ART clinic (known as becoming lost to follow-up, LTFU). Overall, median attrition from care due to deaths (11%) and LTFU (11%) was equal, with a median of 5% of patients transferring-out and a median of 3% stopping ART. At 6, 12, 36, >42 months, a cumulative median of 5%, 11%, 13%, 14% of patients had died, 8%, 11%, 9%, 12% were LTFU, and 3 - 7%, 5%, 5% and 7% had transferred elsewhere for care, respectively. The proportion stopping ART increased from 1% in the first few months to a maximum of 18% after 56 months of cohort follow-up.

For ART-LINC cohorts, the majority of cohort losses were due to deaths and LTFU. As per the individual studies reviewed, most deaths occurred in the first year on ART with cumulative deaths at 6, 12, 18, 22, 24 and 36 months of 3 – 9%, 6 - 8%, 5%, 8%, 7 – 12% and 13%, respectively [79, 80, 82-87]. LTFU increased over time, accounting for 3 – 16%, 13%, 9%, 31%, 7 - 32% and 25 - 29%, respectively at 6, 12, 18, 22, 24 and 36 months [79, 80, 82-87].

Table 2.2 demonstrates the challenges arising from comparing retention in one cohort against another without considering reasons for losses from care, even when reported retention rates are similar. For example, at 12 months one study reports

Table 2.2 Cohort follow-up period, median time in follow-up and retention and attrition at end of follow-up/median follow-up (ordered by maximum length of cohort follow-up, with shortest follow-up time shown first)

Country	Cohort size	Cohort f-up time (mths)	Median time on ART (mths)	Deaths (%)	Lost to follow-up (%)	Stopped ART (%)	Transferred-out (%)	Retention on ART at original site (%)
Zambia [106, 107]	142	3	3	18%	23%	-	-	59%
Malawi [100]	370	6	6	9%	-	-	-	76%
South Africa [101]	498	6	6	5%	-	-	-	95%
India [157]	142	6	-	4%	27%	-	-	69%
Malawi [175]	555	6	1	2%	6%	-	3%	90%
Malawi [178]	4347	6	6	13%	8%	1%	7%	71%
Malawi [178]	4347	12	12	13%	11%	1%	10%	65%
Tanzania [112]	486	12	12	11%	12%	-	14%	63%(ART) 55%(&TB)
Barbados [169]	158	12	12	1%	-	1%	-	94%
Curacao [128]	123	12	12	10%	10%	-	-	80%
Malawi [140]	300	12	12	14%	3%	5%	5%	72%
South Africa [160]	609	12	12	19%	15%	-	-	67%
Botswana [155]	349	12	-	20%	13%	-	1%	78%
Uganda [126]	219	12	-	4%	3%	-	4%	83%
Latin America & Caribbean [150]	5152	12	-	8%	6%	-	-	86%
Malawi [152]	4074	14	-	9%	6%	<1%	2%	83%
Rwanda [116]	490	15	12	1%	3%	4%	-	-
Uganda (no mental illness, mentally ill) [102]	773	15	15	1%, 2%	-	-	-	65%,47%

Country	Cohort size	Cohort f-up time (mths)	Median time on ART (mths)	Deaths (%)	Lost to follow-up (%)	Stopped ART (%)	Transferred-out (%)	Retention on ART at original site (%)
Cambodia [166]	1735	24	13	11%	2%	-	-	87%
China [120]	3457	24	21.3	13%	4%	3%	0%	84%
Zimbabwe [99]	898	36	15	8%	11%	-	-	81%
Nigeria [103]	4785	36	28	3%	21%	8%	5%	53%
Uganda [133]	559	36	33	18%	4%	-	2%	74%
Uganda [125]	559	36	36	18%	6%	-	5%	71%
Senegal [136]	404	42	42	26%	-	-	-	73%
South Africa [171]	829640	51	-	5%	8%	1%	8%	76%
South Africa [149]	1480	54	25	11%	11%	-	6%	72%
Tanzania [111]	88875	54	10	12%	36%	-	11%	56% (m), 60% (f)
China [144]	512	56	27	22%	-	18%	-	81%
China [146]	48785	60	17	13%	10%	-	-	70%
South Africa [142]	7322	60	60	16%	23%	-	-	65%
Ethiopia [108]	4210	60	31	7%	13%	0%	3%	76%
Burma [109]	5963	82	36	14%	7%	-	4%	76%
South Africa [130]	3162	84	29	10%	19%	-	10%	63%
Cote d'Ivoire [170]	129	-	2	12%	-	-	-	88%
Indonesia [141]	626		12(IDU), 8.4(non IDU)	16%	13%	-	4%	67%
South Africa [118]		-	19	5%	24%	-	-	71%
DRC [104]	1450	-	19	6%	18%	-	1%	57%
Cote d'Ivoire [164]	187		19	9%	2%	-	-	89%

Country	Cohort size	Cohort f-up time (mths)	Median time on ART (mths)	Deaths (%)	Lost to follow-up (%)	Stopped ART (%)	Transferred-out (%)	Retention on ART at original site (%)
Uganda [139]	5982	-	20	6%	15%	-	10%	69%
South Africa [132]	7536	-	21	7%	14%	-	-	79%
South Africa [119]	15060	-	22	18%	23%	4%	15%	40%
Lao [98]	913	-	22	12%	4%	-	11%	73%
Burkina Faso [115]	5608	-	23	12%	7%	-	4%	77%
sub-Saharan Africa [151]	249	-	32	10%	3%	-	3%	84%
Uganda [96]	6970		36	-	-	11%	3%	86%
Uganda [117]	22315	-	36	7%	8%(m), 6%(f)	-	-	85%(m), 87%(f)
South Africa [153]	7512	-	-	6%(TB), 4%(no TB)	20%(TB), 19%(no TB)	-	-	74%(TB), 77%(no TB)

retention of 65% while another reports retention of 67% [160, 178]. However, for the second study, all of the reported losses are due to deaths (19%) and LTFU (15%), while for the first study, 10% of patients have transferred-out and are receiving ART elsewhere. Further challenges arise when interpreting widely-varying proportions retained in care. For example, at 36 months, one cohort reports retention in care of 53% while another reports 74% of the cohort retained in care [103, 133]. It would be understandable to assume that the ART programme reporting the lowest proportion retained was doing less well. However, only 3% of that cohort's patients had died compared with 18% of patients in the other cohort. Neither study reported whether patients LTFU were traced to ascertain vital status which may have inflated the proportion of deaths and reduced the proportion LTFU. For example, one reviewed study traced a sub-sample of patients LTFU and ascertained that 29% of those traced had died [145]. Without adequate information, comparing these cohorts is challenging.

Cohorts appear to report consistently that at 12 months post ART-initiation, nearly half of the 20% of losses from care are due to deaths. Continued efforts are needed, therefore, to encourage people to seek HIV testing and access care earlier in disease to reduce early morbidity and mortality. The remaining half of losses from care is due, in the main, to LTFU with the vital status of lost patients unknown. Official transfers-out of care or patients electing to stop ART make up a smaller proportion throughout time on ART. LTFU by 12 months in LMIC is double that seen in HIC, where it has been reported to be 5% among ART-Cohort Collaboration (ART CC) cohorts [182]. It is, therefore, essential to encourage patients attending clinics to remain in care and to ascertain and address reasons for LTFU in LMIC.

Being able to understand and report reasons accurately for patients dropping out of ART care is complex as it can be hard to ascertain the vital status of patients who have become LTFU. Some sites invest vast resources into tracing patients LTFU to ascertain if patients have died, transferred unofficially elsewhere for care or whether they have defaulted from ART completely. Some patients, in fact, may default from care but resume after some time. One study reported that the probability of resuming ART within 3 years of default can reach more than 40% [134]. Comparing cohorts who trace patients with cohorts without resources to do so will lead to inaccurate conclusions about the relative performance of the programmes.

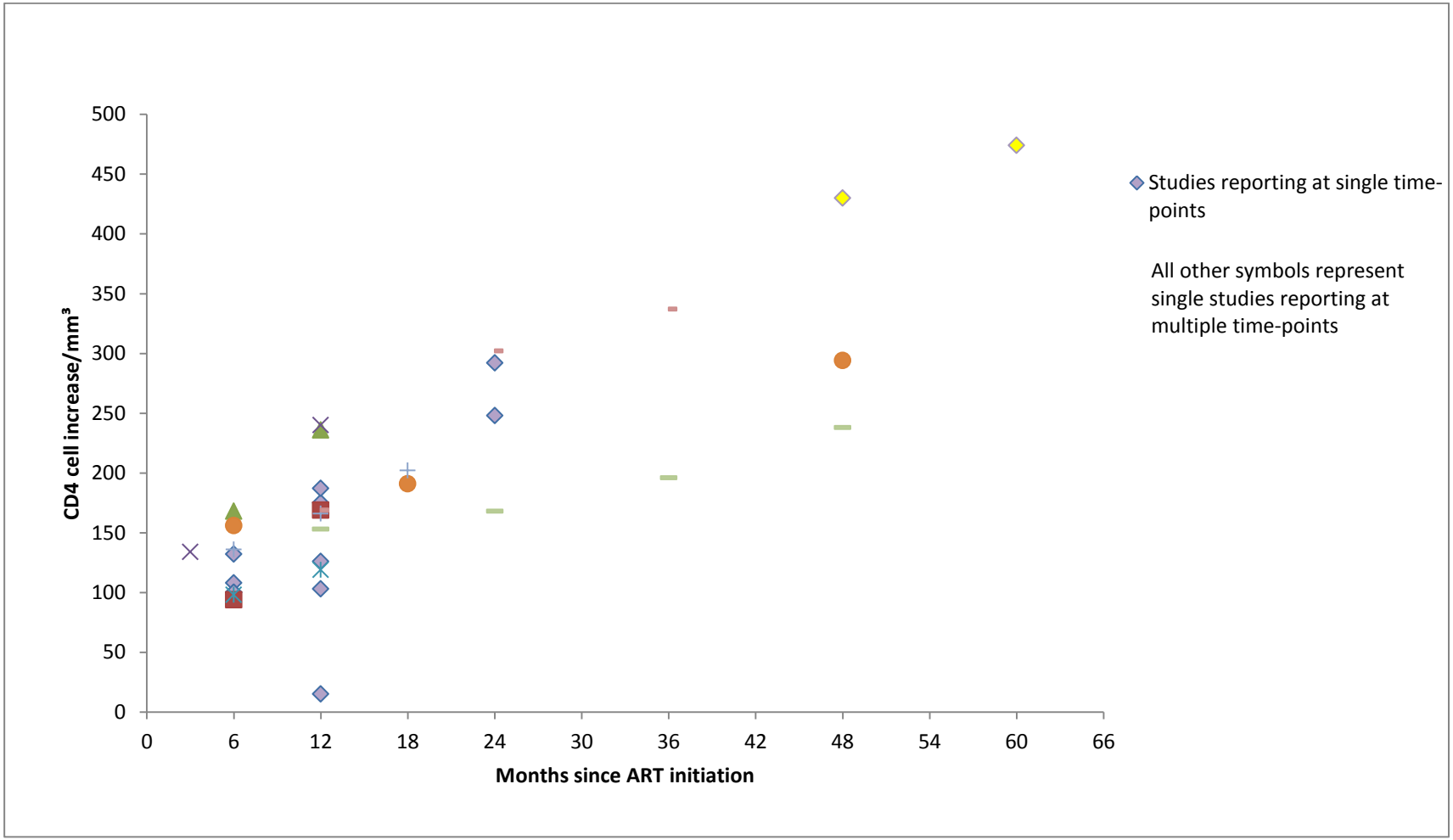
Collating data on observable-outcomes such as the proportion retained, died, LTFU or transferring-out appears feasible and data are reported by more than half of cohorts in this review. It is surprising, in fact, that UNAIDS only present the proportion alive and on ART 12 months after initiation, not collecting or publishing data on reasons for attrition from ART programmes. However, interpreting retention and attrition must be done with caution, particularly when comparisons between programmes are made.

2.3.5 Immunological response

Thirty-two studies reported the median increase in CD4 cell count since ART initiation, the median absolute CD4 cell count or the proportion with poor immune response [80, 98, 101, 103, 113, 116, 118, 123, 128, 130, 131, 136, 139, 143, 144, 147-149, 151, 155, 157-162, 164, 166, 168, 169]. For all cohorts reporting CD4 cell count changes, the median CD4 cell count at ART initiation was low at 123 (IQR 80 – 152) cells/mm^3.

The greatest increase in CD4 cell counts (Figure 2.3) was observed early after ART

Figure 2.3 Median increases in CD4 cell count over time



initiation, as expected. At 6 and 12 months, the median increase in CD4 cell count from ART initiation was 108 (IQR 100 – 136) cells/mm³ and 168 (IQR 124 – 178) cells/mm³, respectively. Fewer studies reported at other time-points though these demonstrated a positive trend over time: 191 and 202 cells/mm³ (18 months), 168 – 302 (n=4, 24 months), 196 and 337 cells/mm³ (36 months), 238 – 430 cells/mm³ (n=3, 36 months) and 474 cells/mm³ (60 months). The median absolute CD4 cell counts at 6, 12, 18 and 24 months were, respectively, 222, 264 - 312, 354 - 355, and 348 - 372 cells/mm³ (n=10). The proportions with poor immune response at 6 and 12 months were 19% - 43% and 25% - 42%, respectively (n=10). However, the threshold for definition of poor immune response varied across the studies from < 50 to <500 cells/mm³.

Of two ART-LINC studies, increases in median CD4 cell counts at 12 and 24 months were 166 and 292 cells/mm³, respectively [81] [80].

Cohorts initiating ART at lower CD4 cell counts reported greater increases in CD4 cell counts. At 6, 12 and 24 months, for study cohorts initiating ART with CD4 <120 cells/mm³ (median of all studies), the median increase was 156, 178 - 292, and 302 cells/mm³. This compares to increases at the same time-points of 100, 136 - 168, and 248 cells/mm³ among cohorts whose participants initiated ART with CD4 count ≥ 120 cells/mm³. No other baseline factor (geographical origin of cohort, cohort size, date of initiation, proportion female, WHO stage, age) appeared to explain the ranges observed in increases in CD4 cell counts. These results are similar to significantly greater CD4 cell count gains among patients starting ART with lower CD4 cell counts, compared to higher counts reported by UK CHIC and CASCADE HIC cohorts [180, 183]. These earlier gains, however, do not appear to continue and

stabilise over time [180].

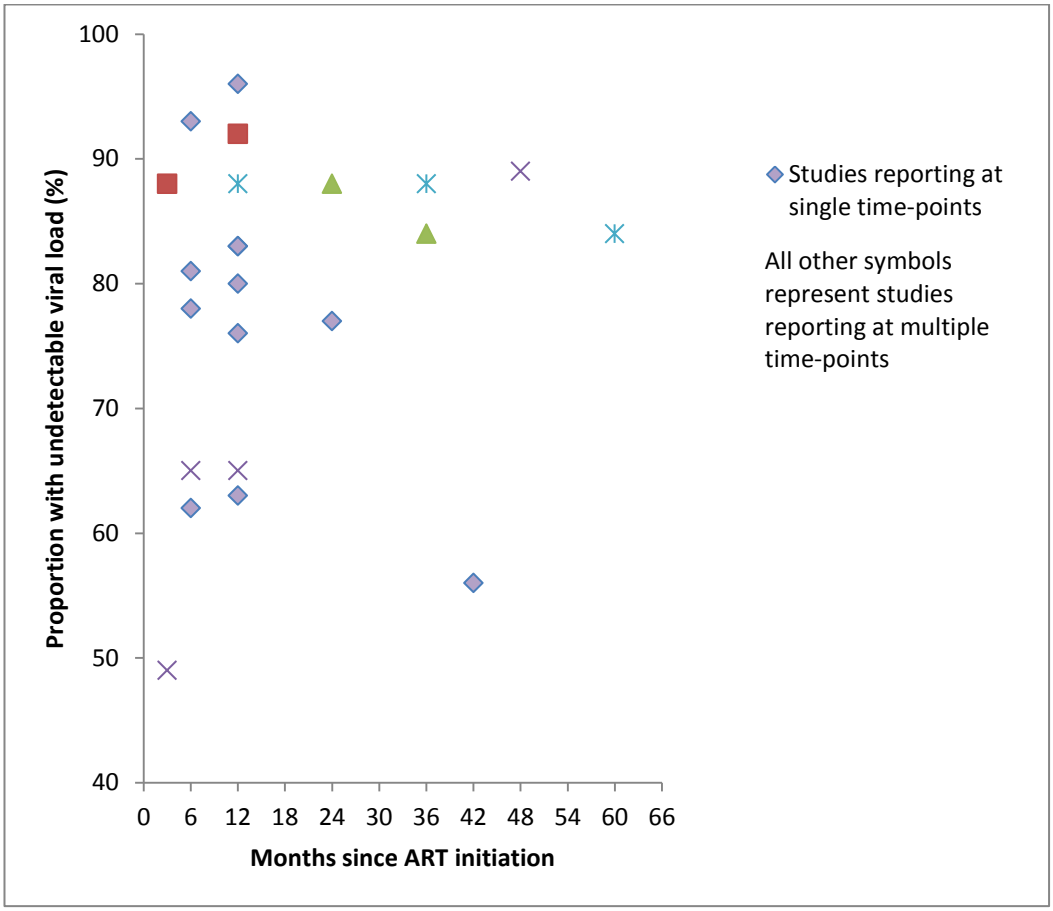
There appears consistency in reported increases in CD4 cells at 6 (around 110 cells/mm³), 12 (around 170 cells/mm³) and 24 (just under 300 cells/mm³) months. These gains are similar to gains reported among ART-CC cohorts in HIC at 6 months and similar to gains among the UK CHIC cohort [182, 184]. The median absolute CD4 counts at 6 and 12 months were also similar to median absolute values reported in a previous systematic review of LMIC cohorts at 3, 6, 12, 18, 24 and >24 months of 244, 249, 277, 274, 298 and 374 cells/mm³ [74]. Most data, however, relating to CD4 increases or absolute counts were reported at 6 and 12 months after ART initiation and while the studies included here suggest a continued increase in CD4 count gain over time, more data are needed to examine the longer-term effect on CD4 counts among patients who remain in care.

However, interpreting cross-sectional medians over time must be done with caution. As individuals who are most sick are likely to drop out of care or die, the risk-set used to calculate median increases will decrease over time. At each reporting time-point, the median CD4 is, therefore, likely to appear to have increased as those left in the risk-set will be the healthiest proportion of the population.

2.3.6 Virological response

Sixteen studies reported the proportion of patients achieving undetectable viral load over time (Figure 2.4) [80, 101, 113, 128, 130, 136, 140, 142, 144, 151, 155, 159, 160, 162, 169, 170]. Among these, median viral load at ART initiation was 5.1 (IQR 5.0 – 5.2) log copies/mL, though this was only reported by 4 of these cohorts.

Figure 2.4 Proportion with undetectable viral load



At all time-points, wide-ranges in the proportions achieving undetectable viral load were reported. Only two studies reported at 3 months, and at least half of these participants who remained in care and had a viral load measured achieved virological suppression (49% and 88%). By 6 and 12 months, the median proportion with undetectable virus was 78% (range 62 - 93%) and 83% (range 63% - 96%), respectively. An increasing trend in the proportion achieving undetectable viral load was reported over time: 77% and 88% (24 months), 84% and 88% (36 months), 56% and 89% (48 months) and 84% (60 months) (n=7 studies).

Of the cohorts reporting the greatest proportion with undetectable viral load at 6 and 12 months, however, median viral load at ART initiation was 4.9 and 5.1 log copies/mL respectively, compared, somewhat counter-intuitively, to slightly lower levels of viremia at ART initiation (4.8 and 5.0 log copies/mL) among the cohorts reporting the lowest proportions undetectable at 6 and 12 months. These observations of greater proportions undetectable being linked to higher viral load at baseline have previously been observed among ART-CC cohorts in HIC: 79% of patients with viral loads >100,000 copies/mL at ART initiation were suppressed (<500 copies/mL) at 12 months, compared to 78% among patients with 10,000 – 1000,000 copies/mL, and 72% among patients with <10,000 copies/mL at ART initiation [185]. However, it is worth noting that the main aim of the analysis of the ART-CC cohorts was to estimate probability of death after 36 months, therefore analyses were limited to patients who survived to a minimum of 36 months, thus the sicker patients who were likely to be those with higher viremia at ART initiation are not captured here.

There appeared to be no other baseline factors (cohort country of origin, cohort size, year of ART initiation of patients in the cohort, proportion female, median age, proportion initiating ART at WHO stage III/IV, or CD4 count at ART initiation) which were related to virological outcomes. The threshold for detection, however, varied widely across the cohorts from < 50 - < 1,000 copies/mL which may explain much of the variability in response rates reported. Viral load assays have differing lower limits of detection. However, given their cost and limited availability within LMIC, every effort should be made to ensure maximum information is gained when viral load tests are employed. If they are to be used as a reporting measure within ART programmes, standard threshold levels based around the highest viral load threshold to classify undetectable viremia need to be agreed upon.

The proportions with undetectable viral load at 6 months (78%), 12 months (83%) and 24 months (77% - 88%) are higher than proportions reported in an earlier systematic review at 3, 6, 12, 18, 24 and >24 months of 73%, 75%, 67%, 68%, 65% and 74% [74]. They are also higher than another review which reported 78%, 76% and 67% with undetectable viral load at 6, 12 and 24 months [73]. These differences across reviews may be explained by a calendar time effect, with the more recent studies in this review reporting on cohorts in more experienced ART programmes. The differences, however, may also be explained, in part, by the high threshold level employed by some of the studies in this current review, which accepted limits of <1,000 copies/mL to meet definitions for undetectable viremia, compared to thresholds of below 400 copies/mL in the first review and between 200-500 copies/mL in the latter [74] [73].

The proportion of cohorts in LMIC with suppressed viremia appears similar to

proportions suppressed among cohorts in HIC, however HIC cohorts tend to use stricter thresholds to define levels of undetectable viremia [182] [180, 184].
As viral load tests are costly, many cohorts in LMIC did not report HIV RNA changes. It is likely that programmes which were able to conduct viral load tests have greater resources than other cohorts. Improved resources may lead to improvements in care and it is feasible that cohorts reporting viral load changes have better overall outcomes. Reports of high proportions with undetectable viremia may not, in fact, be representative of controlled viremia in ART programmes in LMIC.

Furthermore, comparing any reported immunological or virological changes should be interpreted with caution. Firstly, the baseline health status of the treated population should be considered. Here, cohorts with low CD4 at initiation appeared to have greater increases in CD4 counts and cohorts with higher viral loads appeared to have greater proportions with undetectable viremia over time. This is because the less healthy a cohort at initiation, the greater scope for early viral suppression and immune recovery. A cohort, therefore which reports smaller increases in CD4, may indeed reflect a population which was healthier at initiation. Secondly, care must be taken when interpreting gains to ensure knowledge is available on who is included in the risk set at all time-points. Measures reported at ART initiation (baseline measures against which increases are compared) are often only given for those who also have an immunological or virological measure at follow-up. The baseline values will likely be higher for these patients than if the value also included patients who go on to die or drop out of care, and were likely more sick, before there is an opportunity for a follow-up immunological or virological assessment. When using this information to assess the health of a treated cohort, or to compare treated cohorts, even if a remarkable response is

noted, this should only be interpreted alongside information on other key outcomes for individuals from the original treatment cohort (e.g. number of deaths, number transferred elsewhere, and number of losses to follow-up).

2.3.7 Other clinical responses: TB, AIDS-defining illnesses, IRIS and Hospitalisations

Eleven studies reported the overall proportion of patients with TB throughout time on ART, though the maximum number of studies reporting at any one time-point was 4 [97, 100, 108, 112, 126, 132, 139, 149, 157, 168, 170]. After the original increase in cases, the cumulative proportion experiencing active TB did not change greatly over time: at 6, 12, 24, 36, 48 and 60 months, 14%, 6%, 8%, 9%, 8 - 10%, and 21% had TB. Seven studies reported the overall incidence rate of TB while on ART, ranging from 3.1 – 7.3/100 person years (py). TB incidence rates increased sharply in the first 3 months on ART (11.3 and 13.9/100py) and then slowed over time, dropping to 2.5 – 12.5/100py between 6 - 12 months, 1.0 – 4.5/100py between 12- 24 months, 1.6 – 3.2 between 24 – 36 months and reached 0.4 – 2.2/100py by 60 months. Reducing rates of TB as time on ART increases have been shown previously in LMIC [186]. The high early rates may be due to IRIS as the risk of TB-associated IRIS has been shown to be very high, particularly for patients with low baseline CD4 cell counts initiating ART early in the course of anti-TB treatment [187]. However, early TB may be due to unmasking of asymptomatic or minimally symptomatic disease pre ART initiation [188, 189].

Among ART-LINC cohorts, by 12 and 18 months on ART, 6% of patients had developed TB, with an overall incidence rate of 7.4/100py in the first 12 months, and 8.2/100py over the first 18 months [88] [86]. The highest incidence rate of TB was reported early after ART initiation, dropping from 10.7/100py during months 1-

3, to 7.4 - 7.5/100py during months 4 – 6, to 5.2/100 py during months 7 – 12 months [88].

Eight studies reported information about other AIDS defining illness (ADI), including IRIS or hospitalisations, though only three provided details about the time-point at which the estimates were made [101, 126, 128, 131, 136, 140, 154, 172]. The median overall proportion hospitalised, with IRIS or with an ADI was 13% (range 1% - 38%), with incidence rates ranging from 1.6 – 20.5/100py. This is similar to the range of estimates (9 – 39%) found in a recent systematic review of IRIS among HIV-infected persons [77].

One ART-LINC cohort reported the proportion with ADI. At 12 months, incidence rates of cryptococcal meningitis, PCP, KS and non-Hodgkin lymphoma were 0.48, 0.35, 0.31 and 0.02/100py, respectively [87]. After a median of 22 months of follow-up, the following proportions had developed ADI: cryptococcal disease (0.4%), KS (0.4%), and PCP (0.3%).

2.3.8 Other outcomes

Ten studies report on patients failing ART, though some reported proportions failing, others failure rates, and few reported at the same time-points [80, 130, 139, 142, 143, 146, 159]. The proportion failing ranged from 7% at 6 months, to between 23% - 26% around 24 months, and between 14% - 50% at 5-years, with failure rates ranging widely from 5.0 – 31/100py. Immunological and virological threshold levels used to determine the proportions failing varied between the studies. One ART-LINC study reported that 26% of patients experienced viral rebound within two years, despite 96% being suppressed (<500 copies/mL) at 12 months [80].

Adverse events (AE) were reported by 10 studies, though only two studies reported at the same time-point [110, 118, 120, 138, 140, 144, 157, 164, 165, 173]. The proportion with an AE varied considerably in the reports: at 6, 12, 24, 36 and 72 months, 38%, 3% -7%, 28%, 17 - 56%, and 19 – 72% had an AE. The most commonly reported AE were: peripheral neuropathy (11 – 17%), headache (12%), lipoatrophy (5% – 7%), symptomatic hyperlactataemia (3% - 6%, rate 3.2/100py), hepatoxicity (3%), lactic acidosis (1% - 3%, rate 1.4/100py) and others (percentages not given) fever, cough, diarrhoea, lymphadenectasis, weight loss, tetter, weakness and fungal infections. The difference in proportions with AE is likely due, in part, to the different diseases considered clinically-important enough to report. Some cohorts may have included only serious AE and report a low proportion, while others may have included all AE and report a high proportion. Moreover, a number of these adverse events (e.g. neuropathy, raised lactate and lactic acidosis) are related to treatments such as d4T (stavudine) which are being phased out. Comparing the proportion of patients with AE in different cohorts should be done alongside a knowledge of which regimen was in use.

Eight studies reported changes in weight or BMI over time, though few reported the same measure at the same time-points and two studies reported no aggregated measure (only disaggregated by sex or weight at ART initiation) [114, 118, 121, 124, 148, 155, 160, 166]. At 3, 6 and 12 months, median weight increased by 2.5 and 2.6kg, 3kg and 10kg. At 6 and 12 months, median BMI increased by 0 – 2.4kg/m² and 1.6 – 4.8/m², respectively.

While 21 studies reported the overall proportion of patients interrupting, switching or substituting ART combinations, terminology was used interchangeably and it was

unclear if all switches truly represented changes between drug classes or were substitutions within the same drug class [80, 101, 110, 112, 123, 127, 128, 133, 140-143, 148, 151, 158, 159, 161, 166, 167, 173, 176]. I, therefore, did not summarise this information. One ART-LINC study reported that 22% of patients changed their first-line regimen in the first two years [80].

Though this review excluded studies specifically reporting on adherence as an outcome on ART, 3 studies included for other outcomes also reported on adherence [116, 137, 147]. Good adherence was reported among 26% of participants at 3 months and among 62% - 100% of participants at 12 months. However, different methods were used to measure and different definitions were used to define 'good' adherence making comparing reported adherence challenging.

Other outcomes reported included changes in renal function, TLC, lipid changes and changes in haemoglobin but were reported by too few studies to summarise [124, 147, 166, 173, 176].

2.3.9 Outcomes as predictors of retention in care

Very few studies reported an immunological, virological, clinical (TB, IRIS, ADI, hospitalisations) or other (AE, weight changes, switches, adherence) outcome at an intermediate time-point together with the proportion retained in care at a later point in time. It was, thus, only possible to examine the potential relationship between immunological and virological indicators and retention in care.

Plotting increases in CD4 cell count at 6 and 12 months against the proportion retained in care up to 24 months suggests that the greater the increase in CD4, the

lower the proportion retained in care (Figure 2.5). Similarly, plotting the proportion achieving virological suppression at 3, 6 and 12 months against up to 60-month retention in care appeared to suggest a similar, though less clear, negative relationship between increasing proportions suppressed and lower proportions retained in care (Figure 2.6). While this may seem counter-intuitive, it is possible that as patients regain their health and feel they need less health services, retention in care may fall. However, this component of the review was limited by the small number of studies reporting intermediate outcomes and future retention making assessing potential relationships between intermediate outcomes and longer-term retention nearly impossible.

2.4 Discussion

The median length of cohort follow-up has increased to 24 months, from the 10-months observed in reviews of studies published before this work as more data are emerging on the longer-term health of treated populations [75] [76]. However, this review has highlighted the lack of commonality of outcomes reported and the large discrepancy in time-points at which outcomes are reported. Monitoring the health of patients in ART programmes using clinic-measurable data, such as retention, losses from care, transfers-out, patients stopping ART, incidence of TB, other ADI, and hospitalisations appears feasible for a number of ART programmes, while the use of routine immunological and virological measures remains limited to health centres with adequate resources. For a life-long condition and for ART programmes in LMIC which have been funded widely since around 2004, more information is urgently needed on outcomes on ART after two, three and five years in treatment programmes. Indeed, for patients who initiated ART in 2004, it would be of value to know how they are doing after nearly 10 years on ART. There remains a need

Figure 2.5 Median CD4 increase at 6 and 12 month and up to 24 month retention in care

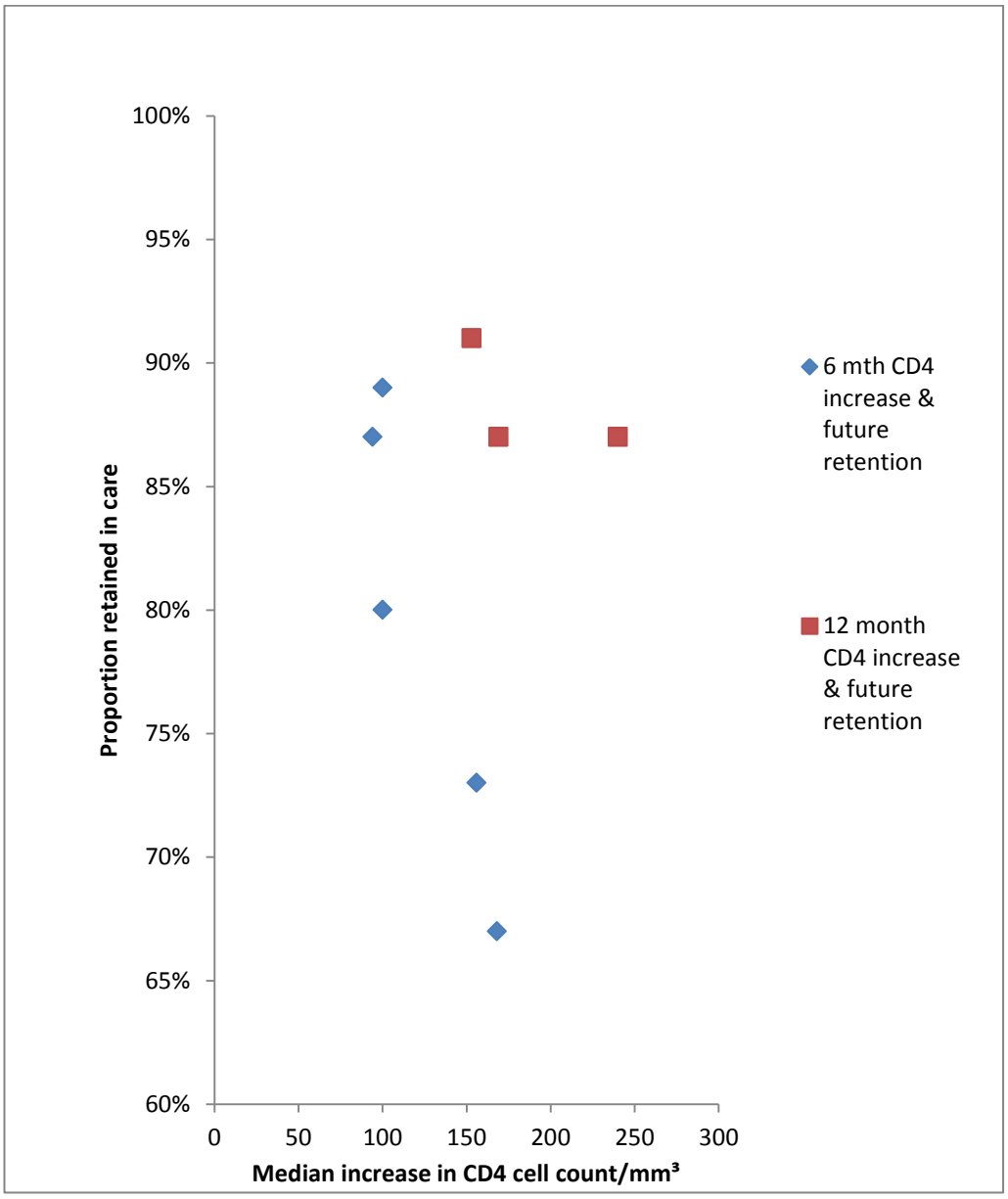
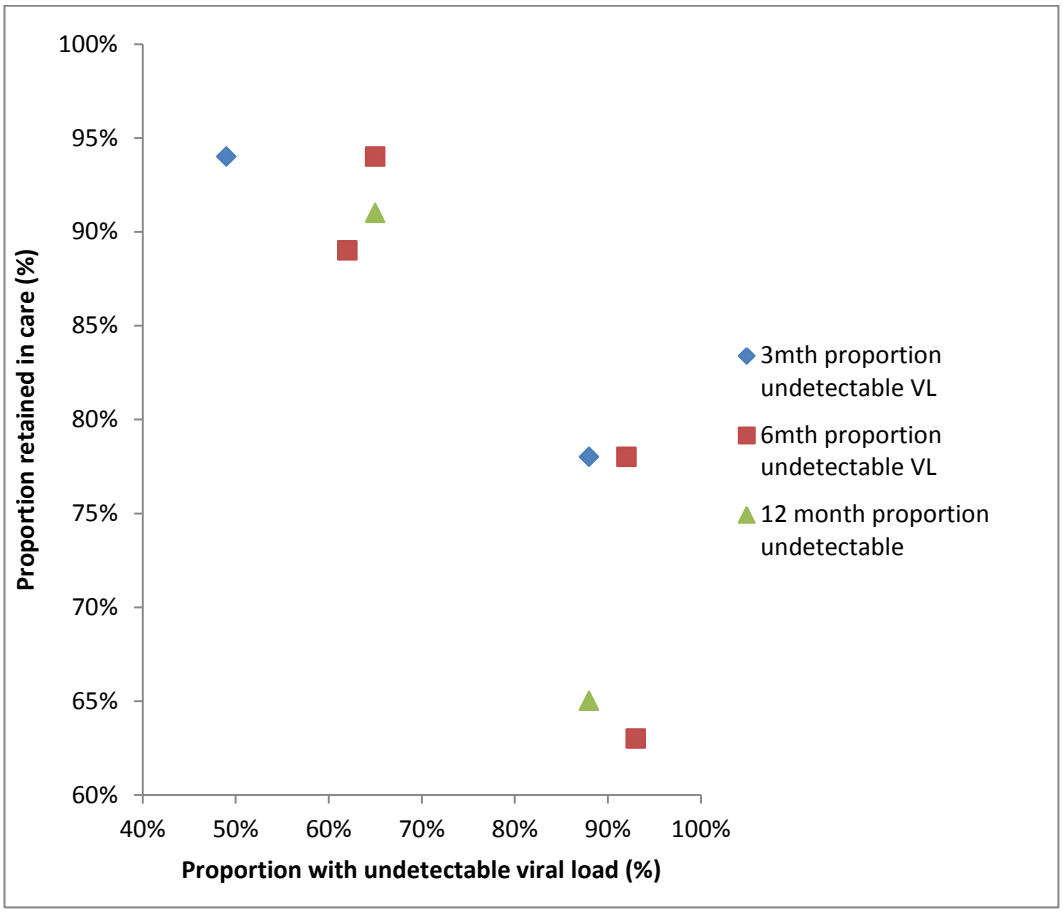


Figure 2.6 Proportion with undetectable viral load and up to 60 month retention in care



for data from more studies from outside of Africa. There is also a need for increased reporting at intermediate time-points rather than just the end of cohort follow-up. Moreover, there is a clear need for better descriptions of how numerators and denominators are derived to enable cross-programme comparisons.

Monitoring outcomes for the increasing number of patients accessing ART is challenging. It may be that random, systematic or consecutive sampling techniques, which have demonstrated similar proportions retained in care as full-cohort data analyses, could provide a feasible method to monitor the health of increasing numbers of patients in care in LMIC [94]. A less resource-intense monitoring method, such as this, may provide increased scope for greater accuracy and more detailed descriptions of reported data.

The lack of common reporting outcomes and time-points shown in this review has highlighted a lack of knowledge of which outcomes, reported at which time-points provide the best insight into the progress of the treated population. Non-standardised data make comparisons across geographical areas, programmes and time challenging [190]. Furthermore, gaps in monitoring the treatment and health of patients in care remain.

Notably, tools do not exist to monitor long-term access to Cotrimoxazole preventative therapy (CPT) and a review of access to CPT is needed. I undertook this work and present the results in Chapters 3 and 4. Furthermore, a set of outcome measures to monitor depression in the context of HIV does not exist [191]. Given the implications on adherence to treatment and faster disease progression for HIV-positive patients with comorbid mental health disorders, an evaluation of the

burden of mental health disorders among HIV-positive patients is needed. I undertook this work and present the results in Chapter 5. Furthermore, while most funders and MoH require reports on the health of the treated population, a comparison of which outcomes are currently used by ART programmes in LMIC is needed to identify which outcomes are perceived by national MoH as most relevant. I undertook this work and present the results in Chapter 6. Moreover, as it is not known how accurately currently reported outcomes reflect the welfare of the population in care, an evaluation of the validity and predictive value of such measures is needed [20] [68] [56]. I present the design of such a study in Chapter 7 of this thesis. These studies will provide the evidence-base to determine which data should be collected by programme managers to monitor the health of the population in their care, enabling them to respond to predictors of failure early. This is crucial to provide a clearer understanding of the health of the treated population and to enable best practice in ART roll-out in LMIC.

Chapter 3 Reported access and barriers to Cotrimoxazole Preventive Therapy

This chapter describes a study I undertook to evaluate access to Cotrimoxazole Preventive Therapy (CPT). The study aimed to estimate time to CPT initiation following HIV diagnosis or birth to an HIV-infected mother and time on CPT. The study also aimed to compare these derived estimates with data reported in monitoring reports. I designed and conducted the study in Uganda and Tanzania between May 2009 and December 2011. In this chapter, I present the results of pilot work which influenced the design of the study and describe differences in health care worker prescribing practices and barriers which may impede regular access to CPT. The main findings of the study are presented in the following chapter.

3.1 Background

The drug Cotrimoxazole (CTX) acts as a broad-spectrum antimicrobial agent that targets a range of aerobic gram-positive and gram-negative organisms, fungi and protozoa [59]. Today, CTX is used widely in LMIC to treat infections including acute respiratory infections, diarrhoea and *Pneumocystis pneumonia* (PCP) [192]. As a prophylaxis, CTX is used for the prevention (primary prophylaxis) and against the recurrence (secondary prophylaxis) of opportunistic infections (OI). It has been used in high income countries (HIC) since the early 1980s to prevent bacterial infections in HIV-negative people with granulocytopenia [193]. In HIV, Trimethoprim-Sulphamethoxaole (TMP-SMZ) was recommended as the drug of choice for the treatment of AIDS-related PCP as early as in 1983 and prophylaxis with CTX, the official generic name for the co-formulation of TMP-SMZ, was first

used to prevent PCP in HIC in 1985 [40] [194]. Prophylaxis with CTX is known as Cotrimoxazole Preventive Therapy (CPT).

Evidence for the use of CPT to prevent OI in HIV-positive individuals in LMIC first emerged in 1999 in the Côte d'Ivoire [195] [196]. Further retrospective and prospective cohort studies, randomised controlled trials and cost-effectiveness studies have added to this evidence [195-205]. In 2006, the WHO updated earlier guidelines and issued revised ones stating that CPT should be used as a key element in the HIV chronic care package [59].

The 2006 WHO guidelines state that CPT should be provided to:

- all HIV-exposed children under 18 months until HIV infection has been excluded,
- children aged more than 1 year who are asymptomatic (WHO stage 1) but have a CD4 cell of less than 25%,
- children aged more than 1 year who are symptomatic (WHO stage 2, 3 and 4) regardless of CD4 count or percentage,
- adults with advanced disease (WHO stage 3 and 4) regardless of CD4 count or with less severe disease (WHO stage 2) and a CD4 cell count less than 350 cells/mm^3.

WHO also recommends a 'universal option' in countries with high prevalence of HIV and limited health infrastructure whereby CPT is recommended for all patients living with HIV [59].

Furthermore, WHO guidelines recommend that CPT should be continued throughout care, because patients living with HIV are at high risk of bacterial infections in LMIC.

However, patients who are stable on ART, with good adherence, secure access to ART and with a CD4 and clinical evidence of immune recovery can be reassessed and consideration given to discontinuing CPT [59].

Despite the 2006 WHO guidelines for the use of CPT as a key element of the HIV care package, the process of creating national level policies on CPT has varied between African countries, with some countries still not advocating the use of CPT in 2008 when I embarked upon the work included in this thesis [193]. For example, in Zambia, there were no national CPT guidelines. This was despite the country having been host to a large clinical trial (the CHAP trial) of CPT in HIV-infected children which had led directly to the formulation of the WHO 2006 guidelines [198]. Moreover, in 2008, concerns had been raised that the routine use of CPT had only partially been translated into practice and was only partially implemented in LMIC health centres [38, 193, 206, 207]. These concerns had been particularly voiced in relation to CPT access for children in sub-Saharan Africa [208] [209]. In 2006, UNAIDS estimated that, globally, only 4% of adults and 1% of children living with HIV had access to this key element of HIV care [210].

Therefore, firstly, I reviewed published literature to summarise the proportion of eligible patients initiating CPT in LMIC and their time spent on CPT after initiation. Secondly, I designed the current study to describe how well, following national CPT policy formulation, CPT was being accessed in Uganda and Tanzania. I examined existing records to assess access to CPT in routine HIV care in the two countries.

3.2 Literature review

The aim was to evaluate access to CPT in LMIC as reported in published literature

by synthesising estimates of the proportion of patients initiating CPT, and summarising information relating to retention on it. A secondary aim was to synthesise from commentary pieces information relating to perceived barriers to CPT scale-up and recommendations on ways to improve the implementation of CPT.

My search strategy involved multiple stages. Firstly, I used broad search criteria to identify English language studies which assessed access to CPT in HIV care in LMIC published since 1999, when the first evidence emerged supporting the use of CPT as prophylaxis in HIV care [195]. I searched Medline through PubMed. The search was last updated on 29-01-2014. I used both Mesh terms and Text fields to capture HIV care and Cotrimoxazole (TMP-SMZ). This resulted in 880 titles. Secondly, having read the 880 titles, I excluded titles which described the following:

a. Efficacy studies (e.g. randomised controlled trials and systematic reviews)
b. Safety studies or adverse reactions to CPT
c. Case-series
d. Cost-effectiveness studies
e. Mechanism of action of CPT (e.g. role of CTX in prevention of bacteraemia, PCP, anaemia)
f. Treatment outcomes for patients on CPT

After the above exclusions, 50 titles remained. Where abstracts were available (n=44), I read the abstracts and where abstracts were not available via the literature search, if available I accessed the full texts of the articles and reviewed the abstracts (n=4). Two titles had no abstract available and I was unable to retrieve the full text. These titles, however, suggested that the articles described efficacy of CPT and no further attempts were made to find these articles.

Therefore, having read the 48 abstracts, I selected 36 texts that met at least one of the following criteria:

a. Described proportions of patients in need of CPT initiating it
b. Described access to HIV care services (including CPT)
c. Provided a commentary of CPT scale-up or barriers to the implementation of CPT

Having read the full texts of 34 of these articles (2 articles were not found), I further excluded 4 which: described access to CPT in an American cohort, systematically reviewed the effectiveness of CPT, reviewed the efficacy of CPT in pregnant women, and described the efficacy of CPT in HIV-infected children. I was unable to retrieve the full text of 2 of the selected abstracts but as they met the above inclusion criteria, I included their data directly from the abstracts. This review, therefore, includes 32 papers.

Twenty-three studies reported quantitative data on the proportion of patients initiating and retained on CPT or the proportion of sites providing CPT (Tables 3.1 – 3.5). CPT is recommended for different population groups: HIV-infected patients, HIV-TB co-infected patients and HIV-exposed infants. The articles are tabulated accordingly. Eight articles were commentary pieces describing challenges associated with scaling-up access to CPT, and one article described the number of patients in need of CPT (Table 3.6). From the quantitative studies, I extracted information on study country, year and design, study population and sample size, the proportion initiating CPT and the proportion still on CPT after initiation. From the commentary pieces, I extracted reasons given that might explain slow scale-up of CPT and recommendations to improve the implementation of CPT. I present the quantitative data first, followed by a summary of the key points from the commentary pieces.

Table 3.1 Proportion of HIV positive adults and children initiating CPT (ordered by year of study data-collection)

Authors	Country	Data-collection year	Sample	Design	Proportion initiating CPT
Desmonde [211]	Côte d'Ivoire	04 - 09	405 children, median age 4.5yrs	prospective cohort in 2 urban facilities	67% of all HIV positive children 90% of eligible children (WHO guidelines) 36% of infants < 12 months
Khoza [212]*	Zimbabwe	04	234 adults	retrospective record review	19%
Nakigozi [213]	Uganda	05 - 06	1145 adults	review of surveillance records of a community cohort	69%
Ong'ech [214]	Kenya	08 - 10	363 mothers	prospective cohort in HIV care & Mother and Child Health clinics (MCH) in 2 hospitals	81% in MCH clinic 97% in HIV clinic

*Full text not available

Table 3.2 Proportion of HIV-exposed infants initiating CPT (ordered by year of study data-collection, firstly for studies reporting patient data, then programmatic data)

Authors	Country	Data-collection year	Sample	Design	Proportion initiating CPT
Steel-Duncan [215]*	Jamaica	04	132	prospective cohort	90%
Ong'ech [214]	Kenya	08 - 10	363	prospective cohort in HIV care & mother child health clinics in 2 hospitals	98% of mothers in HIV care & 100% of mothers in MCH clinics
Moodley [216]	South Africa	09 - 10	400	record review & mother interviews in 1 child immunisation clinic	67% of all HIV-exposed 93% of HIV-exposed infants discovered HIV positive 64% of HIV-exposed infants discovered HIV negative 71% of HIV-exposed infants of unknown HIV status
Luo [217]	LMIC	04 - 05	71 countries	review national programme data	4% globally; ≥15% in only 5 countries: Ukraine 88%, Botswana 58% South Africa 26%, Guyana 18% Georgia 15%. 14% Laos (highest in Asia) 10% Benin (highest in W Africa)
Ginsburg [218]	LMIC	05 - 06	52,342	PMTCT indicators review	9% across 18 countries

*Full text not available

Table 3.3 Proportion of TB-HIV co-infected patients initiating CPT (ordered by year of study data-collection)

Authors	Country	Data-collection year	Sample	Design	Proportion initiating CPT
Maher [219]	LMIC	00	25 countries	national indicators review	38% in 1 country (Zimbabwe) <10% in 7 countries 0% in 8 countries 9 countries provided no data
Chimzizi [220]	Malawi	03	956	descriptive study of patients in 15 hospitals being scaled up to deliver CPT	77% - 100% (average 97%) 91% within 7 days of starting TB treatment
Chakaya [221]	Kenya	05 - 08	25,558	national TB case notifications review across 1605 facilities	85%
Pevzner [222]	Rwanda	05 - 09	122	retrospective data review in 23 TB clinics	2.5% in 04 15% in 05 92% in 09

Authors	Country	Data-collection year	Sample	Design	Proportion initiating CPT
CDC [223]	Kenya	06 - 09	36,136 in 06 43,954 in 07 41,174 in 08 42,210 in 09	review TB surveillance data from approximately 2,200 TB clinics	87% in 06 86% in 07 92% in 08 92% in 09
Raizada [224]	India	07	734	retrospective record review across 154 primary health care facilities	97% overall 44% within 1 week of starting TB treatment 62% within 1 month 70% within 4 months
Louwagie [225]	South Africa	08 - 09	1283	retrospective cohort from 46 TB treatment centres	65% in semi-integrated & 69% in separate facilities
Kapata [226]	Zambia	06 - 10	33, 748	record review & surveillance data across multiple sites	31% in 06 70% in 10
Harries [227]	Malawi	10	by 2010 250,987 ART patients 13,677 TB-HIV co-	record review from multiple sites in 2 districts	86% in 03 97% in 04 96% in 05 93% in 06

Authors	Country	Data-collection year	Sample	Design	Proportion initiating CPT
			infected		89% in 07 96% in 08
Lawn [188]	sub-Saharan Africa	12	-	descriptive study	76% in 10 (cited from WHO Global report)

Table 3.4 Availability of CPT (ordered by year of data-collection)

Authors	Country	Data-collection year	Sample	Design	Provision of CPT
Filler [228]	sub-Saharan Africa	06 - 07	45 PEPFAR-supported sites	interviews & record review	98% of sites provided CPT
Date [229]	multi-country	07	41 countries	WHO officer survey	93% of all countries have policy for CPT provision & 66% cite nationwide implementation Africa 94% (policy) & 69% (implementation) Americas 100% & 67% Eastern Mediterranean 100% & 67% Europe 86% & 50% SE Asia 100% & 50% W Pacific 75% & 100%; 90% & 75% of ART & HIV care facilities provided CPT 70% of staff report erratic supply

Table 3.5 Retention on CPT (ordered by year of data-collection)

Authors	Country	Data-collection year	Sample	Design	Retention on CPT
Zachariah [230]	Malawi	01	87 HIV positive/TB co-infected adults	cross-sectional study to assess CPT compliance while on TB treatment in 4 centres in 1 district	94% had CTX in urine at 4 – 6 months
Alkatout [231]	Zimbabwe	01 - 04	908 HIV positive adults	prospective study in 1 rural hospital	Mean time 32 weeks 34% <1 month 67% < 6months (47% at 4 months) (18% at 8 months)
Kohler [232]	Kenya	05 - 07	1024 HIV positive adults	retrospective cohort from 1 urban health centre	63% at 12 months before free CTX 84% at 12 months after free CTX
Ong'ech [214]	Kenya	08 - 10	363 HIV-exposed infants	prospective cohort in 2 hospitals	56% in HIV care & 75% in MCH clinic at 6 months 40% lost to follow-up at 12 months

Table 3.6 Commentary pieces describing barriers to scaling up widespread access to CPT and recommendations (ordered by publication year)

Authors	Country	Year published	Study population	Barriers	Recommendations
Bortolotti [32]	sub-Saharan Africa	02	HIV positive adults and children	-Questionable efficacy of CPT & concerns about increased resistance and duration on CPT if efficacy diminishes over time	-identify HIV positive patients -ensure life-long adherence -monitor adverse events -understand cost-effectiveness -increase capacity of health care staff -ensure adequate drug supply -enhance monitoring & follow-up
Boerma [233]	LMIC	05	HIV-exposed & HIV positive children	-4 million children & infants in need of CPT sub-Saharan Africa 3.5million, Asia 309,000, Latin America 99,000, N Africa/Middle East 59,000, Eastern Europe/Central Asia 18,000	-greater monitoring will lead to more accurate data which will lead to more accurate understanding of numbers in need of treatment & better resource allocation

Authors	Country	Year published	Study population	Barriers	Recommendations
Harries [234]	sub-Saharan Africa	06	HIV-TB co-infected	-Malawi - 23% of hospitals had complete stock-outs, remainder of clinics had insufficient supplies	-add columns to TB registers for CPT start date -provide CPT asap to HIV positive/TB co-infected patients -test all TB patients & initiate on CPT all HIV positive -provide easy dispensing of 1-2mth supplies (e.g. in 120 tablet packs) -pharmacy CTX register to aid forecasting; -integrate TB-HIV services to aid dispensing of TB, CPT & ART drugs
Zachariah [207]	LMIC	06	HIV-TB co-infected		-supply CPT through existing TB clinics free of charge -implement CPT register to monitor follow-up, side-effects & drug requirements -train TB counsellors & staff -increase patient education

Authors	Country	Year published	Study population	Barriers	Recommendations
Zachariah [38]	LMIC	07	HIV-exposed infants & HIV positive children	-original objections to the evidence (particularly in areas of high resistance) -lack of policy of CPT in infants & children -inability to diagnose infants <18 months & lack of available testing for children -need to visit hospital to pick up CPT (not MCH clinic) -insufficient patient knowledge re CPT -drug supply/stock-outs: 55% of facilities out of stock in Malawi, 2007 -lack of implementation plans & funding	-develop national drug procurement systems -develop registers of CPT use & monitoring systems to aid drug forecasting - develop surveillance systems to monitor resistance - develop guidelines on when to stop CPT - develop accessible diagnostic tests for < 18 months & increase compulsory HIV testing -provide CPT at lower level health centres -provide 3-mth supply not 1-mth (particularly when journey distances are long) -educate patients on CPT
Callens [235]	LMIC	08	HIV-exposed infants & HIV positive children	-lack of guidelines -limited drug availability -cites the estimate that 4 million children are in need of CTX but only 4% are on it	

Authors	Country	Year published	Study population	Barriers	Recommendations
Msellati [208]	Africa	08	HIV positive children	-inadequate policy guidance -limited availability of CTX due to public health authorities not considering it a rationale choice of resource allocation -lack of HIV testing, particularly in children -cites the estimate that 4 million children are in need of CPT but only 4% are on it	
Coutsoudis [236]	LMIC	10	HIV-exposed infants		-advocates breastfeeding over CPT as benefits of breastfeeding outweigh risks of CPT -rationale: as PMTCT services increase & transmission decreases & option B+ aims to get infection to <2%, risks of mass prophylaxis with CPT become more relevant (skin reactions, gastro, resistance)

3.2.1 Study populations and study designs

The studies providing quantitative data were conducted in Côte d'Ivoire, India, Jamaica, Kenya, Malawi, Rwanda, South Africa, Uganda, Zambia and Zimbabwe, 1 multi-country study in sub-Saharan Africa and four studies conducted in multiple-LMIC. Commentary pieces referred to the use of CPT generally in LMIC. CPT is recommended for different populations groups, namely HIV-infected patients, HIV-TB co-infected patients and HIV-exposed infants. As such, the study populations for the quantitative and qualitative data were heterogeneous, but covered the key groups of patients eligible for CPT: HIV-infected adults (8 articles) and children (1 article), HIV-exposed infants (10 articles) and HIV-TB co-infected patients (13 articles). The smallest study estimated CPT initiation among 87 patients and the largest study among 250,987 patients.

Study designs were heterogeneous and included retrospective cohorts reviewing patient records, prospective cohort studies, reviews of clinic programmatic data, reviews of national programme data or surveillance data, cross-sectional interviews and surveys with programme staff or staff at international organisations. One study estimated the number of HIV-infected children and HIV-exposed infants in need of CPT (4 million) in 2005, the majority of whom were seen in sub-Saharan Africa (3.5million) [233].

3.2.2 Proportions of patients initiating CPT and availability of CPT

Three studies estimated the proportion of HIV-infected adults initiating CPT: two examined adults within HIV clinics and one described initiation among mothers in antenatal care. The earliest study was from 2004 and reported coverage among adults at 19% [212]. The two other studies reported that the proportion of adult

patients initiated on CPT was 69% in 2005 - 2006, and 81% of mothers (within Mother and Child Health clinics, (MCH)) and 97% of mothers (within HIV care clinics) between 2008 - 2010 [213, 214].

One study estimated coverage among HIV-infected children. This estimated that 67% of all HIV-infected children in care and 90% of all CPT-eligible children in care, when using the WHO guidelines for initiation eligibility, initiated CPT between the period from 2004 - 2009. However, the same study estimated that among infants < 12 months only 36% initiated CPT [211].

Five studies estimated the proportion of HIV-exposed infants initiated on CPT, with the earlier studies tending to report lower proportions initiating CPT. The earliest study, however, was conducted in 2004 and estimated access to CPT in Jamaica at 90% [215]. While this estimate appears high, the full text of this article was not available and a complete understanding of the study population or definitions was not therefore possible, precluding any interpretation of this high estimate. One study, reviewing national programme data in 71 countries in 2005, reported that, globally, only 4% of HIV-exposed infants accessed CPT and that only in 5 countries out of those surveyed did ≥ 15% of HIV-exposed infants initiate CPT [217]. This study has been widely cited as evidence of CPT scale-up being slow, notably in the commentary articles included in this review [208, 235]. One further study, examining data from 2005 - 2006, reported similarly low proportions of HIV-exposed infants accessing CPT (9%) [218]. This study also reported that in 2005 and 2007 only 11% and 17% of sites, respectively, reported any data on CPT use. The two most recently published studies examined data collected between 2008 - 2010 and between 2009 - 2010, respectively. The earlier of these, estimated the

proportion of HIV-exposed infants initiated on CPT within MCH clinics in Kenya to be 100% and within HIV clinics to be 98% [214]. The most recent study estimated that 67% of all HIV-exposed infants in clinics in South Africa initiated CPT [216].

Ten studies estimated the proportion of TB-HIV co-infected patients in TB clinics who were initiated on CPT. The studies examined data from 2000 – 2010, with some studies reporting at multiple time-points to provide assessments of changes in coverage over time. The earliest report of access to CPT among TB-HIV co-infected patients was a global survey conducted in 2000. This cited one country (Zimbabwe) with 38% of patients initiating CPT, seven countries with <10% nationwide coverage and 8 countries with 0% national coverage [219]. Reports in 2004 and 2006 estimated similarly low levels of initiation of CPT, at 2.5% and 31%, respectively [222, 226]. One study estimated 97% of patients initiating CPT in 2003, however this study described the initial period of an MoH-supported CPT scale-up programme in 15 hospitals in Malawi [220]. It is likely that this high coverage reflected the resources for CPT which were being invested into specific health centres and the additional monitoring at the time. The most recent reports (2009 and 2010) among TB-HIV co-infected patients estimate access between 65% - 92%, of which three studies reported <80% and two reported >90% [188, 222, 223, 225, 226] . The lowest estimate was extracted from a study examining retrospective data and the authors suggested that the low coverage may reflect poor record keeping, or challenges during their analyses when trying to match records in the absence of unique patient identifiers.

The relative increases in the proportion of patients initiating CPT among TB-HIV co-infected patients reported by four studies demonstrate the achievements in scaling

up CPT access within TB clinics: one study reports access at 86% in 2003 and 96% in 2008; one estimated access at 2.5% in 2004 increasing to 15% in 2005 and reaching 92% by 2009; a further study estimated access at 31% in 2006 increasing to 70% in 2010, while another reports an increase from 86% in 2006 to 92% in 2009 [222, 223, 226, 227].

The proportion of clinics at which CPT was available was reported by two studies, both at the end of 2007: one described PEPFAR-supported sites in one-country (98% providing CPT) and the other was a global WHO survey describing the proportion of ART facilities (90%) and the proportion of HIV-care facilities (75%) dispensing CPT [228, 229]. The WHO survey also reported that in 2007, 66% of countries had achieved 'nationwide' implementation of CPT.

3.2.3 Retention on CPT after initiation and risk factors for non-initiation

Retention on CPT was estimated among HIV-infected adults in two studies, one reporting 18% of those initiated still on CPT after 8 months, with the other reporting that 84% of patients were still on CPT after 12 months [231, 232]. Retention on CPT was estimated in one study among HIV-exposed infants (60% at 12 months), but differed depending on whether infants were seen in MCH clinics (75% at 6 months) or HIV-care clinics (56% at 6 months) [214]. No study described retention on CPT among HIV-infected children.

Adherence to CPT was estimated among HIV-TB co-infected patients in three studies: 29% of patients collected > 80% of CPT prescriptions in one study; 65% of staff reported that CPT was routinely prescribed to patients in another study; and a further study reported 94% of patients with laboratory detectable CTX after 4 - 6

months on CPT [222, 224, 230]. One study conducted among HIV-exposed infants reported that 47% of carers did not provide CPT to infants on weekends [216].

Three studies reported on factors associated with non-initiation of CPT or with retention on CPT. One study reported that non-initiation of CPT was higher among men than among women (38% vs 29%) and that younger individuals (15 - 24yrs vs > 24yrs) were more likely not to initiate (RR 2.22) [213]. A second study similarly found that being female was positively associated with initiating CPT, as was being on ART (RR not given) [212]. A third study reported that being aged < 15yrs or > 30yrs or having a deceased partner were associated with longer time on CPT [231].

3.2.4 Barriers to scaling up CPT and recommendations

Two studies described health-care worker knowledge or national policies relating to CPT. The first study, reporting on a survey conducted in 1999 - 2000, estimated that 6% of clinicians and 50% of health care workers had never heard of CPT, and that only 13% of clinicians had accurate knowledge of the correct dosing and prescribing practices for CPT [237]. The second study estimated that by 2007, 93% of countries globally had a policy relating to CPT [229].

Three studies provided quantitative data on stock-outs or inadequate supplies of CTX and all were conducted in 2006 or 2007. Reasons for stock-outs of CTX include its prescribing for prophylactic and therapeutic use, poor drug forecasting and interrupted drug supply chains. One study in Malawi reported that 23% of hospitals had complete stock-outs and the remainder of clinics had insufficient supplies on the day of the study visit, while another Malawian study reported that 55% of facilities were experiencing stock-outs of CTX on the day of the study visit

[38, 234]. The third study was a 41-country survey, which reported that 70% of health centres experienced erratic supplies and stock-outs of CTX [229].

The commentary pieces discussed barriers and recommendations to scaling up CPT among HIV-infected adults (1), HIV-exposed or infected children (5), and TB-HIV co-infected patients (2) and were published between 2002 and 2010.

Early barriers to CPT scale-up related to lack of national policies due to concerns about the efficacy of CPT, particularly in areas of high bacterial resistance, and concerns about the development of resistance to CTX given the requirement for life-long adherence to CPT [32, 207]. Early recommendations, therefore, included the need to monitor adverse events and to understand cost-effectiveness [32].

Existing barriers to increased access to CPT or retention on CPT include: limited ability to diagnose infants <18 months easily and challenges ensuring regular testing for children and adults; a continued perceived low priority of CPT among health care workers due to lack of adequate and accurate monitoring; inadequate guidance for health care workers on its use; inadequate patient education relating to the reasons for taking it and correct dosing, particularly among mothers; lack of implementation plans and funding for CPT, due in part to public health authorities not considering it a rationale choice of resource allocation; lack of integrated TB/HIV clinics and a concern among TB patients that receiving CPT stigmatises them as being HIV-infected; a lack of integrated CPT dispensing within MCH clinics resulting in additional visits required at other health facilities; and limited availability of CTX [38, 188, 208, 214, 216, 224, 227, 229, 235].

Specific recommendations from the commentary pieces include: increase HIV diagnosis, particularly among children and TB patients, and improve identification of patients in need of CPT; develop accessible HIV diagnostic tests for < 18 months; increased compulsory HIV testing; increase patient understanding of and staff capacity to deliver CPT; ensure life-long adherence to CPT and continuous supply of CTX to facilitate this; dispensing larger numbers of pills (3- or 2-month supply rather than 1-month supply, particularly when journey distances are long); dispense CTX in special 120-tablet packs rather than nurses manually counting pills from 1000 tablet tins; scale-up integrated TB-HIV clinics to facilitate easier access to TB, CPT and ART drugs for co-infected patients or, if not possible, provide CPT within TB clinics; evaluate current surveillance systems routinely for completeness and accuracy and ensure adequate monitoring of access and retention on CPT; develop pharmacy CTX dispensing registers to aid drug forecasting; add columns to TB registers to collate data on CPT use; create CPT registers to monitor initiation, follow-up, side-effects and drug requirements; decentralise CTX stocks by providing CPT at lower level health centres and ensure regular supplies of CTX; and develop guidelines on when to stop CPT to ease the demand burden for CTX [32, 38, 221, 222, 227, 229, 231, 233, 234].

3.2.5 Review discussion

The literature available to evaluate the implementation of CPT was limited in quantity. Furthermore, there was heterogeneity of study populations including HIV-infected adults, HIV-infected children, HIV-exposed infants and TB-HIV co-infected patients, resulting in only a small number of studies for each population group. The majority of articles included in this review reported initiation among HIV-TB co-infected populations, with only 1 article describing the proportion initiating CPT

among HIV-infected children and only 2 describing initiation among adults in HIV care clinics. The years in which the studies were conducted varied widely over a 10-year period. There were in addition, ranging estimates of CPT initiation within and between each population group, with notably low estimates for HIV-exposed infants. This likely reflects the different challenges in scaling-up CPT to the different populations. Moreover, the time since HIV diagnosis by which CPT was initiated was rarely provided, making it difficult to compare proportions.

The included studies do not provide enough details to comment on risk factors for not initiating CPT and more work is needed to enable the identification at the time of HIV diagnosis of patients that are at risk of not initiating CPT. Moreover, few studies examined the duration of time spent on CPT, and the time-point at which retention on CPT was estimated differed between studies. This makes drawing any conclusions about retention on CPT challenging. The lack of reported information on time spent on CPT may be because there are no monitoring tools for continuation on and adherence to CPT. This position, for example, is held by representatives from the national MoH, Malawi [Jahn A., personal communication March 2010, Lilongwe, Malawi]. Retention rates on CPT are important to quantify and report because maintaining patients on CPT is vital for OI prevention. This is particularly true for individuals not yet accessing ART, who remain susceptible to bacterial infections, and for whom CPT may have the greatest impact, especially as there is the potential to delay the need for initiation of ART [203].

Despite these limitations, the studies provide valuable information about CPT coverage. Most notably, many commentary pieces discuss the poor scale-up of CPT, citing the 4% coverage estimate from 2005. This review has shown a clear

calendar time effect with coverage rates across all population groups far higher than 4% and increasing substantially in recent years. These increases likely reflect enhanced services but it is worth noting that this may, in part, reflect improved record keeping. Where the data on HIV-exposed infants suggest low coverage, they may also reflect the late integration (2005) of a CPT indicator relating to infants by many MoH and associated poor data recording by health care staff [217]. One study demonstrated that access to CPT among HIV-exposed infants was low (9%), while noting that the number of sites reporting data on CPT was also low (between 11 – 17%). There may be some truth in the statement that 'what gets monitored gets done' [229]. Many commentary pieces cited poor record keeping and insufficient monitoring as key barriers to scaling-up access to CPT, particularly relating to ongoing access to CPT after initiation. If monitoring systems remain poor, the scale-up of CPT, and ensuring continued access to CPT for those initiated, may also remain poor. There is a need to evaluate current monitoring systems routinely for completeness and accuracy [222].

The lack of studies describing access to CPT among newly-diagnosed patients in HIV care facilities and continued access to CPT after initiation demonstrates the need for further studies to examine this. I, therefore, designed and conducted a study to estimate access to CPT among newly-diagnosed patients and time spent on CPT after initiation.

3.3 Study design

3.3.1 Aim, objectives and outline

The aim of this study was to assess access to CPT for patients in HIV care in outpatient clinics in Uganda and Tanzania. The objectives were:

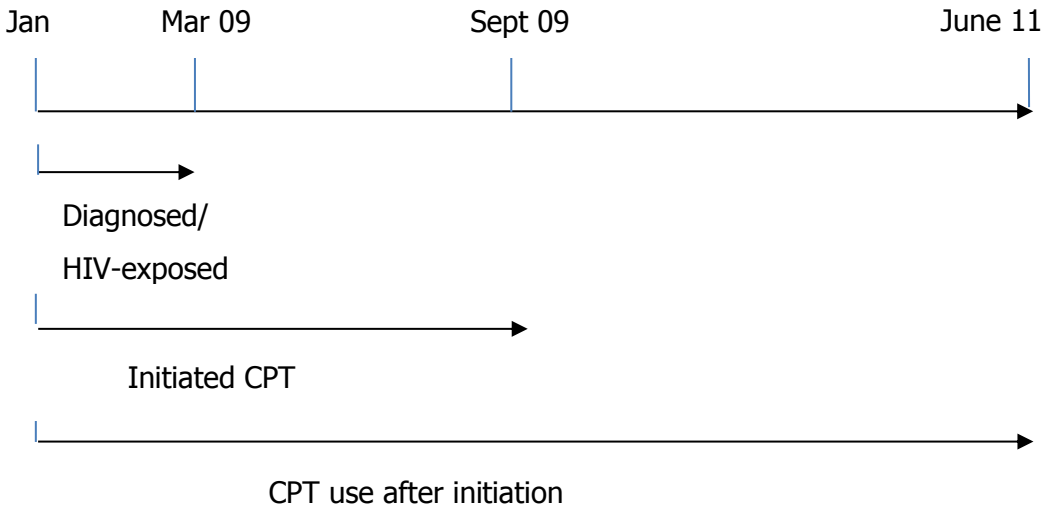
- to describe CPT prescribing and dispensing practices as reported by clinic staff, and to describe challenges that may impede regular access to CPT,
- to estimate time from HIV diagnosis or birth to an HIV-positive mother to CPT initiation among patients newly-diagnosed with HIV/birth and to examine risk factors associated with this (sex, age and diagnostic clinic),
- to estimate the proportion of time interrupting CPT for those who initiated and risk factors associated with this (sex, age, clinic and WHO stage), and
- to compare these derived estimates with data reported in monitoring reports.

This study included pilot site visits and interviews with clinic staff to identify practices for CPT prescribing and dispensing and to identify issues which may influence study design. The staff interviews were also used to identify perceived barriers to CPT scale-up. The main study was conducted in 8 clinics in Uganda and in Tanzania using 2 data-sources:

- all patients newly-diagnosed with HIV and HIV-exposed infants during January - March 2009. These data were extracted from HIV care clinic diagnostic registers and exposed-infant registers.
- all patients who initiated CPT in the same health centre during January - September 2009. These data were extracted from HIV care clinic pre-ART enrolment registers.

The records of all patients diagnosed with HIV or infants identified as HIV-exposed during January - March 2009 were linked to the records of patients enrolling into HIV care by September 2009, and these patients were assumed to have initiated CPT (Figure 3.1). For patients initiated on CPT, longitudinal data on CPT use during

Figure 3.1 Time-line for data-collection from HIV diagnosis or birth to an HIV positive mother to CPT initiation and CPT use after initiation



their time in care were gathered from their patient files up until data-collection in June 2011. The study was facilitated through EfA partners at the MRC/UVRI in Uganda and at MITU, Tanzania.

The remainder of this chapter describes issues identified during the pilot site visits which influenced study design, describes the design of the main study and presents the results of the clinic staff interviews which provide a background to CPT provision in the Ugandan and Tanzanian study clinics. The main results of the study, estimating the cumulative probability of initiating CPT after HIV diagnosis, time interrupting CPT, and comparisons to official monitoring reports are presented in the following chapter.

This work provides a summary to national government representatives and international researchers of CPT use in 2 African countries. It is anticipated that the results will feed into national implementation strategies for ensuring CPT is accessed by those most in need.

3.3.2 Pilot phase and implications for study design

The pilot phase involved visits to 10 health centres in Uganda and Tanzania in October - November 2010 to assess the feasibility of quantitative data collection. I visited a variety of HIV care health centres including those eventually selected for inclusion in the study and I examined how data about CPT use were recorded.

The health centres for the pilot phase visits aimed to meet the following site eligibility criteria, which were the criteria used to select sites for the main study:

- sites conducted HIV testing,

- site provided HIV care to both adults and children,
- sites provided CPT through the national MoH system, and
- the provision of CPT was not dependent upon external support, such as a research study.

Sites for the pilot visits and main study were selected in collaboration with the national MoH and the local EfA partner and aimed to provide a mix of peri-urban and rural sites and to include at least one large hospital and one smaller health centre in each country. I sought to include the greatest number of sites which were feasible to visit within the study time-line. In Uganda, included sites were in the Wakiso district and in Tanzania sites were in the Mwanza and Shinyanga districts. The districts were selected due to their proximity to the base of the local study EfA study partner. The provision of CPT in two sites from the pilot visits was dependent upon external support as sites were involved in research studies and these sites were not included in the main study.

The main study, therefore, was conducted in 8 HIV outpatient clinics, 4 in each of Uganda and Tanzania. In Uganda, the study was conducted in 2 peri-urban hospitals (1 specialising but not limited to paediatric care) and 2 rural health-centres. The Ugandan sites were Entebbe district hospital, MildMay International, Kasanje Health Centre II and Kigungu Health Centre III. All children who are diagnosed with HIV within the Wakiso district of Uganda are referred to one of the Joint Clinical Research Centre (JCRC), The AIDS Support Organisation (TASO) or MildMay (all non-governmental organisations (NGOs) working in collaboration with the national MoH), and as such, few other MoH facilities have a normal distribution of adults and children accessing HIV care. MildMay International was included as

the largest of these organisations treating children. In Tanzania, the study was conducted in 2 peri-urban hospitals, 1 rural health centre and 1 rural dispensary. The Tanzanian sites were Sekou Toure Regional Hospital, the Hindu Union Hospital, Pansiansi Dispensary and Buzuruga Health Centre. The Hindu Union Hospital was included because much HIV care in Tanzania is provided through the MoH with support from faith-based organisations. A map of the location of the study sites can be found in Appendix 3.1. The selected health centres were similar to other peri-urban hospitals and rural health centres in terms of distance from major cities, number and cadre of staff in clinic, facilities available at each clinic and populations served.

In each health centre visited during the pilot phase, I obtained spare blank copies of the HIV diagnostic registers, pre-ART and ART registers, pharmacy records, monitoring and evaluation (M&E) reports and forms used in patient records. I compared the data tools used and their degree of completion across the sites and across the countries and established which data items were feasible to collect in the main study. The following issues were identified which influenced study design.

Firstly, all patients who enrol into HIV care (pre-ART patients as well as ART-eligible patients) are enrolled in the pre-ART register for pre-ART care, where pre-ART and ART-eligible patients receive CPT. ART-eligible patients enrol firstly in the pre-ART register because they spend a short period in pre-ART care receiving ART adherence counselling before commencing ART. Therefore, the pre-ART register is useful to gather information on all patients enrolling into care. Only clinics where the diagnostic and pre-ART registers and the submitted clinic monitoring reports were available for the same time-period were included in the main study. As the

ability to retrieve historical diagnostic and pre-ART enrolment registers and monitoring reports varied between sites, I selected the first quarter of 2009 as the entry point for diagnosis.

Secondly, in larger health centres, different diagnostic registers are used in different clinics (e.g. within tuberculosis clinic as well as the HIV clinic), and patient identification numbers are not always unique, or moreover, linked, between the registers. Furthermore, data are sometimes copied over from one register into the 'main' diagnostic register meaning that any individual patient's information could appear twice. In order to avoid double-counting, the names and initials of each patient were, therefore, temporarily recorded. After establishing which register the health facility considered the 'main' diagnostic register, the main register was searched for the names of all patients recorded in the secondary registers (e.g. the tuberculosis register), and, recognising that names of patients may be the same for family members, additionally matched on sex, age and date of diagnosis. Immediately after cross-checking, the full names of patients were destroyed.

Thirdly, as the date of CPT initiation was rarely recorded in the pre-ART register, I used the date of enrolment in the pre-ART register as a proxy for CPT initiation.

Fourthly, to gather longitudinal data on those who initiated CPT, I matched patients manually while in clinic on sex, age and date of diagnosis, between the diagnostic and pre-ART register, for patients diagnosed/born January – March 2009. This was necessary as no identification number linking records exists, and information on patients transferring-in was rarely recorded. Similarly, in order to assess time from HIV diagnosis to CPT initiation in the absence of a unique patient identifier, I

matched patients on the diagnostic and pre-ART enrolment registers on clinic, age, sex and date of HIV diagnosis (perfect matching) and further matched on clinic, age, and date of diagnosis, but not sex (imperfect matching). I then matched on clinic, but allowed the following variation on any one variable: age by up to 1 year difference, date of diagnosis by up to 1 month difference, and allowing variation in sex (imperfect matching). This matching was used to derive a minimum estimate of the proportion initiating CPT. I further matched the records of patients in the pre-ART register without a date of HIV diagnosis on clinic, age and sex. I also assumed that the number of patients who could not be matched in the minimum estimate had transferred-in for care unofficially and I assumed the same number of patients per clinic would transfer-out unofficially and initiate CPT elsewhere. These patients were not included in the main analyses but can be seen to provide a maximum estimate of the proportion initiating CPT.

3.3.3 Study population and period

In each health centre, a nurse directly involved in patient care was selected for the interviews and, if available, the clinician in charge of HIV care was also interviewed. Clinic staff members were selected for the interviews based on who was available during the days of data-collection. This was due to many of the health centres having a limited number of staff members involved in HIV care and interviewing a large number of clinic staff would have unreasonably detracted valuable staff time from routine patient appointments.

All patients diagnosed or infants identified as HIV-exposed during January - March 2009 whose details were entered into the HIV diagnostic register were included. There was no exclusion criterion. A three-month period for diagnoses/births was selected to allow an adequate number of patients to be included from both large

and small health centres. For example, small rural sites may diagnose around 15 patients a month whereas urban hospitals may diagnose around 70. The study captured data on all patients who enrolled into the clinic's pre-ART register by September 2009. This allowed a six-month delay for patients diagnosed/born at the end of March until enrolment into care, and was selected because a 6-month period had previously been used as a marker of significant delay in seeking care in a previous study in Uganda [213]. In Tanzania, as the date of HIV diagnosis was always provided in the pre-ART register, details of patients enrolling in the pre-ART register by September 2009 were only gathered for patients diagnosed January – March 2009. By selecting September as the cut-off date for CPT initiation, it allowed for a minimum 18-month follow-up period between CPT initiation and data-collection in June 2011 in which to assess continued access to CPT for patients after initiation. Longitudinal data on participants from the diagnostic cohort who initiated CPT in the same health centre by September 2009 were gathered up until the time of data-collection in June 2011.

The sampling frame used for this study is outlined in Table 3.7.

3.3.4 Data collection

A copy of the data collection tools used to gather the qualitative and quantitative data can be found in Appendix 3.2.

The following data were gathered from the staff interviews:

- Interviewee demographics: staff cadre, sex, duration of time in role

Table 3.7 Sampling frame to assess access to CPT

Unit	Selection
Districts	Wakiso district Uganda, Mwanza and Shinyanga districts Tanzania
Health Centres	Entebbe district hospital, MildMay International, Kasanje Health Centre II and Kigungu Health Centre III, Uganda; Sekou Toure Regional Hospital, the Hindu Union Hospital, Pansiansi Dispensary and Buzuruga Health Centre, Tanzania,
Sample size	Number of health centres: 8 total (4 per country) Number of staff for interview: 2 per health facility
Health centre staff	1 HIV-care nurse per health centre and, if available, the clinician working in the HIV clinic of the days of data-collection
Diagnostic cohort	all patients (adult and children) diagnosed with HIV (within clinic or via outreach) and HIV-exposed infants, January-March 2009, according to the diagnostic register
Proportion enrolling into care and on whom long-term access to CPT assessed	all patients diagnosed January – March 2009 who enrolled for care between January – September 2009, as identified in the pre-ART register, in the same health centre (i.e. did not transfer-in)

- Health centre logistics: location of HIV diagnoses registers (e.g. TB clinic, maternity unit, inpatient wards, STI clinic, HIV unit) and exposed-infant registers
- CPT prescribing information: criteria used to prescribe CPT to exposed infants, infected infants, children and adults (pre-ART and on ART) and criteria used to stop prescribing CPT to the same groups; drug availability (tablets, syrups, part-adult tablet for infants); number of days-worth of CPT prescribed routinely, and estimated frequency of CPT stock-outs,
- Potential barriers to CPT scale-up: availability of CPT specific guidelines and training,
- Perceived reasons for challenges to scaling-up CPT; reasons reported by patients for not taking CPT; staff opinion of importance of CPT
- CPT monitoring information: type of monitoring and evaluation reports which ask for information on CPT (monthly or quarterly) and CPT data reported.

I described the aims and objectives of the study to clinic staff invited to interview, who were given an information sheet and informed consent form. If all questions were satisfactorily answered, written consent was obtained. To minimise the potential for observer bias, the interview used for the most part closed-ended questions with multiple choice responses. Where questions solicited a short concise response (e.g. "if you feel CPT for patients on ART is not very important, please explain briefly why you think this?"), a small space was provided for free-text responses, though the use of such questions was kept to a minimum. To minimise the potential for reporting bias and to avoid influencing the responses of the interviewee, no reference to details of the international or national CPT guidelines

was given at any point in the interview. The interviews took around 15 minutes to complete and staff were compensated for their time by a small monetary allocation to purchase their midday meal. To ensure confidentiality of responses, the interviews were conducted in a room separated from patients and other staff members. If both the person in charge and a nurse were interviewed, these took place separately. In Uganda, I conducted all the interviews myself. In Tanzania, I conducted a practice interview together with the local research assistant in a site not used for the study, after which the research assistant conducted the study interviews.

Data were collected on HIV-diagnosed patients from all HIV diagnostic registers used in each clinic. Information about HIV-exposed infants was recorded from antenatal care registers or Mother and Child Health registers. The following data, if available, were gathered from the registers:

- sex
- age
- date of HIV diagnosis/birth
- unique diagnostic patient identification number
- name (temporarily) and initials of patients

At diagnosis/birth, no information was recorded in the register on WHO stage, CD4 count or TB status and it was thus, not possible to examine the association of these factors on initiation of CPT.

The following data, where available, were gathered on all patients enrolling in the pre-ART register, January - September 2009:

- sex
- age
- date of enrolment in pre-ART register
- date of HIV diagnosis
- unique diagnostic patient identification number
- CPT start date

From the longitudinal patient records, the following data, if available, were gathered:

- Demographic information: sex, data of birth, unique pre-ART identification number
- HIV care baseline information: date of HIV diagnosis, date enrolled into pre-ART register, WHO clinical stage or CD4 count at enrolment, date initiated ART (if appropriate)
- Appointment information: appointment date, WHO stage, CD4 count or percentage, whether CPT was prescribed or not, CPT formulation (tablet or syrup), number of CPT tablets/amount of syrup prescribed, number of days/weeks/month-worth of tablets or syrup prescribed, whether there was a stock-out of CPT that prevented prescribing, date of next appointment

From the official monthly monitoring reports the following data were gathered, if available:

Number of patients diagnosed HIV-infected

Number of male/female patients diagnosed HIV-infected

Number of patients diagnosed HIV-infected, by age (<14, 15 – 24, 25 – 34, 35 – 49, 50 plus, Tanzania)

Number of patients diagnosed HIV-infected, by sex and age (<5, 5 – <18, 18 years plus, Uganda)

Number of babies born HIV positive (Uganda)

Number of live births to HIV-infected mothers (exposed infants) (Uganda)

Number pregnant women HIV-infected (Uganda)

Number of males/females started on CPT, by age (Uganda)

The following data were gathered from official quarterly monitoring reports in Tanzania:

Number of patients enrolled into HIV care (and by sex, and by age and sex; <1, 1 – 4, 5 – 14, 15 years and above)

Number enrolled into HIV care who transferred-in from elsewhere

Number of pre-ART patients who received CPT

The following data were gathered from official monitoring reports on CPT stock-outs:

Number of CTX stock-outs in each month

Duration of CTX stock-out (<1 week, > 1 week)

3.3.6 Statistical methods

The following describes the analytical methods, which were, in the main, the same in Uganda and Tanzania. Important differences are noted.

Survival analyses were used to estimate the cumulative probability of CPT initiation after HIV diagnosis among newly-diagnosed patients/ after birth among infants born to HIV positive mothers. A life table was derived and a Kaplan Meier curve plotted to estimate and show the cumulative probability of CPT initiation from HIV diagnosis/birth. Follow-up time was censored at the end of September 2009 if the event had not been experienced. Dates of initiation which occurred before, but within 1 month of, the date of HIV diagnosis (7 Uganda, 36 Tanzania) were assumed to be data recording errors and individuals were assumed to have initiated CPT on the same day as the date of HIV diagnosis.

Cox models were used to examine differences in the time to CPT initiation by sex, age and diagnostic clinic. In Uganda, the multivariate model was adjusted for sex and age but did not adjust for clinic effect due to the age distribution of clinic attendees (as expected, the paediatric clinic only had paediatric patients and no paediatric patients were diagnosed in other clinics). In Tanzania, models were stratified by diagnostic clinic to allow for differences between clinics. I also considered various transformations of age, as a continuous variable, as a binary variable below and above the median age, and with four age categories. I examined all two-way interactions.

I estimated the proportion of time interrupting CPT after initiation by calculating the number of days without CPT tablets, and the total follow-up time on CPT (total number of days between first day on CPT and the expiry day of the last CPT prescription). Where the number of days-worth of tablets prescribed was not provided but the number of tablets prescribed was, I calculated the number of days-worth by dividing the number of tablets prescribed by two (as CPT was normally given in twice-daily doses). Where neither the number of tablets nor the

number of days-worth was recorded but CPT was given, I estimated the number of days-worth based on the number of days until the next scheduled appointment (which assumed no shortfall or surplus of tablets prescribed).

Using Poisson models, I examined differences in the proportion of time interrupting CPT by sex, age, clinic and WHO stage. Models were then adjusted for the effects of all variables. In Uganda, again, the multivariate model did not adjust for clinic effect due to the age distribution of clinic attendees (as expected, the paediatric clinic only had paediatric patients and no paediatric patients were treated in other clinics). Further, I restricted the Ugandan analyses to patients aged > 2 years because staging additionally differed between adults/adolescents/children and very young paediatrics (85% of < 2 year olds were WHO stage I and 8% were WHO stage II compared to 60% of > 2 years olds in WHO stage I and 32% in WHO stage II). I considered various transformations of age, as a continuous variable, as a binary variable above and below the median age, and with four age categories. I examined all two-way interactions.

I examined potential explanations for the proportion of time interrupting CPT in three ways. Firstly, I calculated the proportion of appointments where CPT was out of stock and examined reported monitoring data on CPT stock-outs. Secondly, I calculated the proportion of patients who were, on average, prescribed a short-fall of tablets until their next scheduled appointment. Thirdly, I calculated the proportion of patients who, on average, attended appointments late. No period of grace was given as even one day late or with a shortfall of tablets prescribed means an interruption to continuous CPT.

3.4 Background to CPT use in Uganda and Tanzania

In Uganda, one interview was conducted in each of the four health centres; three

with HIV-care nurses or nursing assistants (all female) and one with an HIV-care clinical officer (male). Health care workers had been in their current role for a minimum of 56 months. In Tanzania, seven interviews were conducted; three with nurses or nursing assistants, three with clinical officers and one whose cadre was not recorded. Tanzanian health care workers had been in their current role for a minimum of 36 months. The sex of Tanzanian staff was not recorded.

3.4.1 Barriers to wide-spread CPT use

Perceived barriers to CPT scale-up were similar in Uganda and Tanzania, and mirror those identified in the commentary pieces included in the literature review at the beginning of this chapter. I describe the barriers in three categories: clinic-level, training-related and patient-level barriers. All health-care workers in both countries believed that there have been problems scaling up access to CPT.

Clinic-level barriers

- perceived priority to fund ART over CPT,
- difficult drug distribution due to the supply of CPT tablets being in large tins to be counted out by the health care workers, rather than as pre-packaged strips of tablets,
- CTX stock-outs: these were reported to occur more frequently than ART drug stock-outs, with CTX reportedly "hardly ever available" (sustained periods without stock of CTX were reported to have occurred in the previous 2-year period two or three times in Uganda, and two, four and five times in Tanzania, with one Tanzania health care worker reporting that for "one quarter of the last 2 years there was no CPT"); poor CTX drug forecasting in pharmacies and poor supply chain management led to limited supplies of CTX which impeded the ability to prescribe CPT for extended periods

between appointments; and limited supplies of CTX resulted in e.g. 60 tablets prescribed, but the pharmacy only able to dispense 30 tablets, with advice given to the patient to procure the remainder independently.

Training and guidelines-related barriers

- inadequate training and prescribing knowledge with any training received on CPT having been incorporated into the general HIV care training; and a need for refresher courses for HIV care nurses,
- a perception that there were no CPT-specific guidelines, or staff not having seen specific guidelines; a lack of clarity in the guidelines about who should receive CPT, particularly among children, or about when it was safe to stop CPT, and a lack of dosing charts, and
- an inadequate number of health care staff.

Patient-level barriers

- transport costs,
- difficulties keeping frequent appointments if a patient's job requires travel, or missing appointments to collect CPT from a health centre which may be a long walk from home when CPT is sometimes available locally and cheaply on the black market,
- toxicities,
- barriers for pre-ART patients included frequently missed appointments and poor adherence due to lack of experience with any regular drug regimens prior to CPT, and
- barriers for ART patients included, having an increased pill burden and the additional need to cope with advanced HIV-related illnesses.

3.4.2 Prescribing practices

In Uganda,

- all described prescribing CPT in line with the WHO's Universal Access option, for all HIV-infected children and adults, whether pre-ART or already initiated on ART, irrespective of CD4 count or WHO stage,
- in 2 centres CPT was never stopped, mostly due to the lack of CD4 monitoring on which to base a decision about improvements in clinical status,
- in 1, CPT was stopped for adults if the CD4 count was above 800 cells, and in the remaining clinic CPT was stopped if there was a 'good CD4 count, good adherence measures and the patient is stable',
- CPT was never stopped for children,
- all health centres provided CPT to patients monthly, and 2 health centres provided CPT to ART patients corresponding to the number of months of ART supply given, and
- CPT for children was supplied in strengths of 120mg tablets (n=2 health centres), part-480mg adult tablets (n=1), and in part-960mg adult tablets (n=1). CPT was not available in syrup formulation for children in any health centre. Adult tablets were available in 480mg tablets in three centres and in 960mg tablets in one.

In Tanzania, prescribing practices varied widely from the WHO international guidelines and between clinics.

- A universal access option for CPT was not being implemented,

- for children 1 -5 years, 5 of the health care workers prescribe CPT irrespective of clinical status, while 2 health care workers use clinical criteria, based on unspecified weight or CD4 count below 350 cells,
- for children 5 – 18 years, 4 of health care workers prescribe CPT irrespective of clinical status. The remaining health care workers used a variety of measures of clinical status, depending on ART status, including CD4 below 350 cells or below 15%, a combination of WHO stage III and body weight, or unspecified body weight,
- for adults, 3 health care workers prescribe CPT to pre-ART patients based on having a WHO stage of III and above or WHO stage II and a CD4 count of less than 350 cells and 1 health care worker prescribed based on these criteria to ART patients. The remaining 3 health care workers prescribed CPT either based on a CD4 count of below 200 cells, below 350 cells, below 500 cells, based on WHO stage II irrespective of CD4 count, or irrespective of clinical status,
- 5 of the 7 health care workers stop prescribing CPT if there are good clinical reasons, which differed between health care workers: if CD4 count increases to above 400 cells (n=4), above 350 cells (n=3), and also if WHO stage is I (n=1)
- pre-ART and ART patients in all centres are given CPT supplies to last for one month, dependent on availability. Pharmacies may dispense less than is prescribed if stock is low, and
- CPT for children is supplied in strengths of 240g syrups in 3 health centres, and part-480g adult tablet in 1 health centre and adult tablets were available in 480mg tablets in 3 centres and in 960mg tablets in one.

Table 3.8 compares the WHO guidelines with the practices described by the health care workers in Tanzania.

3.5 Summary

The literature review, pilot work and staff interviews have provided a background to the issues affecting the wide-spread implementation of CPT in LMIC. Gaps in knowledge were identified about CPT use, particularly relating to HIV-infected children, and patients in HIV care facilities, and about continued use of CPT after initiation. I, therefore, designed the study outlined in this chapter to estimate access to CPT in HIV care facilities in Uganda and Tanzania. The pilot work identified challenges affecting the design of the study associated with tracking CPT access among patients from diagnosis to long-term care, in the absence of unique patient identifiers and in clinics using paper-based registers and filing systems. The interviews describe a background to CPT use in Uganda and Tanzania, highlighting perceived barriers to scale-up and providing information on prescribing and dispensing practices.

The following chapter estimates the cumulative probability of initiating CPT after HIV diagnosis/birth, time from HIV diagnosis/birth to, and risk factors for, CPT initiation, and CPT use while in care, in Uganda and Tanzania and discusses the study findings.

Table 3.8 Comparison of WHO criteria to prescribe CPT with those reported by seven Tanzanian health care workers

Age-group	WHO guidelines	Tanzanian health care workers
HIV-exposed or HIV-infected infants	All infants until infection is ruled out	All, irrespective of clinical status (all 7 health care workers)
Children (1– 5 years)	WHO stage II & above or WHO I & CD4 <25%	All, irrespective of clinical status (5 health care workers), or based on an unspecified weight (1 health care worker), or those with a CD4 count below 350 cells (1 health care worker)
Children (5 – 18 years)	WHO stage II & above or WHO I & CD4 <25%	All, irrespective of clinical status (3 health care workers), or based on CD4 cell count below 350 (2 health care workers), or with a CD4 percentage below 15% (1 health care workers), or with WHO stage 3 or 4 and unspecified body weight (1 health care worker)
Adults	WHO III & above or WHO II & CD4 <350 cells	All patients on ART, irrespective of clinical status (1 health care worker), or WHO stage 3 or CD4 below 350 cells/below 500 cells (3 health care workers/1 health care workers), or WHO stage 2 (1 health care worker), or unspecified CD4 count or WHO stage (1 health care workers) All patients not yet on ART, irrespective of clinical status (2 health care workers), or in WHO stage 3 or with CD4 count below 350 cell (3 health care workers), or WHO stage 3 or CD4 count below 200 cells (1 health care worker), or WHO stage 2(1 health care worker)

Chapter 4 Use of Cotrimoxazole Preventive Therapy in Uganda and Tanzania

This chapter presents the results of the study I undertook to estimate access to Cotrimoxazole Preventive Therapy (CPT). The study used data from diagnostic, exposed-infant and pre-ART registers and patient records to estimate time from HIV diagnosis/birth to CPT initiation among newly-diagnosed/-exposed patients, and time spent on CPT. The study also compares these derived data with data on CPT use in official monitoring and evaluation reports.

4.1 Initiating CPT after HIV diagnosis

In the 4 health centres in Uganda, 429 people, aged 1 month to 70 years, were diagnosed during the period January to March 2009. During the period January to September 2009, 681 patients, aged <1 month – 74 years, were enrolled in the pre-ART registers, of whom 243 were diagnosed January - March 09 (Table 4.1).

On matching details of these 243 patients against the diagnostic register, 205 matched (108 perfectly and 97 imperfectly). The records for the remaining 38 individuals could not be matched and these patients were assumed to have transferred-in unofficially. Therefore, by September 2009, 205 of the 429 (48%) patients who were diagnosed with HIV during January – March 2009 were estimated to have initiated CPT. Males accounted for 47% of initiations, and the median age of those initiating CPT was 5 years (IQR 1 – 18 years). The paediatric clinic accounted for 77% of initiations.

Table 4.1 Numbers enrolling in the pre-ART register between January – September 2009 in 4 health centres in Uganda, by study eligibility status

Study eligibility status	Number of patients
Total on pre-ART register	681
Diagnosed January – March 2009	243
Not diagnosed January – March 2009	365
HIV diagnosis date not recorded	73

The cumulative probability of CPT initiation was 26% (95% CI 22 – 30%), 33% (29 – 38%), 39% (35 – 44%), and 45% (40% - 49%) on the same day, within 2 days, 1 week and 1 month of diagnosis, respectively (Figure 4.1). The hazard of CPT initiation was no different among females compared to males (p=0.61), but differed by age and clinic (Table 4.2) (Figures 4.2 and 4.3). Within one month of diagnosis/birth, the most notable difference in initiation was by clinic. The hazard of CPT initiation in the combined rural clinics was significantly lower than that of the other settings (HR 0.42, CI 0.22– 0.79 compared to the peri-urban hospital). When examining the rural clinics individually, the hazard of CPT initiation was lower in both, (rural clinic number 1, HR 0.55, 0.23 – 1.31, and rural clinic number 2, HR 0.35, 0.15 – 0.78). Compared to children < 3 years, the hazard of CPT initiation was higher among patients aged ≥ 3 years (HR 1.32, CI 1.00 – 1.75). After adjustments for sex and age, the effect of these variables remained virtually unchanged (Table 4.2). There was no evidence of any interaction between sex and age (p=0.97).

In the 4 health centres in Tanzania, 492 people, aged 1 month to 70 years, were diagnosed during the period January to March 2009. During the period January to September 2009, 429 patients, aged <1 month – 83 years, were enrolled in the pre-ART registers, of whom 402 were diagnosed January – March 2009 (Table 4.3).

On matching details of these 402 patients against the diagnostic register, 294 matched (167 perfectly and 127 imperfectly). The records for the remaining 108 individuals could not be matched and these patients were assumed to have transferred-in unofficially. Therefore, by September 2009, 294 of the 492 (60%) patients who were diagnosed with HIV during January – March 2009 were

Figure 4.1 Cumulative probability of initiating CPT between January - September 2009 after HIV diagnosis/birth in four health centres in Uganda

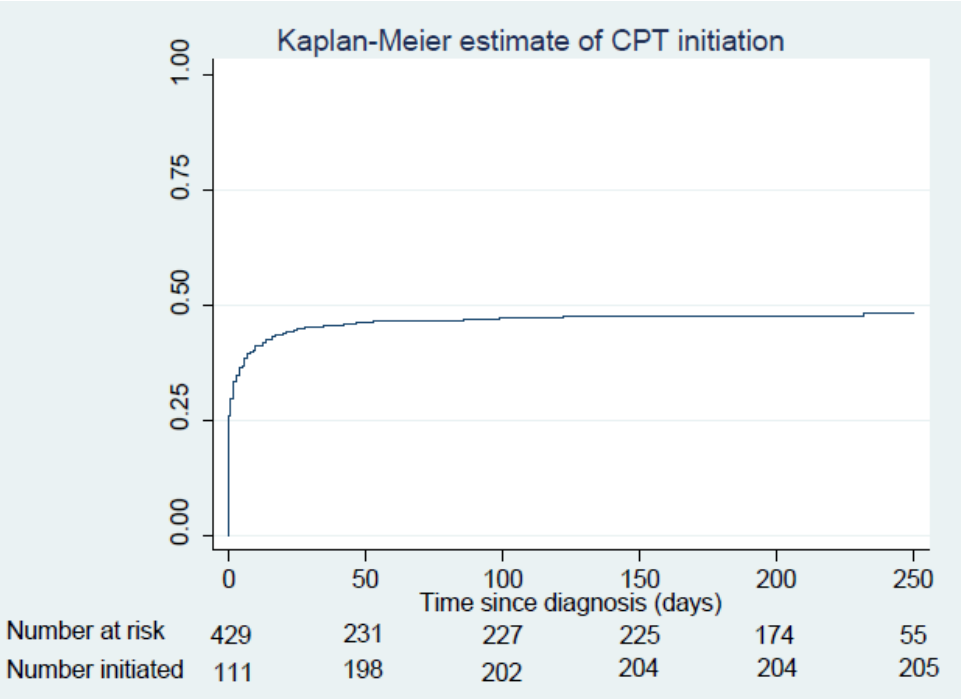


Table 4.2 Number diagnosed with HIV/HIV-exposed initiating CPT and factors associated with CPT initiation after HIV diagnosis/birth in four health centres in Uganda, January – September 2009

Variable	Diagnosed/ exposed (n=429, %)	Initiated CPT (n=205)	Hazard ratio	p-value	Adjusted hazard ratio	p-value
Sex				p=0.61		p=0.40
Male	203 (47%)	99	1		1	
Female	226 (53%)	106	0.93 (0.71 - 1.22)		0.89 (0.67 – 1.17)	
Age						
0 - < 3yrs	207 (49%)	85	1	P=0.04	1	P=0.03
≥3yrs	219 (51%)	120	1.32 (1.00 -1.75)		1.35 (1.02 – 1.80)	
Missing	*3*					
Clinic						
Adult hospital	66 (15%)	35	1	p<0.01	-	-
Paediatric centre	310 (72%)	157	1.05 (0.73 – 1.52)			
Rural clinics	53 (12%)	13	0.42 (0.22 – 0.79)			

*notes: the model was adjusted for sex and age.

Figure 4.2 Cumulative probability of initiating CPT after HIV diagnosis/birth, by age, in four health centres in Uganda

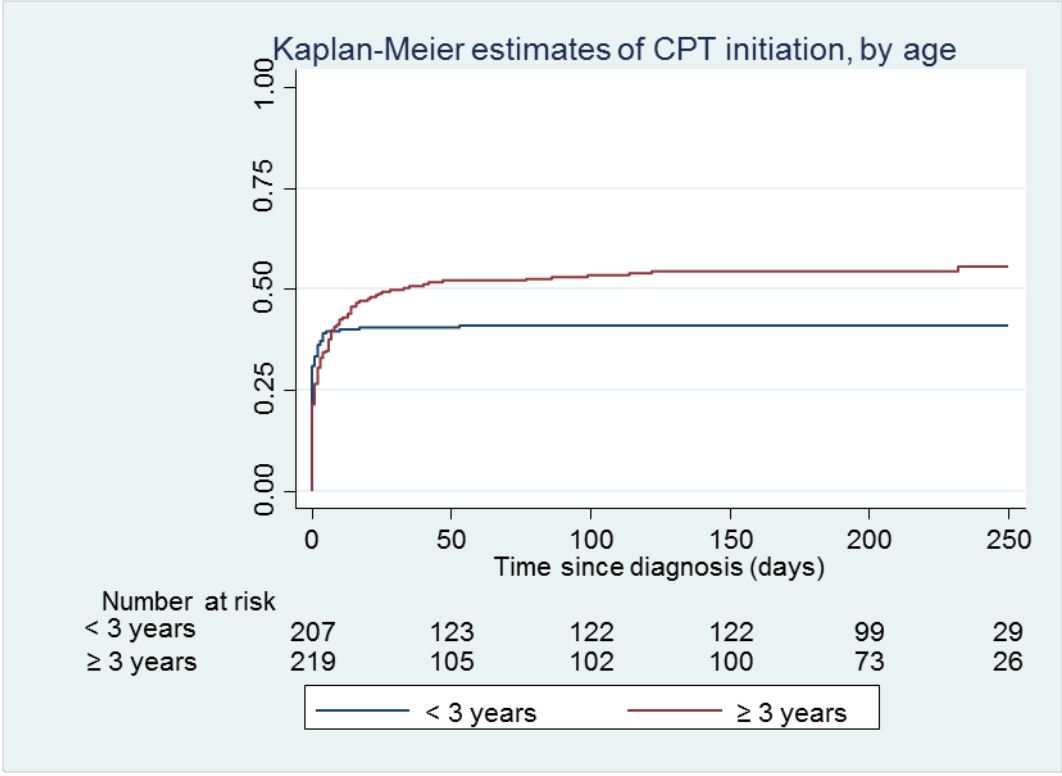


Figure 4.3 Cumulative probability of initiating CPT after diagnosis/birth, by clinic, in four health centres in Uganda

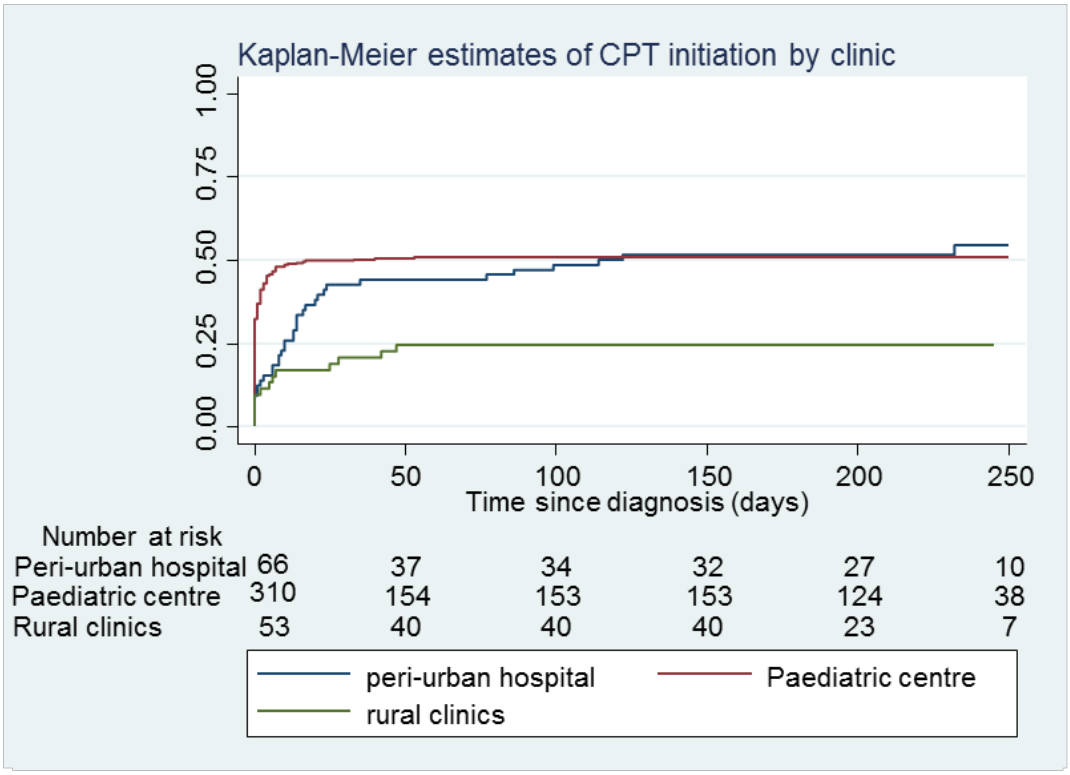


Table 4.3 Numbers enrolling in pre-ART register between January – September 2009 in four health centres in Tanzania, by study eligibility status

Numbers on pre-ART register	
Total number on pre-ART register	429
Diagnosed January – March 2009	402
Later found not diagnosed January – March 2009	27

estimated to have initiated CPT. Males accounted for 32% of initiations, and the median age of those initiating CPT was 32.5 years (IQR 26 – 40 years). The large MoH hospital accounted for 43% of initiations.

The cumulative probability of CPT initiation was 40% (95% CI 36 - 45%), 50% (46 – 55%), 55% (50 – 59%), and 59% (55% - 63%) on the same day, within 2 days, 1 week and 1 month of diagnosis, respectively (Figure 4.4). The hazard of CPT initiation was no different among females compared to males (p=0.24), or among patients of different age (p=0.23) (Table 4.4). The hazard of CPT initiation in the rural clinic, where all of 74 patients initiated CPT, was significantly higher than that of the other settings (HR 2.71, CI 2.01– 3.67 compared to the large MoH hospital) (Figure 4.5). After stratifying the models by clinic, the effects of sex and age remained virtually unchanged (Table 4.4). There was no evidence of any interaction between sex and age (p=0.97).

The maximum estimate of the proportion initiating CPT was 259/429 (60%) and 402/492 (82%) of diagnosed individuals in Uganda and Tanzania, respectively. In Uganda, this comprised the patients in the minimum estimate plus 38 patients assumed to have transferred-out and 16 patients matched from the 73 with no date of diagnosis recorded in the pre-ART register. In Tanzania, this comprised the patients in the minimum estimate plus 108 patients assumed to have transferred-out. Of the 681 and 429 patients enrolling in the pre-ART register in Uganda and Tanzania, respectively, the date of enrolment into care and the date of CPT initiation were available in the pre-ART register for 282 patients in Uganda, and 168 patients in Tanzania. For these patients, the median number of days between enrolment into the pre-ART register and CPT initiation was 0 (IQR 0 – 1) days in

Figure 4.4 - Cumulative probability of initiating CPT between January - September 2009 in four health centres in Tanzania

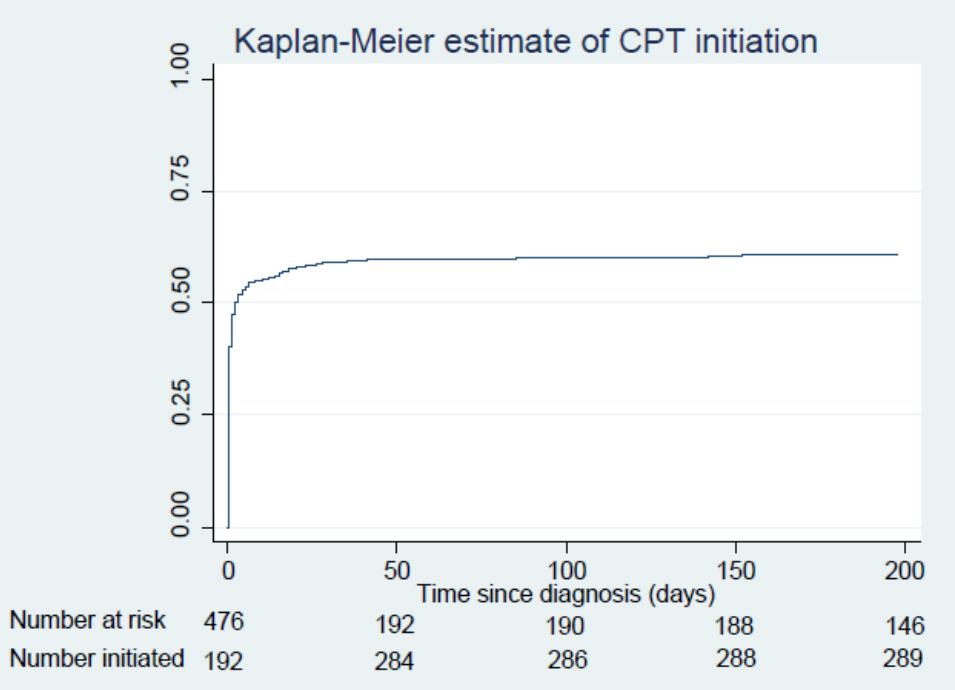
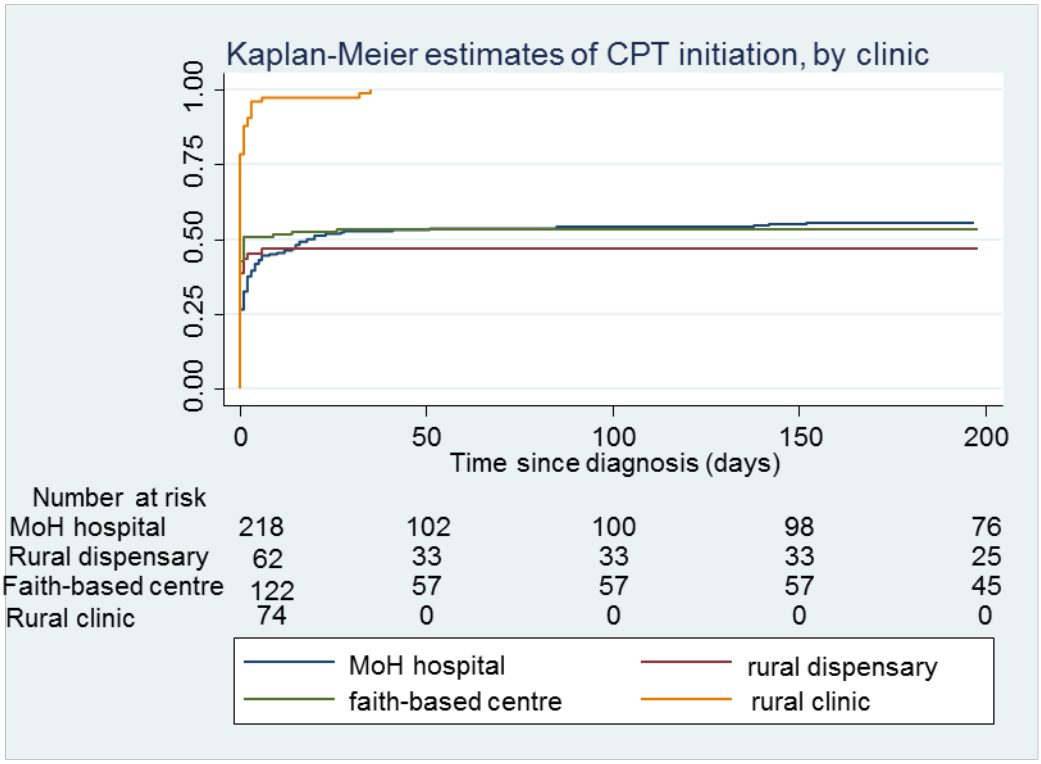


Table 4.4 Number diagnosed with HIV/HIV-exposed initiating CPT and factors associated with CPT initiation after HIV diagnosis/birth in four health centres in Tanzania, January – September 2009

Variable	Diagnosed/ exposed (%) (n=476)	Enrolled (n=289)	Hazard ratio	p-value	Stratified hazard ratio	p-value
Sex				p=0.24		p=0.31
Male	133 (29%)	95	1		1	
Female	331 (71%)	194	0.86 (0.67 - 1.10)		0.87 (0.67 – 1.13)	
Missing	*12*					
Age (median, IQR)	32 (25 – 40)	33 (26 – 40)	1.01 (0.99 – 1.01)	p=0.23	1.00 (0.99 – 1.01)	p=0.41
0 – <15 years	41 (9%)	28				
15 - < 30 years	138 (31%)	76				
30 - < 45 years	182 (41%)	130				
45 and above	78 (18%)	55				
Missing	*37*	-				
Clinic				p<0.01	-	-
MoH Hospital	218 (46%)	121	1			
Rural dispensary	62 (13%)	29	1.07 (0.71 – 1.60)			
Faith-based centre	122 (26%)	65	1.17 (0.87 – 1.58)			
Rural clinic	74 (16%)	74	2.71 (2.01 – 3.67)			

Notes: Age from the pre-ART register was assigned to 12 CPT initiators who had missing data at diagnosis. Adjusted results are stratified by clinic.

Figure 4.5 Cumulative probability of initiating CPT after diagnosis/birth, by clinic, in four health centres in Tanzania



Uganda and 43 (IQR 0 – 339) days in Tanzania, suggesting that the date of enrolment in Uganda, but not in Tanzania, was a suitable proxy for date of CPT initiation.

4.1.1 Comparison of CPT initiators with monitoring and evaluation reports

In Uganda, data from monthly or quarterly monitoring reports were only available for the 3 months from January – March 2009 from all 4 clinics. The reports provided data on the number (by sex) of patients newly diagnosed with HIV or infants born to HIV-positive mothers (n=370) and the number (by sex) of patients newly starting CPT (n=174) (Table 4.5). These monitoring report data suggest that 47% of diagnosed/exposed patients initiated CPT in the same period. According to the current study's estimates, 193 of the 429 (45%) patients diagnosed with HIV/identified as HIV-exposed January – March 2009 initiated CPT during the same period (Table 4.5). The overall proportions are, therefore, almost identical, although the proportions reported to have initiated CPT in both the rural clinics (10% and 8%) and in the paediatric hospital (28%) are far lower than the study estimates (32%, 15% and 50%, respectively). Yet, in the peri-urban clinic, more patients were reported to have initiated CPT (101) than were diagnosed/born (64) during the same time-period (Table 4.5). It is possible that the number initiating CPT included some patients who initiated CPT after a delay having been diagnosed/born in earlier months, although given the median time from diagnosis/birth to CPT initiation was 0 days (range 0 – 1 day) in Uganda, this number is likely to be low. Moreover, the total numbers HIV-diagnosed/exposed and numbers initiated CPT in the monitoring reports are lower than those estimated by this study.

Table 4.5 Number of patients newly identified as HIV-exposed or HIV-infected and number initiating CPT January - March 2009 in four health centres in Uganda, by monitoring reports and by study estimates

	Monitoring reports			Study estimates		
	Males	Females	Total	Males	Females	Total
Number diagnosed HIV-infected						
Rural clinic 1	6	15	21	7	12	19
Rural clinic 2	15	24	39	15	19	34
Paediatric clinic	126	120	246	159	151	310
Peri-urban hospital	25	39	64	22	44	66
Total	172	198	370	203	226	429
Number initiating CPT						
Rural clinic 1	0	2	2	1	5	6
Rural clinic 2	1	2	3	2	3	5
Paediatric clinic	32	36	68	79	76	155
Peri-urban hospital	23	78	101	9	18	27
Total	56	118	174	91	102	193
Total proportion initiating CPT	-	-	47%	-	-	45%

While data from monitoring reports were available from three of the four health centres in Tanzania, data were not available for the same January – March 2009 period in any clinic and therefore comparing derived data with reported data in Tanzania was not possible.

4.2 CPT use among patients in care

In Uganda, among HIV-diagnosed/exposed patients for whom longitudinal records were retrieved (n=223, 20 files not found or patients were found to have transferred-in), 210 started CPT, of whom 175 had information available with which to calculate the proportion of time interrupting CPT. Of these 175 patients on CPT, the majority (99, 58%) were female, and the median age was 8 (IQR 3 – 23) years (Table 4.6). The majority (121, 69%) of patients were enrolled in the paediatric health centre and the majority of patients (153, 91%) were WHO stage I or II at enrolment into care. The median CD4 cell count at enrolment into care was 350 (IQR 203 - 505) cells/mm³ (though 137 were missing). Sixty-nine (39%) patients on CPT initiated ART while in care.

Of the 175 patients initiated on CPT, 118 (67%) had at least one day of interrupted CPT, with 21 (12%), 30 (17%), 35(20%) and 32 (18%) patients having 1 - 30 days, 31 – 90 days, 91 – 180 days, and > 180 days without CPT, respectively. The overall proportion of time interrupting CPT was 0.17/person year at risk (CI 0.17 - 0.17). The proportion of time interrupting CPT, by patient characteristics, is shown in Table 4.6. This proportion was notably lower for patients aged 0 - 2 years (0.09, 0.09 – 0.10) compared to those aged 2 - < 15 years (0.16, 0.16 – 0.17), 15 - < 35 years (0.22, 0.21 – 0.22) and ≥35 years (0.20, 0.19 – 0.21).

Table 4.6 Characteristics of patients prescribed CPT and proportion of time interrupting CPT, in four health centres in Uganda, January 2009 – June 2011

Characteristics	Patients on CPT (n=175)	Person years at risk	Person years interrupted	Proportion of time interrupted
Sex				
Males	72 (42%)	101.3	18.6	0.18 (0.18 – 0.19)
Females	99 (58%)	134.9	21.5	0.16 (0.15 – 0.16)
Missing	*4*			
Age, median (IQR)	8 (3 – 23)			
0 – <2yrs	16 (9%)	26.3	2.6	0.09 (0.09 – 0.10)
2 - <15yrs	97 (56%)	148.0	24.2	0.16 (0.16 – 0.17)
15 - <35yrs	43 (25%)	46.3	10.0	0.22 (0.21 – 0.22)
≥35yrs	16 (9%)	19.7	4.0	0.20 (0.19 – 0.21)
Missing	*3*			
Clinic				
Peri-urban Hospital	40 (23%)	44.3	8.6	0.19 (0.19 – 0.20)
Paediatric Hospital	121 (69%)	183.4	28.9	0.16 (0.15 – 0.16)
Rural centres	14 (8%)	13.9	3.4	0.24 (0.23 – 0.26)
WHO stage				
I	104 (62%)	180.0	28.9	0.16 (0.16 – 0.16)
II	49 (29%)	47.9	9.4	0.20 (0.19 – 0.20)
III or IV	14 (8%)	12.2	2.2	0.18 (0.17 – 0.19)
Missing	*8*			

Note: Figures are numbers and percentages as indicated. Percentages do not include missing. WHO stages III and IV have been combined due to low numbers.

There was evidence of a difference in CPT interruption proportion by sex, age, clinic and WHO stage (Table 4.7). Females (IRR 0.79, 0.77 – 0.82) spent less time interrupting CPT than males, while patients aged 15 - < 35 years (IRR 1.33, 1.28 – 1.38) and ≥ 35 years (IRR 1.38, 1.31 – 1.46) spent more time interrupting than those aged 2 - < 15 years. There was also significant differences in interruptions by clinic with patients in the paediatric clinic spending less time (IRR 0.82, 0.79 – 0.86) and those in the rural clinics spending more time interrupting (IRR 1.26, 1.18 – 1.34) than those in the peri-urban hospital. Patients in WHO stage II spent more time (IRR 1.12, 1.08 – 1.17) and those in stage III/IV somewhat less time interrupting (IRR 0.93, 0.86 – 1.00) compared to those in stage I. After adjustments for sex, age and WHO stage, the effect of the other variables remained unchanged.

There was evidence of interactions between sex and age ($p<0.01$), sex and WHO stage ($p<0.01$) and age and WHO stage ($p<0.01$) (Table 4.8). Among patients age 2 - < 15 years, the proportion of time interrupting CPT among males was higher than among females whereas for those aged ≥35 years, the proportion among males was lower than among females. Among patients in WHO stages III/IV, the proportion of time interrupting CPT was lower among males compared to females but higher for those in stages I and II. Among patients aged 2 - < 15 years, the proportion of time interrupting CPT was much lower for those at stage II (compared to stages I and III/IV) but similar, or higher, for those in the older age groups.

In Tanzania, 325 longitudinal records were retrieved (77 patients were found to have transferred in or their files were not found). Of these 325, 223 started CPT, of whom 194 had information available on which to calculate the proportion of time

Table 4.7 Factors associated with time interrupting CPT, in four health centres in Uganda, January 2009 – June 2011

Characteristics	Incidence rate ratio (95% CI)	P-value	Adjusted incidence rate ratios (95% CI)*	P value
Sex		p<0.01		p<0.01
Males	1		1	
Females	0.79 (0.77 – 0.82)		0.74 (0.72 – 0.77)	
Age		p<0.01		p<0.01
2 - <15yrs	1		1	
15 - <35yrs	1.33 (1.28 – 1.38)		1.48 (1.42 – 1.54)	
≥35yrs	1.38 (1.31 – 1.46)		1.68 (1.58 – 1.80)	
Clinic		p<0.01	-	
Peri-urban Hospital	1			
Paediatric Hospital	0.82 (0.79 – 0.86)			
Rural health centres	1.26 (1.18 – 1.34)			
WHO stage		p<0.01		p<0.01
I	1		1	
II	1.12 (1.08 – 1.17)		0.95 (0.91 – 1.00)	
III or IV	0.93 (0.86 – 1.00)		0.65 (0.60 – 0.71)	

*note: the multivariate model is adjusted for sex, age and WHO stage

Table 4.8 The proportion of time interrupting CPT (Incidence rates, CI) for variables with significant interactions in four clinics in Uganda

	Incidence rates (CI)				
	Sex		WHO stage		
Age Group	Males	Females	Stage I	Stage II	Stage III/IV
2 - <15yrs	0.20 (0.20 – 0.21)	0.13 (0.12 – 0.13)	0.17 (0.17 – 0.17)	0.09 (0.09 -0.10)	0.37 (0.31 - 0.44)
15- <35yrs	0.22 (0.21 – 0.23)	0.21 (0.20 – 0.22)	0.21 (0.20 - 0.22)	0.25 (0.23 - 0.26)	0.12 (0.11 - 0.14)
>=35yrs	0.15 (0.13 – 0.17)	0.25 (0.24 – 0.27)	0.15 (0.13 - 0.17)	0.29 (0.27 - 0.31)	0.17 (0.15 - 0.19)
WHO stage					
Stage I	0.21 (0.20 – 0.22)	0.15 (0.14 – 0.15)	-	-	-
Stage II	0.22 (0.21 – 0.23)	0.19 (0.18 – 0.20)	-	-	-
Stage III/IV	0.08 (0.07 – 0.09)	0.23 (0.21 – 0.25)	-	-	-

interrupting CPT. Of these 194 patients, the majority (117, 64%) were female, and the median age was 36 (IQR 27 – 42) years (Table 4.9). The majority (104, 54%) of patients were enrolled in the MoH peri-urban hospital and the majority (121, 62%) were WHO stage I or II. CD4 counts were available for 81 patients at their first appointment, for whom the median was 188 (IQR 112 - 353) cells/mm^3. Fifty-nine (30%) patients on CPT initiated ART while in care.

Of the 194 patients initiated on CPT, 114 (59%) had at least one day of interrupted CPT, with 26 (13%), 30 (15%), 16 (8%) and 42 (22%) patients having 1 -30 days, 31 – 90 days, 91 – 180 days, and > 180 days without CPT, respectively. The overall proportion of time interrupting CPT was 0.20/person year at risk (CI 0.20 - 0.21). The proportion of time interrupting CPT, by patient characteristics, is shown in Table 4.9.

There was evidence of a difference in the proportion of time interrupting CPT by sex, age, clinic and WHO stage (Table 4.10). Females spent more time interrupting CPT than males (IRR 1.31, 1.27 – 1.35) as did patients aged 15 – < 30 years and 30 - < 45 years compared to patients < 15 years (IRR 1.80, 1.69 – 1.91, and 1.35, 1.28 – 1.43, respectively). Patients aged ≥ 45 years spent less time interrupting than the younger age groups (IRR 0.64, 0.60 – 0.69 compared to < 15 years). Compared to patients in the MoH hospital, patients in the rural dispensary (IRR 2.14, 2.01 – 2.27), faith-based hospital and (IRR 3.46, 3.35 – 3.57) and rural clinic (IRR 1.25, 1.18 – 1.32) spent more time interrupting CPT. Those enrolled into care at WHO stage II (IRR 0.60, 0.58 - 0.63), III (IRR 0.68, 0.65 – 0.70) or IV (IRR 0.63, 0.57 – 0.70) spent less time interrupting CPT compared to those enrolling at stage I.

Table 4.9 Characteristics of patients prescribed CPT and proportion of time interrupting CPT, in four health centres in Tanzania, January 2009 – June 2011

Characteristics	Number on CPT (194)	Person years at risk	Person years interrupted	Proportion of time interrupted
Sex				
Males	66 (36%)	79.7	13.4	0.17 (0.16 – 0.17)
Females	117 (64%)	155.8	34.2	0.22 (0.22 - 0.22)
Missing	*11*			
Age, median (IQR)	36 (27-42)			
0 – <15yrs	17 (9%)	22.2	3.6	0.16 (0.16 – 0.17)
15 - <30yrs	40 (21%)	47.2	13.8	0.29 (0.28 – 0.30)
30 - <45yrs	96 (51%)	123.3	27.1	0.22 (0.21 – 0.22)
≥45yrs	36 (19%)	51.1	5.3	0.10 (0.10 – 0.11)
Missing	*5*			
Clinic				
MoH Hospital	104 (54%)	140.3	16.4	0.12 (0.11 – 0.12)
Rural dispensary	12 (6%)	13.5	3.4	0.25 (0.24 – 0.26)
Faith-based Hospital	53 (27%)	66.7	27	0.40 (0.39 – 0.41)
Rural clinic	25 (13%)	30.2	4.4	0.15 (0.14 – 0.15)
WHO stage				
I	43 (22%)	47.5	13.7	0.29 (0.28 - 0.30)
II	78 (40%)	109.7	19.2	0.17 (0.17 - 0.18)
III	60 (31%)	87.6	17.2	0.20 (0.19 - 0.20)
IV	12 (6%)	5.9	1.1	0.18 (0.17 - 0.20)
Missing	*1*			

Table 4.10 Factors associated with time interrupting CPT, in four health centres in Tanzania, January 2009 – June 2011

Characteristics	Incidence rate ratio (95% CI)	p-value	Adjusted incidence rate ratio (95% CI)*	p-value
Sex		p<0.01		p<0.01
Males	1		1	
Females	1.31 (1.27 – 1.35)		0.89 (0.85 – 0.92)	
Age		p<0.01		p<0.01
0 – <15yrs	1		1	
15 - <30yrs	1.80 (1.69 – 1.91)		1.40 (1.31 – 1.49)	
30 - <45yrs	1.35 (1.28 – 1.43)		1.50 (1.41 – 1.59)	
≥45yrs	0.64 (0.60 – 0.69)		0.79 (0.73 – 0.85)	
Clinic		p<0.01		p<0.01
MoH Hospital	1		1	
Rural dispensary	2.14 (2.01 – 2.27)		2.91 (2.73 – 3.10)	
Faith-based Hospital	3.46 (3.35 – 3.57)		3.11 (3.00 – 3.23)	
Rural clinic	1.25 (1.18 – 1.32)		1.08 (1.02 – 1.14)	
WHO stage		p<0.01		p<0.01
I	1		1	
II	0.60 (0.58 – 0.63)		0.69 (0.66 – 0.71)	
III	0.68 (0.65 – 0.70)		0.58 (0.56 – 0.61)	
IV	0.63 (0.57 – 0.70)		0.43 (0.39 – 0.48)	

*note: model is adjusted for all variables in the table.

After adjustments for all other variables, the effects of age, clinic and WHO stage remained virtually unchanged. However, the IRR for females compared to males changed direction, with the proportion of time interrupting CPT among females becoming lower (aIRR 0.89, 0.85 – 0.92). This change in direction is likely due to the younger age of the females compared to the males (32 vs 40 years) and a strong interaction between age and sex ($p<0.01$). Interruptions among males and females were similar in all age groups but were much higher for females (0.30, 0.29 – 0.31) compared to males (0.00, 0.00 – 0.00) in the 15-30 year age category.

There was evidence of further interactions between WHO stage and sex ($p<0.01$), clinic and sex ($p<0.01$), age and WHO stage ($p<0.01$), clinic and WHO stage ($p<0.01$) and age and clinic ($p<0.01$) (Table 4.11). Among individuals in WHO stage IV, the proportion of time interrupting CPT among males was much lower than among females, but was more similar for all other WHO stages. Among individuals in the rural dispensary, the proportion of time interrupting CPT was lower among males than among females. Among patients in WHO stage III/IV, the proportion of time interrupting CPT was much lower among those aged 0 – 15 years, 15 - < 30 years and ≥ 45 years compared to those aged 30 - <45. Among patients in all clinics, the proportion of time interrupting CPT was higher among patients in WHO stage I, II or III compared to patients in stage IV, though only slightly higher for those in WHO stage II in the rural clinic. Among patients in the faith-based hospital, the proportion of time interrupting CPT was far higher among patients aged 15 - < 30 years than among patients in the other age categories.

No data were reported in monitoring and evaluation reports, either in Uganda or Tanzania, on the proportion of patients initiated on CPT who remain on CPT over

Table 4.11 The proportion of time interrupting CPT (Incidence rates, CI) for variables with significant interactions in four clinics in Tanzania

	Incidence rates (CI)									
	Sex		WHO stage				Clinic			
Age Group	Males	Females	Stage I	Stage II	Stage III	Stage IV	MoH hospital	Rural dispensary	Faith-based hospital	Rural clinic
0 – 15yrs	0.16 (0.15 - 0.17)	0.16 (0.15 - 0.18)	0.27 (0.25 - 0.29)	0.13 (0.12 - 0.14)	0.09 (0.07 - 0.10)	0.00 (0.00 - 0.00)	0.13 (0.12 - 0.14)	0.25 (0.22 - 0.29)	0.29 (0.26 - 0.31)	0.00 (0.00 - 0.02)
15 - <30yrs	0.00 (0.00 - 0.00)	0.30 (0.29 - 0.31)	0.46 (0.44 - 0.48)	0.12 (0.12 - 0.13)	0.28 (0.26 - 0.30)	0.00 (0.00 - 0.00)	0.06 (0.05 - 0.07)	0.03 (0.00 - 0.08)	0.57 (0.55 - 0.59)	0.04 (0.03 - 0.05)
30- <45yrs	0.22 (0.21 - 0.22)	0.22 (0.21 - 0.22)	0.20 (0.19 - 0.21)	0.22 (0.22 - 0.23)	0.22 (0.21 - 0.22)	0.26 (0.23 - 0.28)	0.17 (0.16 - 0.17)	0.44 (0.41 - 0.47)	0.31 (0.30 - 0.32)	0.17 (0.16 - 0.18)
≥45yrs	0.11 (0.10 - 0.12)	0.10 (0.09 - 0.10)	0.19 (0.17 - 0.20)	0.10 (0.09 - 0.11)	0.10 (0.09 - 0.11)	0.00 (0.00 - 0.00)	0.06 (0.06 - 0.07)	0.05 (0.03 - 0.06)	0.32 (0.30 - 0.34)	0.14 (0.12 - 0.16)
WHO stage										
Stage I	0.19 (0.18 - 0.20)	0.34 (0.33 - 0.35)	-	-	-		-	-	-	-
Stage II	0.13 (0.12 - 0.13)	0.17 (0.17 - 0.18)	-	-	-		-	-	-	-
Stage III	0.19 (0.18 - 0.20)	0.20 (0.19 - 0.20)	-	-	-		-	-	-	-
Stage IV	0.00 (0.00 - 0.00)	0.28 (0.25 - 0.30)								
Clinic										
MoH hospital	0.15 (0.14 - 0.15)	0.10 (0.10 -0.10)	0.13 (0.12 - 0.14)	0.11 (0.11 - 0.12)	0.13 (0.12 - 0.13)	0.00 (0.00 - 0.00)	-	-	-	-

	Incidence rates (CI)									
	Sex			WHO stage					Clinic	
Rural dispensary	0.17 (0.15 - 0.19)	0.37 (0.35 - 0.40)	0.00 (0.00 - 0.00)	0.35 (0.32 - 0.38)	0.26 (0.24 - 0.28)	0.00 (0.00 - 0.00)	-	-	-	-
Faith-based hospital	0.29 (0.27 - 0.30)	0.42 (0.41 - 0.43)	0.65 (0.63 - 0.68)	0.23 (0.22 - 0.25)	0.35 (0.34 - 0.36)	0.00 (0.00 - 0.00)	-	-	-	-
Rural clinic	0.08 (0.07 - 0.09)	0.18 (0.17 - 0.19)	0.15 (0.13 - 0.16)	0.26 (0.24 - 0.28)	0.04 (0.03 - 0.04)	0.00 (0.00 - 0.00)	-	-	-	-

time, or on CPT interruptions among those on CPT. It was therefore not possible to compare the clinic derived data on use of CPT while in care with reported data.

4.2.1 Barriers to adequate CPT use while in care

Data from the Ugandan monthly monitoring reports on CTX stock-outs reported 17 episodes of stock-outs during the 29 month period from January 2009 to the end of May 2011. For 14 months (48%) at least one clinic was without any supply of CTX. For 3 (10%) months during the period, both clinics providing CTX stock-out monitoring data had periods without any CTX. Stock-outs of CTX increased over the observed period in the following ways:

- Frequency: in 2009, stock-outs occurred during 4 months (33%) of the year, 6 months (50%) of 2010, and during 4 (80%) of the first 5 months of 2011,
- Number of clinics affected: in 2009, stock-outs affected one facility in any one month, while in January 2010 stock-outs affected both clinics and in March and April 2011 stock-outs affected both health centres, and
- Duration: 2 (50%) stock-outs in 2009 lasted more than 1 week, while 6 (100%) lasted for more than 1 week in 2011 (of which one clinic had stock-outs of CTX in all of the first four months of the year).

No information on CTX stock-outs was available from monitoring and evaluation reports in Tanzania.

From the patient data, among the 2499 appointments attended by those on CPT in Uganda, information on CPT stock-outs was completed at 104 (4%) appointments. Of these appointments, 17 (16%) had no CPT in stock. The number of patients who, on average, were prescribed a shortfall of tablets at appointments was 36 (27%), with a median of 1.3-day tablet surplus (IQR 0.1-day shortfall – 4-day surplus) prescribed per appointment. During the months in which the monitoring

reports cited stock-outs of CTX, the following proportion of patients were prescribed a shortfall of tablets: January, June, October and December 2009 (4%, 10%, 26% and 35%); January, March, June, September, October, December 2010 (18%, 39%, 37%, 0%, 24% and 35%); and January, February, March, April 2011 (15%, 14%, 25% and 40%). The proportion prescribed a shortfall during months with cited stock-outs was higher than the 27% who on average were prescribed a shortfall in only 5 of the 14 months. The number of patients who, on average, attended appointments late was 75 (56%), with a median of 1 (IQR 1 – 7) days late per appointment.

Information on CPT stock-outs was not completed at any appointment in Tanzania. The number of pills or number of days, weeks or months-worth prescribed was never recorded, making it impossible to calculate whether patients were prescribed a shortfall of pills until their next scheduled appointment. Of the 192 patients on CPT, the number of patients who, on average, attended appointments late was 107(64%), with a median of 1.7 days late (IQR 1 day early – 9.1 days late) per appointment.

4.3 Discussion

This study provides valuable insight into the rate of CPT initiation among newly diagnosed patients in two LMIC in sub-Saharan Africa, yet has highlighted the difficulties in assessing this rate in routine practice. Few studies have reported such information previously, and those that did focused on HIV-exposed infants and HIV-TB co-infected patients. Only three previously reported studies have reported CPT coverage data on HIV-infected adults and only one has reported such data among HIV-infected children. This study adds to the body of knowledge by estimating CPT

coverage in Uganda and Tanzania. Moreover, this study provides important information, not previously described elsewhere, on the amount of time in care spent on CPT in eight clinics in these two countries.

Overall, the cumulative probability of initiating CPT within 1 month of diagnosis was similar in Uganda (45%) and Tanzania (59%). The slightly higher likelihood of CPT initiation in Tanzania might be explained by the inclusion in Uganda of a large health centre specialising in paediatric care. In Uganda, patients 3 years or older were more likely (RR 1.35) to initiate CPT compared to children less than 3 years of age and increased CPT initiation in Tanzania may be due to the population being older. Furthermore, Tanzanian patients had more advanced disease at enrolment into care than Ugandan patients (12% of Ugandans were WHO stage III/IV compared to 37% of Tanzanians). Sicker patients may be more motivated to enrol for care than less sick patients and this may partly explain the increased proportion initiating in Tanzania compared to Uganda, however information on staging or CD4 count was not available at diagnosis and was not possible to examine this effect. The differences in proportions initiating CPT in the rural clinics compared to large hospitals in both countries (lower rate in Uganda and higher rate in Tanzania) suggests that initiation practices in smaller clinics may be dependent on other unmeasured confounders rather than simply the type or size of clinic.

The cumulative probabilities of initiating CPT in Uganda and Tanzania fall within the wide range of proportions (36% - 97%) reported in the literature for adults, mothers in antenatal care, children and infants [211-214]. The higher proportions of patients initiating CPT reported in some of these studies are likely explained by the different settings in which the studies were conducted: mobile health centres

which visited the community rather than in fixed health centres which require the patient to travel; and antenatal care clinics requiring no additional enrolment to initiate CPT. The lowest proportion reported previously (36%) among infants, is in concordance with my findings that the rate of initiation among very young children is lower than among older patients. Furthermore, my results of the cumulative probabilities of enrolling into care to initiate CPT are similar to the 52% of patients who returned for disease staging after diagnosis, summarised in a literature review [238].

Overall, the proportions of time interrupting CPT were similar in Uganda (0.17/person year) and Tanzania (0.20/person year). The lower proportion of time interrupting CPT among females, increased proportion among patients in clinics other than the main MoH hospital (with the exception of the large NGO-supported paediatric hospital) and increased proportions among older patients compared to those < 15 years are also consistent between both countries. While few previously published data are available on the proportion of time with CPT interruptions while in care, evidence from the DART trial in adults and recent evidence from the ARROW trial in children suggests that, even among patients who are stable on ART, stopping CPT increases rates of hospitalisation or death [239] [240]. This highlights the importance of encouraging continuous access to CPT, particularly among males, in smaller/rural clinics and among older patients.

This study, however, has several limitations. Firstly, this study relied upon matching records of patients between two registers: HIV diagnosis/exposure and pre-ART care, as no unique patient identifier exists to link the two registers. My results are, therefore, based on estimates, using perfect and imperfect matching, and should be

interpreted with caution. This highlights the difficulty clinic staff and researchers have in assessing the proportion of diagnosed/exposed patients initiating CPT. For example, while in Uganda, whether estimating the proportion accessing CPT in the three months after diagnosis using this study's methods (45%) or by dividing the number of people who start CPT during the 3 month period with the number HIV-diagnosed/-exposed during the same 3 month period (47%) from the monitoring report data, provided very similar proportions. However, the use of the monitoring report data in this way is confusing. The temptation is to use the two numbers to calculate a proportion started on CPT. However, individual patients starting CPT are not necessarily those diagnosed during the same calendar period. For example, in one of the Ugandan health centres, more patients started CPT (101) during the same quarter than were diagnosed with HIV (64), suggesting the inclusion of patients initiating CPT who were diagnosed in a different period or who transferred-in. In the absence of a unique identification number that the patient carries with them from diagnosis/birth to enrolment, tracking patients who enrol to initiate CPT will remain challenging. Therefore, published estimates of the proportions of diagnosed patients initiating CPT should be interpreted in the context of a thorough understanding of how patients were matched and the calculations derived.

Secondly, this study relied upon data routinely collected in busy diagnostic clinics and busy pre-ART and ART clinics. There were many missing data, particularly relating to clinical stage at diagnosis, dates of CPT initiation within the enrolment register, WHO stage at enrolment, dates of scheduled and actual appointments, and number of days/week/months-worth of tablets or syrup prescribed. This study demonstrated that a high proportion of patients enrolling for care were WHO stage I/II. This is likely, to be an underestimate of WHO stage at diagnosis as it is

possible that sicker patients died before enrolling into care. It was not possible to calculate the information on shortfall tablet supply for one-quarter of all patients in care in Uganda, or for any patients in Tanzania. When this information was not available but CTX was reported to have been prescribed, I assumed that an equal number of tablets were prescribed for the time interval until the next appointment. This is a generous assumption and it is likely that the rates of interruptions I report may be an underestimate. Moreover, no relevant CPT data were available from the Tanzanian monitoring reports. Yet, the MoHs use routinely collected data as the basis for programme funding decisions and for, in particular, drug supplies. This study has, therefore, highlighted important gaps in data collection relating to CPT.

Despite these limitations, this study has shown that the cumulative probability of initiating CPT remains strikingly low, particularly among very young children. This study has also highlighted high proportions of time interrupting CPT while in care and that stock-outs of CTX continue to be a challenge. Encouraging on-time appointment adherence may improve the proportion of time in care with adequate drug supply. However, more complete data are needed on the number of days-worth of tablets prescribed, and the number of times when CPT is dispensed in pharmacy with a shortfall in order to assess whether the problem is due to inadequate drug supply or poor on-time appointment attendance. The proportion of patients prescribed a shortfall of tablets during the months in which monitoring reports cited stock-outs did not appear higher than the median proportion of patients prescribed shortfalls on average. Moreover, it is likely that this study actually underestimates the proportion of time interrupting CPT. I estimated CPT interruptions which occurred before the expiry date of the last prescription, yet some patients remained in care for many more appointments after the last known

CPT prescription date. This study therefore assumes that there were no further prescriptions of CPT, however, the appointments without CPT may represent further interruptions due to stock-outs rather than early stopping of CPT. Moreover, in countries with universal access to CPT policies, CPT should be provided for all diagnosed patients. Yet, in Uganda and Tanzania, the majority of patients took up to 4 weeks to enrol for care, meaning that patients were missing drugs during that time. Providing, for example, a one-month supply of CTX on day of diagnosis would allow patients who take up to 4 weeks to enrol into care the opportunity to have some CPT to cover the time between diagnosis and enrolment. Further work is needed to assess whether the probability of enrolment into care can be improved if CPT were provided at diagnosis. Initiating CPT at diagnosis might highlight the importance of immediate and continuous care to all patients diagnosed with HIV, which might encourage a greater proportion to return and enrol in care.

Based on this work, it is recommended that monitoring reports be revised to reflect the importance of CPT. Cohort reporting, similar to that used for patients on ART, may be a powerful, albeit labour-intensive, mechanism with which to do this. In the same way as is in place for ART patients, data from routine patient appointments on CPT use could be entered into the pre-ART register at every appointment to be used to compile data for monitoring reports. For example, pre-ART cohorts could be formed and indicators compiled on the proportion of patients initiated on CPT still in care and on CPT at 6, 12, 24 etc. months. This will be useful to track retention in care among pre-ART patients. A further indicator reporting the proportion of patients with good CPT adherence, with evidence needed to identify what level that should be set at, could also be gathered. If such mechanisms are to be employed,

it is recommended that resources be put in place to minimise the additional burden on clinic staff while enabling accurate data capture.

As more patients are initiated on CPT, particularly with universal access policies, and remain on CPT for their duration of time in care, ensuring continued access to CTX drugs becomes ever more important. For pre-ART patients, CPT is one of the few interventions available as part of the care package. As the greatest benefit of CPT might be among pre-ART patients, it is vital that better monitoring tools are developed to assess their ongoing access to CPT.

Chapter 5 Mental health

This chapter describes the background, aim, methods and results of a cross-sectional study I undertook among HIV-infected patients accessing care in Uganda. The aim was to estimate the prevalence of common mental disorders (CMD), identify at-risk patients and examine the validity of three concise tools that can be used by HIV health-care workers to screen for mental health disorders.

5.1 Background

Mental disorders reflect anomalies which fit a clinically-recognisable set of symptoms or behaviour relating to how a person feels, thinks, acts or perceives things. An important feature of a mental disorder is the association of these symptoms or behaviour with distress or interference with personal function [241]. Globally, mental disorders are common within the general population: each year one in twenty people will report a depressive episode (the most common mental disorder) with lifetime prevalence considered to be 7%; and depression is the leading cause of years lost due to any disability [242] [243]. Depression often presents with symptoms of generalised anxiety leading to substantial impairment to an individual's every-day responsibilities and, at its worst, leads to suicide [242].

Among HIV-infected populations in LMIC, commonly-observed mental disorders include major depressive disorder (MDD), generalised anxiety disorder (GAD), post-traumatic stress disorder (PTSD), suicidality and alcohol use disorders (AUD) [244]. According to a recent systematic review of mental illness among HIV-infected

patients in LMIC, prevalence of MDD has been reported to range between 0 – 63%, and in Uganda one study reported prevalence to be as high as 82% [244] [245]. Among HIV-infected patients, the consequences of mental disorders can be significant and have been reported to include: increased need and use of health services (OR 1.43, 1.06 – 1.92), poor access to treatment (OR 2.27, 1.30 – 3.98 among patients with alcohol abuse history), poor adherence to treatment regimens (OR 1.05, 1.00 – 1.10 in one study and OR between 1.87 – 5.86 in a systematic review), greater CD4 cell count slope decline (-0.35 vs 0.13, $p<0.01$), more AIDS-defining events (HR 1.97, P=0.04), faster disease progression (OR 4.77, 2.17 – 10.47) and faster mortality (RR 2.0, 1.0 – 3.8) [42-47, 51-53, 246].

Identifying common mental disorders among HIV-infected patients is, therefore, important. The most widely recognised criteria to classify mental disorders are set out in the Diagnostic Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association) and in the International Classification of Disease (ICD10) (WHO) [247] [248]. These criteria have been incorporated into clinical interviews including the Mini International Neuropsychiatric Interview (M.I.N.I.), the Structured Clinical Interview for Diagnosis (SCID), the Clinical Interview Schedule-Revised (CIS-R), and the Composite International Diagnostic Interview (CIDI) [249] [250-252]. Clinical interviews are recognised as a gold standard diagnostic measure of mental illness [253]. However, due to the time required to carry-out structured interviews, they do not lend themselves to rapid administration in a clinical setting or to assessments of large populations. Shorter questionnaires, which are devised to screen patients for symptoms which suggest a disorder, are therefore commonly used in epidemiological studies. Among the 32 studies included in two systematic reviews examining the prevalence and consequences of common mental disorders

among HIV-positive individuals in LMIC, 6 used a clinical diagnostic interview (M.I.N.I., SCID, CISR or the CIDI) and 28 used one of 16 short questionnaires, known as screening tools, or a study-specific questionnaire [244] [246]. As each tool is slightly different, it is possible that they measure slightly different aspects of mental disorders (e.g. feeling sad, feeling blue, feeling tired, lack of appetite) and this may, in part, explain the range of prevalence estimates for MDD reported in the studies [244]. The number of tools in use highlights the lack of knowledge about how best to measure mental disorders. Moreover, the validity of many screening tools against gold standard diagnostic interviews has been questioned making it difficult to have a true understanding of the extent of the burden of mental health disorders among HIV-infected populations [254].

In 2008 the WHO acknowledged that little information about the interaction between HIV, AIDS and mental health, particularly regarding alcohol consumption was available from LMIC [255]. Globally, there had been minimal emphasis on mental health interventions within ART programmes and it was estimated that only 50% of countries in the African region had any form of mental health policy in place [53] [256]. At that time, Uganda was one country with a policy stating that mental health services should be linked to HIV services [257]. Nevertheless, treatment of severe mental health disorders was only available at ten regional hospitals or at the National Mental Referral Hospital. Furthermore, there were only 1.6 psychiatrists (compared to 10 in Europe), 2 psychologists (3 in Europe), 2 psychiatric nurses (25 in Europe) and 2 social workers per 100,000 population [256].

Recognising that that there can be 'no health without mental health', the WHO identified as a priority the assessment of mental disorders and their appropriate

management within HIV care programmes [258] [259]. They recommend that primary health-care providers, including HIV counsellors, should be trained to recognise common mental disorders and substance-use disorders [255].

It is vital to identify tools which accurately reflect the current version of DSM criteria (DSM IV) and ICD 10 criteria and can be used by non-specialist health care workers to screen patients accurately for mental disorders. This will enable scarce resources being invested into mental health services to be well-targeted. Therefore, firstly, I conducted a review of the literature and synthesised the evidence from studies reporting prevalence of mental illness in HIV-infected individuals in LMIC and examining the validity of screening tools used to assess this. Secondly, I undertook a cross-sectional study to estimate the prevalence and risk factors for common mental disorders among HIV-infected patients in Uganda using a structured clinical psychiatric interview. Finally, I aimed to validate three short measurement tools against these diagnoses.

Within this chapter I refer in detail to the following mental health disorders and assessment tools using the given acronyms:

Major Depressive Disorder (MDD)

Generalised Anxiety Disorder (GAD)

Post-Traumatic Stress Disorder (PTSD)

Suicidality (includes suicidal ideation, self-harm and attempted suicide)

Alcohol Use Disorders (AUD), composite of Alcohol Abuse or Alcohol Dependence

Common Mental Disorders (CMD), composite of MDD, GAD or PTSD

Global Psychological Distress (GPD), composite of MDD or suicidality

Centre for Epidemiological Studies Depression Scale (CESD)

Kessler's Psychological Distress Scale (K10 is 10-item version, K6 is 6-item version)
Alcohol Use Disorders Identification Test (AUDIT)

5.2 Review

The aim of the review was to evaluate the burden of, and risk factors for, mental ill-health among people living with HIV in LMIC, and to identify evidence-based screening tools, as assessed in formal validation studies comparing the discriminative performance of screening tools relative to a reference gold standard measure. The first objective was to synthesise prevalence estimates of mental disorders (MDD, PTSD, GAD, AUD) as assessed using clinical diagnostic interviews and to identify reported risk factors. The second objective was to synthesise the evidence for the validity of screening tools.

5.2.1 Review methods

My search strategy involved two stages. Firstly, I used broad search criteria to identify English language studies, published since the advent of ART in 1996, which validated assessment tools for mental health disorders among HIV-infected persons in LMIC. I searched Medline through PubMed. The search was last updated on 21-06-2013. I used the following search terms resulting in the number of references noted to capture mental illness, HIV, LMIC and screening tool validation:

i) mental illness: mental or psychological or psychiatric or alcohol or mental disorders or psychological disorders or psychiatric disorders (1,044,847 references)
ii) combined with terms related to HIV or AIDS: HIV or AIDS or HIV/AIDS (26,077 references)

iii) combined with LMIC regional names: developing countries, low-income countries, Africa, Asia, Europe Eastern or Latin America (4,385 references)

iv) combined with terms relating to validity: validity or validation (92 references)

Having read the 92 titles and abstracts, I selected papers that met the following criteria:

d. participants were HIV-infected
e. studies focused on validation of screening tools relative to a gold standard
f. measurement was of common mental disorders

5.2.2 Reviewed studies

Eight studies met the above inclusion criteria and examined the following mental illnesses: MDD or GAD (8 studies), PTSD (2 studies), AUD (2 studies) (Table 5.1) [243, 260-266]. Seven studies used clinical diagnostic interviews as the gold standard reference measure, 5 using the M.I.N.I., 1 the CIDI and 1 used the SCID. The eighth study used the long version of the self-administered Patient Health Questionnaire (PHQ-9) as the gold standard measure. The following screening tools were validated by the given number of studies: CES-D (3 studies), K10 (2 studies), K6 (1 study), AUDIT (2 studies), PHQ-9 (2 studies; PHQ-short 2 studies), Harvard Trauma Questionnaire (HTQ, 1 study), Edinburgh Post-Natal Depression Survey (EPDS, 1 study), Hopkins Symptoms Check List (HSCL, 1 study). I extracted information on sample size, gold standard prevalence of common mental disorders, the area under the receiver operating characteristic curves (AUROC) for screening tools, optimal cut-off points and sensitivity, specificity, positive and negative

Table 5.1 Prevalence of mental disorders and validity of screening tools

Authors	Country	Study population	Gold standard	Disorder prevalence	Screening tool	AUROC (CI)	Optimal cut-off	Sensitivity	Specificity	PPV	NPV
Akena *et al.*	Uganda [243]	n=368 HIV positive patients from Kampala Hospital Home Care Department	MINI	MDD 17%	CESD	0.94 (0.89 - 0.99)	18	88%	81%	49%	97%
					K10	0.82 (0.72 - 0.93)	23	83%	72%	38%	95%
					K6	0.82 (0.71 - 0.93)	13	77%	67%	33%	93%
					PHQ-9	0.96 (0.92 - 0.99)	10	92%	81%	37%	98%
					PHQ-short	0.82 (0.71 - 0.93)	3	83%	70%	37%	95%
Spies *et al.*	South Africa [260]	n=429 adults enrolled into HIV care	MINI	MDD 13%	K10	0.77 *	28	67%	77%	29%	94%
				GAD 4%		0.78	30	72%	80%	14%	99%
				PTSD 5%		0.77	29	75%	78%	15%	99%
Chishinga *et al.*	Zambia [261]	n=649 new TB treatment or ART initiators, 16 primary care clinics	MINI	MDD 10%	CESD	0.78 (0.72 - 0.84)	22	73%	-	76%	-
						0.98 (0.94 - 1.00)F	24	60%		60%	
				AUD 15%	AUDIT	0.75 (0.66 - 0.84)M	20	55%	-	50%	-
Myer *et al.*	South Africa [262]	n=465 HIV outpatients	MINI	MDD 14%	CESD	0.76 *	-	79%	61%	24%	95%
				AUD 7%	AUDIT	0.96	-	100%	79%	28%	-
				PTSD 5%	HTQ	0.74	75	38%	80%	9%	96%
Pence *et al.*	Cameroon [263]	n=398 ART patients attending	CIDI	MDD 3%	PHQ-9 adapted	-	8	36%	89%	9%	95%

		regional treatment centre									
						-	10	27%	94%	12%	98%
						-	12	18%	97%	14%	98%
Monahan *et al.*	Kenya [264]	n=347 HIV patients attending psychosocial support groups	PHQ9	MDD 13%	PHQ2	0.91 (0.88 - 0.95)	3	91%	77%	37%	98%
				Any Dep 34%	PHQ2	0.97 (0.95 - 0.98)	3	85%	95%	90%	92%
Chibanda *et al*.	Zimbabwe [265]	n=210 postpartum women (HIV positive and HIV negative) attending post-natal check-up	MINI	MDD 33%	EPDS	0.82 *	11	88%	87%	74%	94%
Kaaya *et al*.	Tanzania [266]	n=100 randomly selected women from n=903 HIV positive pregnant women	SCID	MDD 8% GAD & MDD 3% GAD 1%	HSCL 25	0.86 (0.72 - 0.99)	1.06	89%	80%	28%	99%
					HSCL 15 - depression	0.86 (0.73 - 0.99)	1.03	89%	79%	27%	99%
					HSCL-revised	0.88 (0.75 - 1.0)	1.06	89%	85%	33%	91%

*confidence intervals not given

predictive values (ppv, npv). Where ppv or npv were not provided, I calculated these based on available prevalence, sensitivity and specificity information.

5.2.3 Study populations

The studies were conducted in Cameroon, Kenya, South Africa, Tanzania, Uganda, Zambia and Zimbabwe. All studies were conducted among outpatients. Participants were drawn from HIV treatment clinics (4 studies), TB and ART treatment clinics (1 study), a regional HIV treatment centre for pregnant women (1 study), and a post-natal clinic for HIV-infected and un-infected women (1 study). The remaining study population was derived from patients attending a psychosocial support group.

The smallest study validated tools in 100 women and the largest study in 649 patients newly-initiating ART or TB and ART treatment.

5.2.4 Prevalence of mental illness

All 8 studies assessed the prevalence of MDD. Between 3 – 33% of study participants were classified as having MDD. Six of the 8 studies estimated prevalence around a narrow range between 8 – 17%. One of these studies reported prevalence at 53% however, the data appear to have been presented incorrectly and prevalence actually appears to be 13.5% [260]. The remaining two of the 8 studies estimated prevalence of MDD at 3% and 33%. The study estimating prevalence at 3% was conducted only among patients on ART, who have been shown to have lower levels of depression than HIV-infected individuals not on ART [262, 263]. The study estimating the highest prevalence at 33% was conducted among HIV-infected women attending post-natal check-ups, who may be at increased risk of depression regardless of HIV status [265].

GAD was assessed by the M.I.N.I. in only one study, which estimated prevalence at

4% (though data were incorrectly presented at 18%) [260]. One study assessed GAD using the SCID and estimated prevalence at 1% and comorbid GAD and MDD at 3% [266]. PTSD was assessed by the M.I.N.I. in two studies. Both studies estimated prevalence at 5% (though data in the first study were incorrectly presented at 22%) [260, 262]. AUD were assessed by the M.I.N.I. in two studies: one, whose population was 75% female, found prevalence of 7%, while the other, whose population was 56% male, found prevalence at 15% [261, 262].

Of the studies using the M.I.N.I. as a gold standard measure, only 1 reported on risk factors for mental illness. In South Africa, speaking Afrikaans compared to Xhosa was associated with an increased risk of MDD, PTSD and AUD (Odds Ratios not given). Younger individuals were somewhat protected from MDD (OR 0.96), individuals with a higher household income were protected from PTSD (OR 0.12) and females had reduced risk of alcohol use disorders (OR 0.19) [262].

5.2.5 Validity of screening tools

All 8 studies validated screening tools for the detection of MDD. The discriminatory ability to identify true and false positives out of the actual positives and negatives (as assessed by examining the AUROC curves) of the screening tools for the detection of MDD was moderate, ranging as follows: CES-D (0.76 – 0.94), K10 (0.77, 0.82), PHQ-9 (0.96), PHQ-3 (0.82 – 0.91), HSCL (0.86), EPDS (0.82). The best and worst discriminatory ability were offered, respectively, by the PHQ-9 and CES-D, though only one study reported AUROC for the PHQ9. Where more than one study validated a screening tool, there was no consensus on optimal cut-off points to be used to identify probable cases: CES-D (18, 22), K10 (23, 28), PHQ-9 (8, 10, 12), with the exception of the PHQ-3 (where a value of 3 was identified by

two studies). Furthermore, there was large variation in the sensitivity and specificity and the positive and negative predictive values at the identified cut-off scores and one of the four measures (usually ppv) was always compromised. For example, the three studies validating the CESD found the following: in one study, sensitivity and specificity were 79% and 61% with ppv 24% and npv 95% respectively; and another study, sensitivity and specificity were 88% and 81% with ppv 49% and npv 97%; and in the third study sensitivity was 73% and ppv 76% (specificity and npv not provided).

Two studies validated screening tools (K10 and HTQ) against M.I.N.I. diagnoses of PTSD [260, 262]. The AUROCs were similar at 0.74 (K10) and 0.77 (HTQ). Sensitivity and specificity were 75% and 78% with a positive and negative predictive value of 15% and 99%, respectively for the K10. The HTQ demonstrated sensitivity and specificity of 38% and 80% (HTQ), with positive and negative predictive values of 9% and 96%.

The discriminatory ability of the AUDIT to detect AUD was examined in two studies and varied between the studies. One study reported AUROCs for males of 0.75 and for females of 0.98, and the second study reported an aggregated AUROC of 0.96 [261, 262]. In one study, sensitivity and specificity were 60% and 60% (females) and 55% and 50% (males), using a cut-off score of 24 (females) and 20 (males). In the second study, which did not present the cut-off score used, sensitivity and specificity were 100% and 79% with a positive predictive value of 28%. One study validated the discriminatory ability of a short version of the PHQ against a long version of the PHQ to detect AUD, which had been estimated by the PHQ at 34%. The study found an AUROC of 0.97, with sensitivity, specificity and ppv of 80%,

95% and 90% [264].

5.2.6 Review discussion

The literature available to evaluate these screening tools was limited. Furthermore, there was heterogeneity of study populations including TB-HIV co-infected patients, new ART initiators, ART-naïve patients, pregnant women, postnatal women, HIV outpatients, home-care patients, patients attending psychosocial support groups, and a mixture of studies conducted in urban and rural populations. There was in addition, ranging prevalence estimates of all disorders, particularly MDD, reflecting the different populations and differences in the application of gold standard diagnostic criteria.

Despite these limitations, the studies provide valuable information about the prevalence of mental illness, notably MDD, when assessed using clinical diagnostic interviews and about the validity of a variety of screening tools used to measure mental disorders in LMIC. If only studies using strict M.I.N.I. criteria are considered, the range of prevalence estimates of MDD as assessed by clinical interview was narrower (8% - 17%) than estimates using screening tools seen in systematic reviews (0 - 63%). This suggests a tendency of screening tools to over-estimate the prevalence of disorders. These validation studies do not provide enough details to comment on common risk factors for mental illness and more work is needed to enable the identification of at-risk patients using data routinely available within HIV care settings.

The 8 reviewed studies provide some important insight into the validity of screening tools. It is generally accepted that studies with AUROC between 0.50 – 0.70, 0.70 – 0.90, and 0.90 – 1.00 are considered to have low, moderate and high accuracy,

respectively [267]. None of the screening tools validated reported AUROC below 0.70. Five out of seven studies reported moderate accuracy and two reported high accuracy for the detection of MDD. The ppv was often sacrificed at the given cut-offs in order to obtain high sensitivity and specificity scores in the majority of studies. In settings with limited resources, incorrectly identifying patients with a disorder and referring them for future treatment is costly and an expensive sacrifice of a screening tool. Moreover, only a limited number of studies examined each screening tool and these results should, therefore, be interpreted with caution. Given the number of screening tools being used to measure and report on the mental health of HIV-infected patients in LMIC, the lack of studies contributing to this review demonstrates the need for methodologically-sound validation studies.

Therefore, I designed and conducted a cross-sectional study to estimate the prevalence and risk factors for common mental disorders among HIV-infected patients in Uganda using a clinical diagnostic interview and I aimed to validate three short screening tools against these diagnoses.

5.3 Aims, objectives and outline

The aim of this study was to estimate the prevalence of common mental disorders among HIV care outpatients in Uganda, using a structured clinical interview and to examine whether data collected routinely in HIV care outpatient appointments could identify at-risk patients. The study also aimed to validate the CES-D, K10, K6 and AUDIT, which could be used by non-specialists health care workers to screen patients in HIV-care for common mental disorders and global psychological distress. The objectives were to:

• estimate the prevalence of mental disorders among patients accessing HIV care,

• compare case classifications manually-derived by interviewers during the structured clinical interview with electronically-derived classifications,

• examine whether data collected routinely in HIV care could identify patients who are at risk of having a common mental disorder, and

• validate the following three screening tools in this setting:

- the Centre for Epidemiological Studies Depression Scale (CES-D) (20-question version),
- Kessler's Psychological Distress Scale (10-question version and the truncated 6-question version (K10, K6)), and
- the Alcohol Use Disorders Identification Test (AUDIT)

against diagnoses of major depression (the primary target disorder of the screening tools) and against broadly defined common mental disorders (CMD), global psychological distress (GPD), and alcohol use disorders (AUD), using the Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus) [268-270].

This cross-sectional study was conducted in the HIV-outpatient clinics of Entebbe District Hospital and the neighbouring Kigungu Health Centre III, Uganda. Study participants were assessed for mental disorders by trained psychiatric nurses using the latest version of the Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus), and demographic and clinical data commonly collected in HIV-care were gathered through a study-specific questionnaire. Participants were invited to a second interview with HIV health care workers to obtain a mental health assessment using the screening tools.

An important objective of this study is to provide a summary to national government

representatives and international researchers of the burden of and risk factors for mental disorders among patients accessing HIV care in Uganda. This will help determine whether the routine monitoring of the mental health status of patients living with HIV attending peri-urban health centres in Uganda is recommended and whether any data routinely-collected can be used to identify patients who would benefit from further assessments and care. The results of the screening tools' validation will inform the design of methods used to measure mental ill-health in HIV-care clinics in Uganda.

5.4 Methods

5.4.1 Setting, sampling frame and study population

The study was designed to be conducted in the HIV clinic of Entebbe District Hospital, in the Wakiso district of Uganda due to geographical proximity to the EfA partner psychiatric researcher (EK). Entebbe District Hospital is the Municipality and serves a population of around 70,000. It is similar to other peri-urban hospitals in Uganda in terms of number and cadre of staff and population served and in terms of patient characteristics (literacy and education level, employment status and poverty status) [271]. The HIV clinic provides treatment and care to registered out-patients. At the time I designed the study, 1,200 HIV-infected adult patients were estimated by hospital staff to be listed in the HIV treatment and care programme register at Entebbe District Hospital, comprising in majority female patients. I designed the study with the sample size based on an expected 90% participation of the 1,200 patients attending the clinic. Based on the estimates of the prevalence of MDD among HIV-infected patients (0 – 63%) observed in Collins' systematic review, I estimated the prevalence of any CMD at 30% [244]. With the estimated sample size of 1,100 participants, the study had 90% power to detect this (95% confidence intervals 27.3% - 32.8%).

Patients were eligible for the study if they were an outpatient attending the HIV clinic and aged over 18 years old. The study population includes ART-naïve and ART-experienced patients as little was known about mental health disorders in HIV-infected patients in the region irrespective of ART status. All patients waiting for their routine clinic appointment were invited to participate in the study by a psychiatric nurse. The psychiatric nurses described the study to the patients, who were given the Patient Information Sheet and Informed Consent Form. A copy of these forms and all interview tools used can be found in Appendix 5.1. If the patient had all questions satisfactorily answered, they either completed the consent form themself or had the consent form read, and signed or thumb-printed the form. Recruited study participants proceeded to the psychiatric assessment interview.

The screening tools were designed to be assessed in one-fifth (220) of study participants. This was because the HIV healthcare workers administering the tools were not directly employed in this study and it would have been unreasonable to detract a large amount of time from their routine clinical work of patient care. All participants eligible and included in the psychiatric assessment component of the study were invited, by consecutive sampling, to participate in the screening tools validation component of the study until the sample size of 220 patients was reached.

Study recruitment from Entebbe District Hospital was expected to take a period of four months. However, by the end of the first month of the study, it was apparent that recruitment of participants through Entebbe District Hospital alone would not be sufficient to meet this timeline. The study was conducted during the rainy

season and heavy rains impeded access to the clinic for patients and staff on multiple days. In discussion with EK, it was decided to include another HIV treatment and care clinic. Patients were thus also recruited from the neighbouring Kigungu Health Centre III which lies about 5 kilometres from Entebbe District Hospital and is also in the Wakiso district of Uganda. Kigungu Health Centre III is a lower level health centre compared to the District Hospital in terms of staffing and facilities. The clinic serves a population of around 6,500. Patients attending Kigungu health centre III are similar to those attending Entebbe District Hospital in terms of clinical health, educational status and employment status [271]. Table 5.2 depicts the sampling frame used to identify participants for this study.

5.4.2 Psychiatric assessment interview

A structured clinical psychiatric assessment interview was conducted face-to-face by one of six bilingual (Lugandan/English) psychiatric nurses from Butabika Psychiatric Hospital who were employed to undertake recruitment to the study, the demographic and clinical data-gathering and the psychiatric assessment interviews. The interview had been translated into Lugandan by two Lugandan-speaking mental health workers (one psychiatrist and one psychiatric nurse) to allow patients the choice of interview language. The following information, which could be accessed routinely during HIV-care appointments, was gathered through a structured questionnaire before the main psychiatric assessment:

Demographic data

- sex
- age (as reported at interview)
- weight and height (self-reported)

Table 5.2 Sampling frame for cross-sectional study to estimate prevalence of mental health disorders and to validate tools used to monitor it

Health Centres	Sampling: Entebbe District Hospital, extended to include Kigungu Health Centre III, both selected due to geographical proximity to local study lead
Sample size	Patients for prevalence and risk factor estimate: 1,100 Patients for screening tools validation: 220
Population to estimate prevalence and risk factors	Sampling: all adult patients (pre-ART and ART) electing to attend the HIV clinic of the HIV treatment and care programmes within the health centres were invited to participate
Population to validate screening tools	Consecutive sampling: all patients who had completed the clinical diagnostic interview were invited and recruited sequentially until the sample size was met

HIV disease-related data

- length of time since HIV diagnosis (< 3 months, 3 - < 6 months, 6 - < 12 months, ≥ 12 months)
- length of time attending the HIV clinic (< 6 months, 6 - < 12 months, ≥ 12 months)
- most recent CD4 cell count (self-reported)
- ART status (currently on ART, not currently on ART)
- length of time on ART (< 6 months, 6 - < 12 months, ≥ 12 months)
- ART adherence ('in the last three days, have you missed a dose? Yes/no')
- ART combination
- Cotrimoxazole status (currently on Cotrimoxazole, not currently on Cotrimoxazole)
- Cotrimoxazole adherence ('in the last three days, have you missed a dose? Yes/no')

The psychiatric nurses assessed the presence of the following disorders which had been identified in Collins' review as being the most frequently-reported mental disorders among HIV-infected patients: MDD, GAD, PTSD, suicidality and AUD [244]. A definition given by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) of each disorder is given in Appendix 5.2. The psychiatric nurses used the M.I.N.I. Plus to conduct the structured clinical diagnostic interviews [249]. The M.I.N.I. Plus was selected over other diagnostic interviews as it was shown by Collins review to be the most frequently-used structured clinical diagnostic interview [244].

The M.I.N.I. Plus solicits responses about symptoms through separate disorder

modules. General questions screen out individuals who are not likely to be at risk. Sub-questions assess the presence of symptoms and, with exception of the suicidality and AUD modules, a final question assesses whether any of the identified symptoms interfere with normal day-to-day life. The questions require Yes/No responses, with the exception of two questions within the suicidality module which have multiple-choice responses. Affirmative responses score one point and negative responses score zero, with multiple-choice responses scoring between one and three points. The M.I.N.I. Plus uses 71 questions through the individual modules to assess CMD, GPD and AUD. Some questions, however, may be skipped according to previous responses but these 'skip rules' can be numerous and complicated (for example, the suicide module has five skip rules within its 20 questions). Case ascertainment for each M.I.N.I. Plus disorder is based on i) affirmative responses to the screening questions and ii) the number of affirmative responses to the screening and sub-questions combined or the sub-questions alone. However, a disorder is only classed as being present if the final question about whether the identified symptoms cause the patient problems in their daily life is answered affirmatively. At the end of each disorder module the interviewer manually tallied the number of affirmative responses in order to perform case ascertainment. Participants who met the M.I.N.I. Plus criteria for a disorder were informed of their status and offered a referral for further assessment and care within Entebbe Hospital.

Each interview, including the collection of psychosocial data, took 30 - 45 minutes to complete, depending on the skip rules involved in the M.I.N.I. Plus. Each participant was given 5000 Ugandan shilling (USD$2) to cover transport costs.

5.4.3 Screening tool validation interview

The psychiatric nurses invited all participants (identified cases and non-cases) who

had completed the psychiatric assessment interview to complete the short screening tool validation interview until the desired number of participants was recruited. To minimise the potential for reporting bias in the form of quick responses due to tiredness after the psychiatric assessment interview, participants who agreed to participate in the validation interview were given a break and light refreshment between interviews. The screening tool validation interview was conducted by staff working as patient counsellors within the HIV treatment and care clinics.

To screen for CMD and GPD, the HIV care counsellors used the CES-D and Kessler's Scale [268] [269]. While the primary target disorder for both tools is MDD, they also screen for broadly-defined mental disorders and are intended to yield a global measure of distress based on severity of symptoms [269] [272]. The scales solicit responses about feelings or behaviour during the period one week (CES-D) and four weeks (K10/K6) prior to the interview by asking questions with multiple choice responses. While the CES-D has been used and adapted to take account of HIV-specific somatic complaints, at the time of designing this study it had never been validated in peri-urban health centres in Uganda against diagnoses based on the DSM IV or ICD 10 criteria [245]. And, while the K10/K6 has been used in the World Mental Health Surveys in high-income countries and validated in India to identify mental disorders, validity data from other LMIC remain few [269], [272] [273] [274].

To screen for broadly-defined AUD, the HIV counsellors used the AUDIT [270]. The AUDIT was developed by the WHO to pick up the early signs of hazardous drinking, harmful drinking and mild dependence [275]. It has been validated against other screening tests and against blood biomarkers known to reflect heavy drinking [276].

Validation work in New York City supports the use of the AUDIT among HIV-infected persons in busy clinical settings, however data from LMIC are few and it has never been validated among an HIV-infected population in Uganda [277]. The AUDIT solicits responses about consumption of alcoholic beverages during the year prior to interview.

The order in which the screening tools were administered was consistent across all participant interviews (Kessler's Scale, the AUDIT and then the CESD) to give a break between the two tools screening for Global Psychological Distress and MDD. The following number of questions are used in the screening tools to assess broadly-defined disorders: CES-D (20), K10 (10), AUDIT (10) and each interview using all 3 tools took around 10 minutes to complete. The HIV care counsellors administering the interviews were blinded to the initial M.I.N.I. Plus assessment results in order not to influence their manner of administering the screening tools.

All screening tools are scored on a Likert scale where each question, for example, 'were you bothered by things that do not normally bother you?' has the following possible responses: 0=rarely/none of the time, 1=some/a little of the time, 2=occasionally/a moderate amount of the time, 3=all of the time. If a question was positively phrased (for example, 'did you feel you were just as good as other people?'), this required the scores to be reversed (for example, 0=all of the time and 3=none of the time), so that for each tool, a total score was generated where high scores indicate the presence of more symptomatology. As the screening tool interview was aimed at validating the tools rather than providing an assessment of mental ill-health *per se*, while scores were added up by the interviewers to distinguish probable cases from non-cases for the purposes of validation, no results

from the screening tools were given to study participants.

5.4.4 Staff training, ethical considerations and data entry

With the assistance of a psychiatrist employed as study manager, I implemented a four-day training programme for the research nurses in Entebbe, to minimise potential error in the administration of the interviews. Training involved going through each interview question to ensure comprehension on the part of the study team and to ensure the Lugandan translation of words for feelings and emotions would be clear to participants. Furthermore, as it was essential that the psychiatric research nurses were familiar with the complex M.I.N.I. Plus skip rules, we employed role-play to practise their use. During the training we agreed standardised ways to repeat questions if the participant did not understand (e.g. the question would be broken down into shorter phrases and comprehension of each phrase ensured, rather than substituting words). In a similar way, using role-play, the HIV counsellors at the health centres were trained by the study manager in the use of the screening tools. After the training, the data-collection tools were pilot-tested at Entebbe District Hospital. Each research nurse explained the study and invited patients to participate in the pilot work. After obtaining consent, 2 patients were interviewed by each research nurse. This allowed the nurses the opportunity to practise interviews to ensure comprehension of language and become familiar with the M.I.N.I Plus skip rules and scoring methods. After the pilot testing, some very slight linguistic modifications were made to the data-collection tools.

Both the psychiatric assessment and screening tool validation interviews took place in private areas of the HIV health clinics separated from other patients. The psychiatric research nurses with their clinical training and the HIV counsellors with their experience working with HIV patients, were used to soliciting responses in a

sensitive manner and were equipped to handle possible emotions that arose during the interviews.

Data management was carried out by a designated data manager (Gertrude Mutonyi) in the Statistics section of MRC UVRI, according to the standard procedures of the statistics section. A database was created by MRC UVRI and maintained in MS-ACCESS containing tables corresponding to data from the interviews. Data were double-entered into the database in the Statistics section and validated using the Standard Operating Procedures of the Statistics Section. Once data-entry was completed, the interview forms were stored in the Archives of the statistics section, with the same security arrangements that apply to all data forms from MRC/UVRI projects, with data only accessible to the study leads and data entry officers.

5.4.5 Statistical methods

For the purpose of estimating prevalence, identifying risk factors and validating screening tools to identify non-specific mental disorders in the HIV care setting, I generated three variables for the following widely-recognised composite disorder groupings:

i. common mental disorders (any one of: major depression, generalised anxiety, post-traumatic stress) (CMD)
ii. global psychological distress (either major depression or suicidality) (GPD)
iii. alcohol use disorders (either alcohol dependence or alcohol abuse) (AUD)

The above disorder grouping estimates were generated for individuals who completed all the M.I.N.I. Plus modules for the relevant disorders. However, the

interviewers' task to assign cases and non-cases manually is not straight forward due to a complex scoring system and the interview's complex skip rules. Firstly, the scoring methods for case classifications are different for each disorder potentially leading to errors when manually counting scores from the M.I.N.I Plus. Secondly, the complex skip rules mean that the M.I.N.I Plus may not be administered correctly as questions which should have been skipped are answered, leading to a potential over-ascertainment of cases, and questions which should have been answered are skipped, leading to a potential under-ascertainment of cases. Thirdly, a disorder is only said to be present if the final question in each module about problems caused by symptoms is answered affirmatively. However, this question is easily missed and case ascertainment can be incorrectly based only on the total score of the screening and sub-questions. Therefore, I calculated the following three prevalence estimates for all individual disorders and for disorder groupings above:

i. Interviewer estimate: based on the interviewers' manual case classifications,
ii. Maximum estimate: taking account of all questions answered, ignoring errors in the administration of the M.I.N.I Plus skip-rules, and ignoring responses to the final case-defining question which may have been missed in error by some participants,
iii. Gold standard estimate: according to strict administration of the M.I.N.I Plus skip-rules.

I assessed how well the interviewers administered the M.I.N.I Plus and categorised cases and non-cases. To do this, I calculated the validity of the interviewers' manual classifications from the M.I.N.I. Plus for the main outcome of any CMD against the electronically derived maximum and gold standard prevalence estimates,

using the latter two estimates to represent true cases and non-cases. I calculated sensitivity and specificity and the positive and negative predictive values.

Using logistic regression models, I examined the association of the following variables with any CMD (maximum estimate): sex, age (<30, 30 – 34, 35 – 40, >40), BMI (<18.5, 18.5 - <25, 25 - 30, >30), current CD4 (<100, 100 - <200, 200 - <350, 350 – 500, >500), time since HIV diagnosis (< 3, 3 – <6, 6 – 12, > 12 months), time in HIV programmes (<6, 6 – 12, > 12 months), currently on ART or not, time since initiating ART (<6, 6 – 12, >12 months), ART combination, ART adherence (missed a dose or did not miss a dose), currently on Cotrimoxazole prophylaxis, and Cotrimoxazole prophylaxis adherence. Participants with multiple missing data were dropped from the logistic regressions. Factors with a large number of missing values (BMI and CD4 count) were not included in the multivariate regression model. Potentially conflicting responses between variables (e.g. time in HIV programme < 6 months and being on ART 6 - 12 months) were assumed to mean an overlapping time period at 6 months or attendance at a different HIV/ART clinic prior to the current clinic and included. For potentially collinear factors (time since HIV diagnosis and time in HIV programme, and ART status and time since initiating ART, and Cotrimoxazole prophylaxis status and Cotrimoxazole adherence), I used likelihood ratio tests to find the simplest factor which best fitted the data and did not include the other factors in the multivariate model. I forward fitted the multivariate models adjusting for factors found to be independently associated at $p<0.1$ at the univariate level. I used likelihood ratio tests to find the model which best fitted the data, examining age as both categorical and continuous. Other continuous variables (e.g. BMI and CD4 count) were examined as categorical variables using accepted standards or commonly-used

categories. Finally, I estimated the association of the demographic and clinical characteristics with any CMD having adjusted for the significant effects in the multivariate model. I used likelihood ratio tests to assess for any interaction between factors found to be associated at the univariate level and all other factors. Using the same methods, I conducted a sensitivity analyses with the gold standard prevalence estimate which accurately reflects true M.I.N.I. Plus case classifications.

I validated the screening tools against the M.I.N.I Plus using the strict case classifications derived among participants who had followed the skip rules correctly (gold standard estimate). Firstly, I estimated the M.I.N.I Plus prevalence of CMD, GPD and AUD, and for each disorder grouping, and I examined the number of cases of the constituent disorders. I used these estimates as the gold standard measure of disease. Secondly, I estimated the prevalence of CMD, GPD and AUD using the recommended cut-off points for each screening tool. I estimated the sensitivity and specificity of the screening tool case classifications against the M.I.N.I. Plus classifications. Thirdly, I assessed each screening tool's ability to differentiate cases from non-cases by estimating the AUROC curves and I compared how the 3 tools performed. Using the values from the AUROCs, I identified the cut-off scores which gave near equal sensitivity and specificity and I estimated the prevalence of disorders if these cut-off scores were used.

I examined differences in patient characteristics and prevalence of mental disorders between participants who completed the screening tools and those who completed only the M.I.N.I. Plus. I examined the difference in the screening tool scores when the scores were generated manually by the HIV care counsellors administering the tools or electronically. Finally, using the same methods as above, I examined the

validity of the screening tools against the M.I.N.I. Plus maximum prevalence estimates.

5.5 Results

5.5.1 Patient characteristics and disorder prevalence

Between May - August 2010, a total of 692 patients attending the study clinics on the same days as the psychiatric research nurses were invited to participate, of whom 12 (2%) declined. Reasons given for non-participation included no time due to work commitments, the need to think more about participating, wanting to discuss participation with family members, and coming from districts outside of Wakiso district and thus being unable to return for an interview. No further details were gathered on patients who declined participation. 680 patients were screened for enrolment and allocated an interview time. Of these, 62 did not return for their interview despite being contacted by telephone. No data on these individuals were available. 618 participants were recruited to the study and completed the psychiatric assessment interview. Of these, 531 (86%) came from Entebbe District Hospital, 80 (14%) from Kigungu health centre and 7 (1%) were missing this information. Figure 5.1 depicts the recruitment process.

Of the 618 study participants, the majority (449, 73%) were female (Table 5.3). The median age of participants was 35 (IQR 29 – 41) years. The median Body Mass Index was 22 (IQR 20 – 25) kg/m^2. The median latest reported CD4 cell count was 301 (IQR 169 – 469) cells/mm^3 with 176 (34%) of participants with non-missing data reporting their latest CD4 cell count to be less than 200 cells/mm^3.

Figure 5.1 Flow of patient recruitment to the study

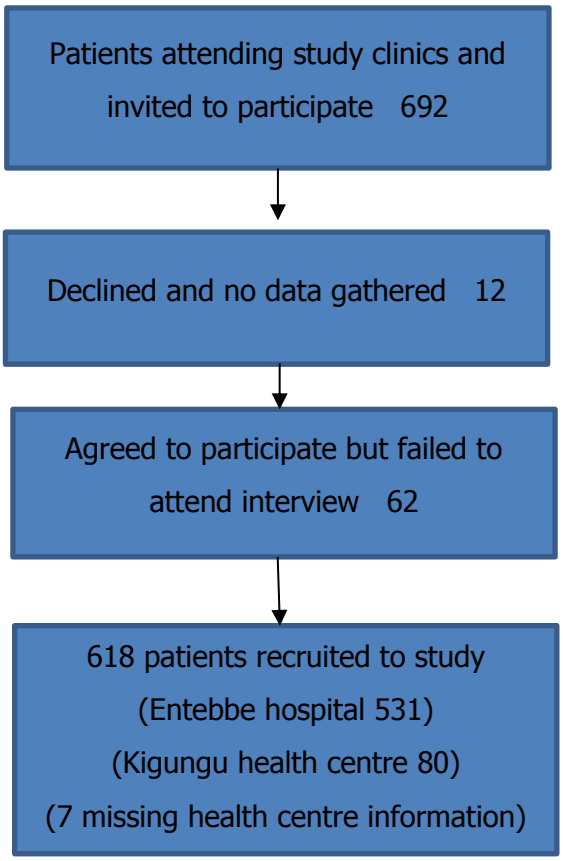


Table 5.3 Characteristics of 618 participants examined for any Common Mental Disorder (CMD) in two health centres in Wakiso District, Uganda

Characteristic	Number (%)	Number (%) with CMD
Sex		
Male	169 (27%)	11 (7%)
Female	449 (73%)	57 (13%)
Age (years)		
Median (IQR)	35 (29 - 41)	
<30	162 (26%)	19 (12%)
30 – 34	134 (22%)	23 (17%)
35 – 40	147 (24%)	13 (9%)
>40	173 (28%)	13 (8%)
Missing	2	
BMI (kg/height2)		
Median (IQR)	22.2 (20.2 – 25.1)	
<18.5 (Underweight)	56 (9%)	6 (11%)
18.5 - (Normal weight)	389 (65%)	47 (12%)
25 - (Overweight)	116 (19%)	10 (9%)
> 30 (Obese)	35 (6%)	4 (11%)
Missing	22	
Most recent CD4 cell count		
Median (IQR)	301 (169 - 469)	
<100	66 (13%)	5 (8%)
100 –	110 (21%)	11 (10%)
200 –	130 (25%)	14 (11%)
350 –	105 (20%)	16 (15%)
>500	115 (22%)	10 (9%)

Characteristic	Number (%)	Number (%) with CMD
Missing	92	
Time since diagnosis (months)		
<3	77 (13%)	8 (10%)
3 –	28 (5%)	1 (4%)
6 –	45 (7%)	7 (16%)
> 12	465 (76%)	51 (11%)
Missing	3	
Time in HIV programme (months)		
< 6	121 (20%)	15 (12%)
6 – 12	66 (11%)	8 (12%)
>12	427 (70%)	45 (11%)
Missing	4	
Currently on ART		
Yes	399 (65%)	38 (10%)
No	212 (35%)	29 (14%)
Missing	7	
Time since initiating ART		
Not on ART	212 (35%)	29 (14%)
On ART < 6 months	33 (5%)	3 (9%)
On ART 6 – 12 months	38 (6%)	4 (11%)
On ART >12 months	326 (54%)	31 (10%)
Missing	9	
ART combination		
Combivir-Nevirapine	319 (53%)	29 (9%)
Triomune	59 (10%)	7 (12%)
Other combinations	15 (2%)	2 (13%)

Characteristic	Number (%)	Number (%) with CMD
Not on ART	212 (35%)	29 (14%)
Missing	13	
ART adherence		
Did not miss dose	375 (62%)	37 (10%)
Missed dose in last 3 days	20 (3%)	1 (5%)
Not on ART	212 (35%)	29 (14%)
Missing	11	
On Cotrimoxazole prophylaxis		
Yes	598 (97%)	65 (11%)
No	18 (3%)	3 (17%)
Missing	2	
Cotrimoxazole adherence		
Did not miss dose	548 (89%)	57 (10%)
Missed dose in last 3 days	49 (8%)	7 (14%)
Not on CPT	18 (3%)	3 (17%)
Missing	1	

Note: Figures are numbers and percentages as indicated. Percentages do not include missing. Feasible inconsistent responses were given by seven participants relating to differences in time knowing HIV status, time of attendance in the study clinic and time on ARVs and their data are included here. Numbers (%) with CMD do not include missing.

The majority of participants 465 (76%) had known their HIV status for more than 12 months, 399 (65%) were on ART (the majority on a combivir-nevaripine regimen) and 598 (97%) were currently taking Cotrimoxazole prophylaxis. A high number of participants reported good adherence to ART (375, 95%) and to Cotrimoxazole prophylaxis (548, 92%). Twenty-five (4%) of the 618 participants were dropped from the logistic regressions as complete information on all variables was not available.

For the 618 patients enrolled into the study, the prevalence of CMD was estimated to be between 6.9 – 11.0%, the majority of cases being MDD (65) (Tables 5.4). Prevalence of GPD varied from 11.1 to 13.4%, which represented a high prevalence of suicidality (7.8% - 8.6%). The majority of cases of suicidality (80% - 98%) were of mild suicidal risk. Very few participants were diagnosed with alcohol use disorders (prevalence 0.7% - 0.8%), nearly all of which was alcohol dependence. Unless otherwise stated in Table 5.4, the sample size for the estimates was 618 participants.

Across all disorders, the interviewers classified as cases a similar number of participants to the number classified in the electronically-derived maximum estimate and closely resembling the number classified in the gold standard estimates (Table 5.5). Compared to the gold standard estimate of CMD, the interviewers correctly identified 36 of the 39 cases (sensitivity 92%) and 510 of the 523 non-cases (specificity 98%). Thirty-six of the 49 cases of CMD identified by the interviewers were true cases (positive predictive value 73%) and 510 of the 513 participants identified by the interviewers as non-cases were true non-cases (negative predictive value 99%). However, an additional fifty-three participants were dropped from the

Table 5.4 Interviewer, Maximum and Gold standard prevalence estimates of mental disorders among 618 HIV-outpatients attending clinics in Uganda, May - August 2010

Disorder	Interviewer Prevalence	Maximum Prevalence	Gold standard Prevalence
Common Mental Disorders			
Any	62 (10.1%)	68 (11.0%)	39 (6.9%)
Missing	5	-	53
Major Depression	65 (10.5%)	65 (10.5%)	43 (7.4%)
Missing	1	-	39
Post-Traumatic Stress	11 (1.8%)	11 (1.8%)	9 (1.5%)
Missing	2	-	5
Generalised Anxiety	14 (2.3%)	6 (1.0%)	2 (0.3%)
Missing	9	-	12
Global Psychological Distress	83 (13.4%)	83 (13.4%)	47 (11.1%)
Missing	-	-	193
Suicidality	48 (7.9%)	48 (7.8%)	38 (8.6%)
Missing	7	-	174
Alcohol Use Disorders			
Any	7 (1.1%)	5 (0.8%)	4 (0.7%)
Missing	7	-	10
Dependence	5 (0.8%)	4 (0.7%)	4 (0.7%)
Missing	7	-	10
Abuse	2 (0.3%)	1 (0.2%)	0%
Missing	14	-	10

Note: Interviewer estimate uses the interviewers' manual case classifications; Maximum estimate ignores errors in the administration of the M.I.N.I.; Gold standard estimate is according to strict M.I.N.I. criteria.

Table 5.5 Classifications of any M.I.N.I. Plus Common Mental Disorder manually by interviewers and by electronically-derived gold standard estimate

	M.I.N.I Gold standard classifications			Total
Interviewer classifications	No CMD	CMD	Unclassified	
No CMD	510	3	40	543
CMD	13	36	13	62
Total	523	39	53	615

Note: 53 participants were dropped from the gold standard estimate due to completion errors but were classified by the interviewers

gold standard estimate due to errors following the skip rules, yet despite the lack of adequate data to assign diagnoses, the interviewers classified 13 of these participants as cases and 40 as non-cases.

5.5.2 Risk factors

Compared to men, women were more likely to be diagnosed with any CMD (OR 1.98, 95% CI 1.01 - 3.89, p=0.03), and younger individuals somewhat more likely (0.77 per 10-year increase, 0.57 – 1.05, p=0.09) (Table 5.6). The effect of age was better explained by linear increase than as age-groups (p=0.06). There was no evidence of an association between CMD and: BMI, current CD4 count, time since HIV diagnosis, time in HIV care programme, having initiated ART, time since initiating ART, ART combination, taking Cotrimoxazole prophylaxis or adherence to ART or Cotrimoxazle.

The multivariate model was adjusted for the effect of sex and age. After adjusting for the effects of sex, younger individuals (OR 0.83 per 10-year increase, CI 0.61 – 1.13, p=0.05) remained more likely to be at risk of any CMD, with borderline significance. After adjusting for the effects of age, females remained at increased risk (OR 1.80, CI 0.90 – 3.61, p=0.05). In addition, after adjusting for sex and age, the increased risk to patients not currently on ART (OR 1.28, CI 0.73 – 2.22, p=0.08) became slightly more important. There was no evidence of any interaction between sex or age and any patient characteristic. The model with sex and age alone fitted the data no worse than a composite model with clinic time (p=0.87), ART status (p=0.39), ART formula (p=0.72), ART adherence (p=0.48) or CPT adherence (p=0.52).

In sensitivity analyses, using CMD as defined by the gold standard prevalence

Table 5.6 Risk factors associated with having any Common Mental Disorder among patients attending two HIV clinics in Wakiso district, Uganda

	Univariate		Adjusted*	
Risk factor	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex				
Male	1	P=0.03	1	p=0.05
Female	1.98 (1.01 - 3.89)		1.80 (0.90 – 3.61)	
Age (trend)	0.77 (0.57 - 1.05)	P=0.09	0.83 (0.61 - 1.13)	P=0.05
BMI (kg/height2)				
<18.5 (Underweight)	0.96 (0.39 - 2.37)	P=0.89	*	-
18.5 - (Normal weight)	1			
25 - (Overweight)	0.75 (0.36 - 1.54)			
> 30 (Obese)	0.97 (0.33 - 2.87)			
Most recent CD4 cell count				
<100	0.86 (0.28 - 2.62)	P=0.62	*	-
100 –	1.17 (0.47 - 2.88)			
200 –	1.26 (0.54 - 2.97)			
350 –	1.76 (0.75 - 4.12)			
>500	1			

	Univariate		Adjusted*	
Risk factor	OR (95% CI)	P-value	OR (95% CI)	P-value
Time since diagnosis (months)				-
<3	1	P=0.50	*	
3 –	0.29 (0.04 - 2.49)			
6 –	1.26 (0.41 - 3.92)			
> 12	1.00 (0.45 - 2.21)			
Time in HIV programme (months)				
< 6	1	P=0.75	1	P=0.19
6 – 12	0.83 (0.32 - 2.15)		0.81 (0.31 - 2.12)	
>12	0.78 (0.42 - 1.47)		0.85 (0.45 - 1.63)	
Currently on ART				
Yes	1	P=0.16	1	P=0.08
No	1.46 (0.87 - 2.47)		1.28 (0.73 - 2.22)	
Time since initiating ART				
Not on ART	1.48 (0.86 - 2.56)	P=0.56	*	-
On ART < 6 months	0.99 (0.28 - 3.43)			
On ART 6 – 12 months	1.16 (0.38 - 3.48)			
On ART >12 months	1			

	Univariate		Adjusted*	
Risk factor	OR (95% CI)	P-value	OR (95% CI)	P-value
ART combination				
Combivir-Nevirapine	1	P=0.47	1	P=0.20
Triomune	1.13 (0.45 - 2.87)		1.10 (0.43 - 2.79)	
Other combinations	1.79 (0.38 - 8.46)		1.93 (0.40 - 9.31)	
Not on ART	1.53 (0.88 - 2.65)		1.32 (0.74 - 2.37)	
ART adherence				
Did not miss dose	1	P=0.27	1	P=0.12
Missed dose in last 3 days	0.48 (0.06 - 3.69)		0.45 (0.06 – 3.48)	
Not on ART	1.42 (0.84 - 2.41)		1.23 (0.70 - 2.15)	
Currently taking CPT				
Yes	1	P=0.35	*	-
No	1.92 (0.53 - 6.91)			
CPT adherence				
Did not miss dose	1	P=0.47	1	P=0.12
Missed dose in last 3 days	1.43 (0.61 - 3.35)		1.37 (0.58 – 3.22)	
Not on CPT	1.98 (0.55 - 7.18)		1.93 (0.53 - 7.06)	

*Notes: the OR is adjusted for factors (sex and age) found to be significant at the P<0.1 level in the univariate analyses. There were 22 missing Body Mass Index values and 92 missing CD4 cell counts therefore these variables were not included in the adjusted models. Time since diagnosis was not fitted to the multivariate due to co-linearity with time in HIV programme and time in HIV programme fitted the data no worse; time since initiating ART was not fitted to the model due to co-linearity with ART status and ART status fitted the data no worse. CPT status was not fitted to the multivariate as 97% of all participants were taking CPT

estimate, there was no longer any evidence for the effect of any patient characteristic, though the results had reduced power. There was, of note, a slight non-significant change in the direction of effect for patients who: were obese (OR 1.32), had been enrolled in care for 6 – 12 (OR 1.04) or >12 (OR 1.11) months, had been on ART for 6 – 12 months (OR 0.86), were on Triomune (OR 0.97) or had missed a dose of CPT (OR 0.97).

5.5.3 Validity of screening tools

Of the 618 study participants, 223 (36%) completed the screening tools. Due to errors in following the M.I.N.I. Plus skip rules, no gold standard M.I.N.I. Plus classifications were made for the following number of patients who answered the screening tools 17 (CMD), 68 (GPD), 4 (AUD) (Figure 5.2). Among screening tools participants, 16 (8%), 22 (14%) and 2 (1%) had CMD, GPD and AUD, respectively, according to the gold standard M.I.N.I. Plus estimate. The majority of cases of CMD were of MDD (13 cases). Table 5.7 shows the number of cases of each constituent disorder contributing to the CMD, GPD and AUD groupings. No validation analyses were undertaken on the ability of the screening tools to detect MDD due to the large overlap between cases of MDD and any CMD. No validation analyses were undertaken on the AUDIT due to the low number of cases of AUD.

Among the participants completing the screening tools, the median scores for the CESD and Kessler's scale can be seen in Table 5.8. When using the case classification cut-off points for the CESD and Kessler's scale recommended by the authors, sensitivity and specificity for the CMD and GPD were low against the gold standard estimates. When using these cut-off points, prevalence of any CMD was 33%, 30% and 32% (CESD, K10, K6 respectively) and prevalence of GPD was 31%, 31% and 35% (CESD, K10, K6 respectively). The median score for the AUDIT was

Figure 5.2 Number of study participants who completed the M.I.N.I. Plus and screening tools, and number who followed the M.I.N.I. Plus skip rules correctly and have a gold standard case classification

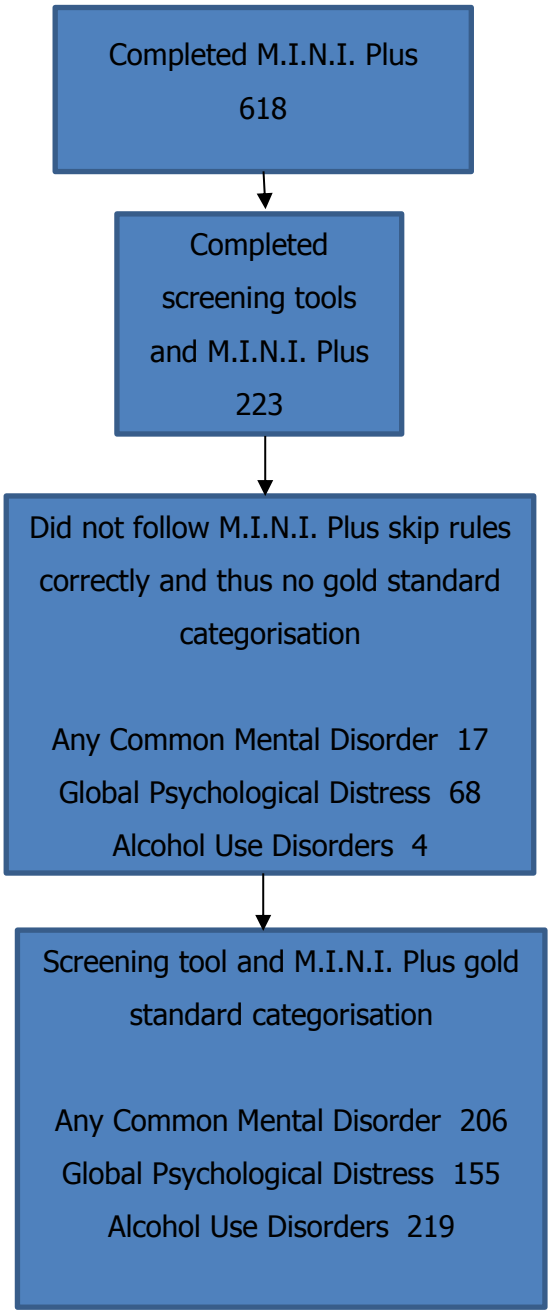


Table 5.7 Number of cases of Common Mental Disorders, Global Psychological Distress and Alcohol Use Disorders, according to Gold standard M.I.N.I. Plus estimate, among participants who completed the screening tools

M.I.N.I. Disorder	Cases
Any Common Mental Disorder	16
Major Depressive Disorder	13
Generalised Anxiety Disorder	0
Post-Traumatic Stress Disorder	1
Comorbidity Major Depressive & Generalised Anxiety Disorder	0
Comorbidity Major Depressive & Post-Traumatic Stress Disorder	2
Global Psychological Distress	22
Major Depressive Disorder	5
Comorbid Major Depressive Disorder & Suicidality	8
Suicidality	9
Any Alcohol Use Disorder	2

Table 5.8 Median score for the CESD, K10, and K6, sensitivity and specificity using screening tool's cut-off points against M.I.N.I. CMD and GPD, and prevalence of CMD and GPD using the screening tool cut-off points

	Median score (IQR)/total	Sensitivity & Specificity CMD	Prevalence of CMD	Sensitivity & Specificity GPD	Prevalence of GPD
CESD	8 (IQR 1 – 20)/60	33%, 68%	33%	30%, 69%	31%
K10	14 (IQR 11 – 21)/50	31%, 71%	30%	27%, 68%	31%
K6	9 (IQR 6 – 13)/30	38%, 68%	32%	36%, 65%	35%

0 (IQR 0 – 1) out of 40 (not included in table).

The CES-D, K10 and K6 differentiated cases of CMD from non-cases poorly with the following AUROCs, respectively: 0.60 (0.45 - 0.75), 0.57 (0.43 - 0.71) and 0.57 (0.42 - 0.71) (Table 5.9). There was no evidence of a difference between the three tools in their ability to differentiate cases from non-cases (p=0.98). Figure 5.3 compares the AUROCs for the three tools. The optimal cut-off scores which provided the best balance between sensitivity and specificity maximised sensitivity at 60%, 56% and 56% and specificity at 60%, 54% and 49% for the CES-D, K10 and K6 respectively. Using these cut-off points, prevalence of CMD was 41% (CESD), 47% (K10) and 51% (K6).

The CES-D, K10 and K6 similarly differentiated cases of GPD from non-cases very poorly, with respective AUROCs of 0.58 (0.45 - 0.71), 0.48 (0.34 - 0.63) and 0.50 (0.37 - 0.64) (Table 5.10). There was no evidence of a difference between the tools (p=0.38). Figure 5.4 compares the AUROCs for the three tools. The optimal cut-off scores which provided the best balance between sensitivity and specificity maximised these at close to 50% for all three tools. Using these cut-off points for the CES-D, K10 and K6, prevalence of GPD was 43% (CESD), 47% (K10) and 51% (K6).

In sensitivity analyses using the M.I.N.I. Plus maximum prevalence estimates, the accuracy of the screening tools in the larger population was little improved. There was no evidence of a difference in the ability of the 3 tools, CES-D, K10 or K6, respectively, when comparing their ability to classify cases and non-cases of CMD (AUROC 0.59, 0.64, 0.65, p=0.36) and GPD (AUROC 0.60, 0.57, 0.61, p=0.51).

Table 5.9 Discriminatory ability to differentiate between cases and non-cases of any M.I.N.I. Plus-defined Common Mental Disorder of the Centre for Epidemiological Studies Depression Scale (CESD) and Kessler's Psychological Distress (K10-item and K6-item) Scales

	CESD scale	Kessler's 10-item scale	Kessler's 6-item scale
Area under Receiver Operating Characteristic curve (CI)	0.60 (0.45 – 0.75)	0.57 (0.43 – 0.71)	0.57 (0.42 – 0.71)
AUROC when 3 tools compared among same participants (P=0.98)	0.60	0.59	0.58
Optimal cut-off point	12	15	9
Sensitivity at optimal cut-off point	60%	56%	56%
Specificity at optimal cut-off point	60%	54%	49%
Prevalence of using optimal cut-off	42%	47%	51%

Figure 5.3 Comparison of the ability of the Centre for Epidemiological Studies Depression Scale and Kessler's Psychological Distress (10-item and 6-item) Scales to detect any MINI-defined Common Mental Disorder

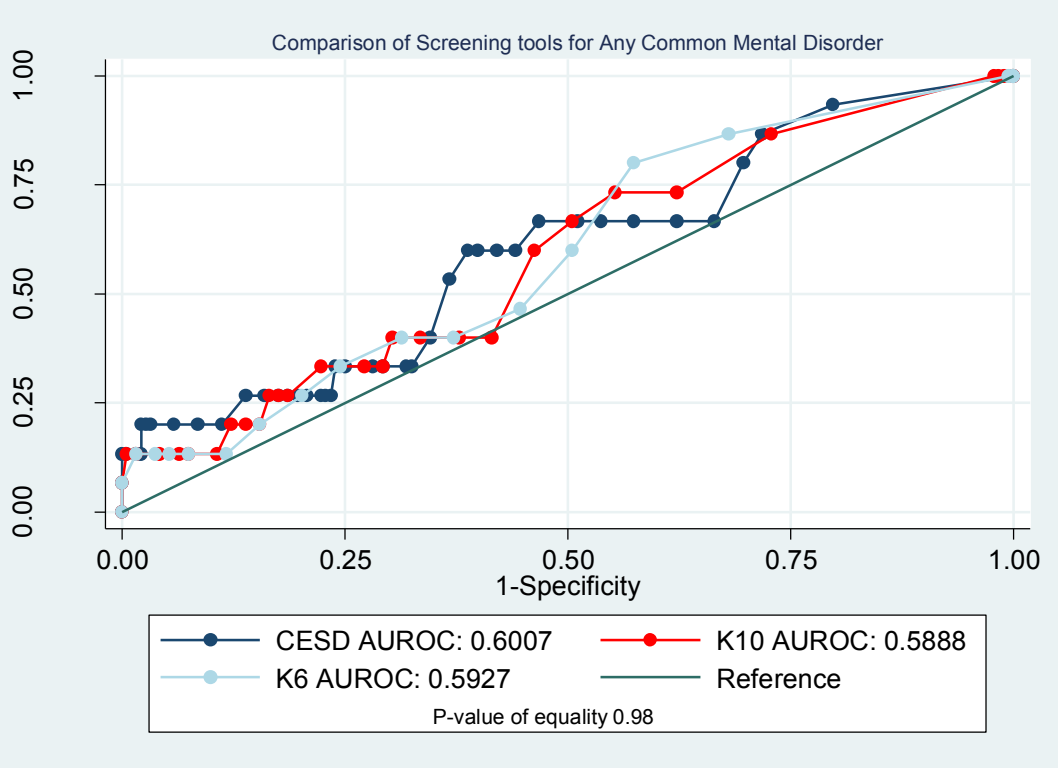
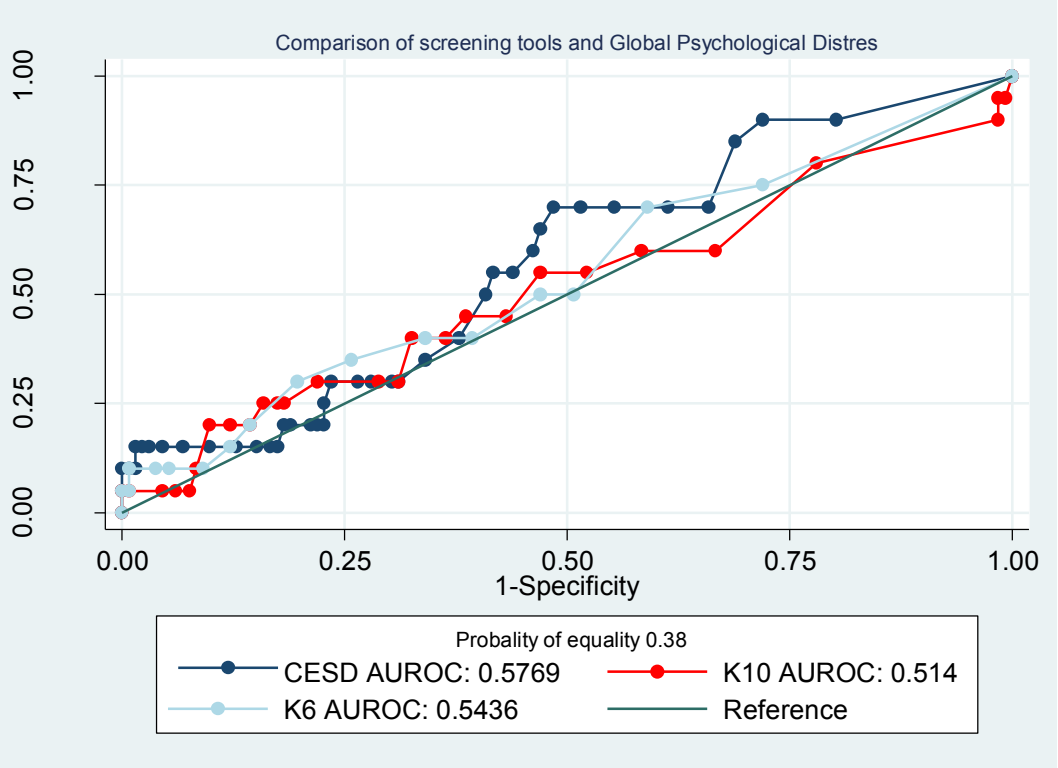


Table 5.10 Discriminatory ability to differentiate between cases and non-cases of Global Psychological Distress of the Centre for Epidemiological Studies Depression scale (CESD) and Kessler's Psychological Distress (K10-item and K6-item) Scale

	CESD scale	Kessler's 10-item Scale	Kessler's 6-item Scale
Area under Receiver Operating Characteristic curve (CI)	0.58 (0.45 - 0.71)	0.48 (0.34 - 0.63)	0.50 (0.37 - 0.64)
AUROC when 3 tools compared among same participants (P=0.38)	0.58	0.51	0.54
Optimal cut-off point	11	15	9
Sensitivity at optimal cut-off point	55%	50%	45%
Specificity at optimal cut-off point	56%	53%	49%
Prevalence when using optimal cut-off point	43%	47%	51%

Figure 5.4 Comparison of the ability of the Centre for Epidemiological Studies Depression Scale and Kessler's Psychological Distress (10-item and 6-item) Scales to detect M.I.N.I. Plus-defined Global Psychological Distress



There was no evidence of a difference in prevalence of CMD or GPD between those who completed the screening tools and those who did not. There was also no evidence of a difference in patient characteristics between the two groups, with the exception of ARV drug formula (P=0.02): of participants who completed the screening tools, more were receiving an ARV formulation other than Combivir-Nevirapine or Triomune compared to those who completed only the M.I.N.I. Plus, though the numbers on other formulations were very low. Median scores for the screening tools as calculated manually by the nurses were similar to the scores generated electronically.

5.6 Discussion

This study is one of only a few studies conducted among HIV-infected individuals in Africa assessing the burden of mental ill-health using structured interviews and assessing the validity of the CES-D, K10 and K6. I found a substantial burden of mental ill-health (6.9% - 11% any CMD and 11.1 – 13.4% GPD) among HIV-outpatients in Uganda. I found younger patients, females and those not on ART slightly more likely to experience any CMD. The validity of the tools, when compared to the gold standard clinical diagnostic interview was poor. Using either the authors' recommended cut-off points for the CES-D, K10 or K6 or the optimal cut-off points identified in this study, the prevalence of any CMD and GPD was between 30% - 51%, in comparison, respectively, to the 8% and 14% estimated when using the M.I.N.I Plus gold standard estimate. The use of these tools may overestimate prevalence considerably and this study, therefore, provides important evidence against the use of these screening tools among HIV-infected patients in health centres in Uganda.

The level of disorders I found was lower than previous study estimates of MDD in Uganda (83%) or found in Collins systematic review (0 - 63%) [244, 245]. This is likely due to the large number of studies using screening tools to report prevalence rather than rigorous clinical interviews. In studies validating screening tools (CESD, K10, AUDIT) among non-HIV infected populations in LMIC, reported prevalence of MDD (2% – 73%) and of AUD (8 - 67%) when not using clinical diagnostic interviews was also high [278-286]. The current study results are in line with prevalence estimates of MDD (3 – 17%) from the studies using clinical diagnostic interviews among HIV-outpatients which I reviewed [243, 260-263, 266]. My results are also similar to a large multi-country study reviewed by Collins, where prevalence of MDD was between 2 - 15% [244, 287]. The highest prevalence estimate of MDD (17%) was derived in the only other study validating screening tools against a clinical interview in Uganda. However, disease classification in that study did not include the final case-defining question and reported prevalence is possibly an overestimation of cases [243]. I found that when estimating prevalence of CMD by not including the final case-defining question prevalence was 4% higher than when based on strict M.I.N.I. criteria.

The comorbidity of MDD and suicidal risk I found among validation study participants (8/17 participants with suicidality also were diagnosed with MDD) is consistent with review findings that GAD and MDD are related to suicidal ideation among HIV-infected patients in LMIC [244]. This study found lower levels of AUD (1%) than those found in the studies reviewed by Collins which used diagnostic interviews to estimate AUD prevalence (7% - 44%), though some of these studies were small and conducted among inpatients [244, 261, 262, 288-290]. It is possible that the current study findings reflect the true burden of AUD in this

population, who were 73% female, as lower levels of alcohol abuse have been reported among HIV-infected females compared to males in South Africa [262]. However, it is feasible that the majority of female participants did not feel comfortable discussing alcohol consumption with clinic staff. More research on the burden of alcohol use disorders among HIV-infected patients is needed, particularly in peri-urban and rural health clinics where the majority of patients may be female.

I found that younger individuals and women were slightly more likely to have CMD, and that patients not currently on ART had a slight increased risk. Findings from a study in South Africa suggested, in fact, that decreasing age (OR 0.96, CI 0.92 – 0.99) was inversely associated with MDD, though details of the number of years per decrement were not given [262]. Most research regarding risk factors for CMD or MDD has focused on psychosocial risk factors rather than data routinely collected in ART clinics [244]. In this study, no clear risk factors among data collected in routine HIV care emerged. While it may be important to target women, younger individuals and those not yet on ART for mental health screening and management, more research assessing which routinely collected clinic data can identify at-risk patients is needed.

The CES-D, K10 or K6 did not reliably detect any CMD or GPD with good precision in comparison to the M.I.N.I. Plus in this peri-urban clinical setting. The study population was made up of immune-compromised individuals (34% of the current study had CD4 cell counts < 200) with low levels of literacy (58% had either only primary or no formal education) [291]. These factors, which are not unusual among HIV-infected individuals in peri-urban clinical settings in LMIC, may have influenced participants responses to the screening tools: one characteristic of the

screening tools is their use of tiered responses ('none of the time', 'some of the time', 'most of the time', 'all of the time') compared to the binary 'yes'/'no' responses in the clinical assessment. It has been suggested that self-reported rating scales in this tiered format may bias responses depending on the literacy level of respondents [260]. Furthermore, the performance of the CESD has been shown to be better among individuals with CD4 cell counts > 200 cells, than among individuals with advanced disease cognitive impairment may mask reporting of depressive symptomology [262].

When validated against diagnoses of any CMD, I found AUROC estimates for the CESD (0.60 at detecting CMD, 0.58 for GPD) and K10 (0.57 CMD, 0.48 GPD) lower than estimates observed in previous studies validating the CESD (0.76, 0.78) and K10 (0.77) against MDD among HIV-infected populations in LMIC [260-262]. However, 2 of the 3 previous studies excluded patients from participation if they had a significant degree of cognitive impairment, whereas the current study had no selection criteria based on cognitive impairment status. In the previous studies therefore, the screening tools were not validated in patients who may have struggled to understand the tiered response system and this may, in part, explain the higher degree of validity attributed to the screening tools [260, 262]. One further study, conducted in an urban hospital in Kampala, Uganda, found the CESD, K10 and K6 to be highly accurate at identifying MDD (AUROC 0.94, 0.82, 0.82, respectively) in an HIV-infected population. However, the population in the Kampala study had a higher level of education than the current study population (only 46% of the Kampala study population had only primary education) and was healthier (only 17% of the Kampala population had CD4 cell counts < 200) [243, 291]. The greater number of years of education and healthier status may have

influenced the ability of the Kampala study participants to interpret and respond to the tiered options of the screening tool questions and may explain the higher degree of validity attributed to the screening tools.

I found, respectively for the CESD, K10 and K6, low sensitivity (60%, 54%, 49% for CMD and 55%, 50%, 40% against GPD) and low specificity (60%, 54%, 49% against CMD and 56%, 53% and 49% against GPD) at the identified cut-off points. This is in keeping with the reviewed studies. Even when AUROCs appeared acceptable, if data were presented they showed that one of sensitivity, specificity or the predictive value was usually compromised: for example despite an AUROC of 0.77 for the K10 in South Africa, the associated specificity of 77% resulted in a sensitivity of 67% and a ppv of 29%; and in the second South African study reviewed, when an AUROC for the CESD of 0.76 was selected with the associated sensitivity of 79%, specificity was 61% and ppv only 24% [260, 262]. The validity of findings for these screening tools among HIV-infected populations in LMIC are consistent with findings of high AUROCs and low sensitivity, specificity or PPV in studies validating the CESD and Kessler's Scale among non-HIV infected individuals. For example, the K10 and K6 were found to be moderately accurate with an AUROC of 0.77 and 0.75, respectively, in Burkina Faso among post-natal women. However, while they detected 91% and 85% respectively of true non-cases both detected correctly only 59% of true cases [283]. In a household survey in South Africa the K10 and K6 had an AUROC of 0.73 and 0.72 respectively, against gold standard diagnoses, but no cut-off points were identified and to obtain a ppv above 50% sensitivity was only 4% [292]. And according to the authors of an Indian study, the K10 showed considerably compromised ppv (53%) at the given sensitivity (65%) [274].

The importance of using a screening tool with a good balance of sensitivity, specificity and predictive value cannot be underestimated in countries with limited resources. There is a need not to miss true cases for whom the potential impact of a mental health disorder may be serious (e.g. suicide), but it is also important not to refer non-cases for further expensive and time-consuming assessments in a setting with already over-stretched resources and a limited number of trained psychiatric professionals. Furthermore, the stigmatising effect of being diagnosed with a mental health disorder must be considered and care must be taken not to misdiagnose, particularly when the presence of mild symptoms may not cause measurable morbidity or mortality [293].

Among validation study participants, while I found a substantial burden of suicidality (17/22 cases of GPD included cases of suicidality), the CES-D, K10 and K6 correctly identified respectively only 55%, 50% and 45% of true cases of GPD and only 56%, 53% and 49% of true non-cases of GPD. This lack of validity is in line with previous suggestions that the limited breadth of items in the screening tools do not cover important clinical domains relating to suicidality [260]. Given the high level of suicidality observed in this study, finding a screening tool which is able to identify patients at risk is vital.

There are potential limitations to the generalisability of the current study findings. From my review of the literature the current study is the only study to have examined the validity of the CESD and K10 in HIV-infected patients in a LMIC against the composite diagnosis of any CMD (which included PTSD and GAD as well as MDD) or against GPD (MDD or Suicidality). It is worth noting that MDD, not composite groupings of CMD or GPD, is the primary target disorder for the CESD

and K10, though both tools are designed to detect general distress. Nonetheless, 15/16 cases of M.I.N.I. defined CMD were of MDD in the validation sample and the results can therefore also apply to the accuracy of the tools at detecting MDD in this population.

A limitation of this study is that while the study aimed to recruit 1,100 patients, the nurses were only able to recruit 618 participants in the time available for the study. This was due to the study being conducted during the rainy season and for 3 consecutive weeks heavy rains fell on the days that the ART clinic was open at Entebbe hospital resulting in two main problems. Firstly, some of the psychiatric research nurses were travelling from Kampala and were unable to make the journey due to the heavy rains, and secondly, the research nurses who were able to attend Entebbe hospital and Kigungu health centre reported severely reduced number of patients attending the clinic on those days as there is no place at either health facility to shelter from the rains. This reduction in sample size will have reduced the power of the study when estimating prevalence and examining risk factors. This study identified no clear risk factors for CMD from routinely collected clinic data. It is possible that a larger study may enable the identification of risk factors. A further limitation to the generalisability of the findings is that of the 692 patients who were invited to participate, 74 (11%) either declined, or accepted but never returned for interview. It is likely that patients not participating differ from those who took part in the study. It is possible that they may have higher prevalence of CMD making them less likely to take part.

A further limitation of this study is that the validation component was conducted in just over 200 participants and data, in particular, for the validation of GPD were

only available for 155 patients who correctly answered the M.I.N.I. questions on suicide. The validation analyses therefore were conducted against a relatively small number of M.I.N.I. defined cases of CMD (16) and GPD (22). However, even the upper limits of the confidence intervals for the AUROCs for CMD and for GPD did not suggest that the tools were accurate at detecting these disorder groupings. It is worth noting that the original validation component was planned to be conducted in one-fifth of the original 1,100 sample whereas the reduced overall number of recruited study participants (n=618) actually meant that the validation analyses were conducted in a greater proportion of the total study population. A further possible limitation is that I validated the tools against very strictly applied M.I.N.I. criteria, including only participants who correctly followed all the skip rules. It is not clear how strictly other studies validating tools against gold standard interviews followed diagnostic criteria. However, my sensitivity analyses when using the maximum prevalence estimates also found that the tools performed poorly in this population.

A further possible limitation is that the present study was limited to two health centres in one district of Uganda. However, the socio-demographic characteristics of this study sample reflect those of patients attending other peri-urban health centres in the country and there is no reason to believe that prevalence, risk factors and screening tool validity would be different in other peri-urban health centres in Uganda.

In the study population, data on weight and height and latest CD4 cell count were gathered from self-reports which may have introduced a level of inaccuracy. It had been hoped to gather such data through clinical assessments but after discussion

with the clinic staff, it was felt that this additional work would have detracted time from routine tasks of clinic appointments. Data on ART status were also taken from self-report and for patients who responded as 'currently not on ART', the interviewers did not further explore whether a patient was ART naïve or had interrupted ART.

A further possible limitation of this study is that it did not exclude patients previously diagnosed with a mental disorder. It has been suggested that validation studies are at risk of bias by the inclusion of previously diagnosed patients, as this will lead to an overestimation of prevalence within a given study cohort and the identification by the screening tool of an increased number of cases compared to that which would be identified within a routine clinical setting [293]. However, assessments of mental ill-health are not routinely conducted among patients in HIV-care or in general outpatient clinics in peri-urban health centres in Uganda and formally recognised cases of mental disorders would be unusual. Therefore, the risk of bias by any potential inclusion of previously identified cases would be low.

The burden of mental illness, particularly MDD and mild suicidal risk, found among HIV-infected patients in this study is concerning. The current study focused on patients attending outpatient appointments, and while more than one-third of the study population reported CD4 <200 cells/ml, it is possible that they are a healthier population than HIV-infected individuals not attending clinic appointments for whom the burden of mental illness may be even greater. The impact of untreated mental illness on adherence to HIV treatment has been demonstrated in multiple studies [246]. However, there are few clear factors among data commonly collected in HIV care which could be used to identify patients at risk of CMD. The attractiveness,

therefore, of screening tools with few questions which can be self-administered or interviewer-administered in a number of minutes to each patient attending HIV care appointments or which could be used easily in home-based care visits is clear. Yet, the area of screening tool validation against gold standard diagnostic interviews has received little attention in the context of HIV in LMIC and particularly little among patients with extremely low CD4 counts, or in peri-urban and rural health centres treating patients with limited years of education and low levels of literacy. These health centres, manned by HIV clinic staff with little or no psychiatric training, are likely to become the mainstay of the majority of future services as countries move towards decentralised HIV care. More research is urgently called for to assess which screening tools are valid measures of mental illness among HIV-infected patients in these settings.

In this study, I found a substantial burden of mental ill-health among HIV-outpatients in Uganda with women, younger individuals and those not yet on ART slightly more likely to have CMD. This is important information for targeting mental health screening, management and referrals within HIV-care programmes. However, compared to the M.I.N.I. Plus, neither the CESD nor Kessler's scale reliably detected CMD or GPD, and vastly overestimated prevalence. I do not recommend their use in HIV clinics in Uganda.

Chapter 6 ART programme monitoring tools

This chapter describes the background, aim, methods and results of a cross-sectional study I undertook among ART programmes in Malawi, Uganda, the Ukraine and Tanzania. The aim was to compare the implementation by national Ministries of Health (MoH) of tools recommended internationally to monitor the health of the population on ART and to compare other outcome measures used to assess the health status of the treated population. A secondary aim was to discuss challenges arising from monitoring the health of the HIV-infected population on ART using currently recommended or collected indicators.

6.1 Background

The outcome measures used to assess and report on the health of the treated population are not homogenous, as was seen in Chapter 2. The reasons for the lack of uniformity in reporting methods may be, in part, due to heterogeneous reporting requirements of different ART treatment programmes. Programme funders have their own reporting requirements and MoH also require reports on the status of their national care programmes. In 2008, it was not known what monitoring systems were being used to assess the health of the treated population in different treatment programmes in LMIC.

When the number of patients on ART in LMIC were few, clinic staff and programme managers initially monitored the health status of the population in their care by

manually aggregating data from individual patient treatment cards and sending reports to programme funders and MoH [294]. Subsequently, as the number of patients in care grew, paper-based clinic registers were introduced and remain in practice. Upon entry into an HIV care programme, each patient is assigned one line in the clinic register across which data on their health status at HIV enrolment, ART initiation and follow-up visits are entered. Programmatic monitoring became, and remains, based on extracting and aggregating data from the register and reporting on patients in care, in the form of totals, proportions, means and medians, at regular intervals [294]. For example, data are reported on the proportion of the population in a treatment programme alive and on first line therapy 12 months after initiating ART [295]. These data are called 'indicators', defined as a brief proxy measure that represents summary information and that is capable of measuring changes [296]. In LMIC, indicators for monitoring reports are usually calculated manually from the paper-based register, as electronic record systems are rare. For example, 95% of sites visited by a MoH Team in Malawi employed paper-based reporting [297]. Indicators are reported on the cumulative number of patients in care in cross-sectional monitoring reports. Additionally, to assess the long-term progress of groups of patients in care, a unique monitoring system has evolved with the creation of life-long reporting cohorts, to be monitored continuously over time. A cohort is derived by grouping patients who enrol in the ART register during, for example, the quarter January – March. Indicators are calculated for this cohort routinely throughout the life-time of their follow-up. For patients who enrol in the following quarter, another reporting cohort is formed and indicators relating to their follow-up are calculated over time.

Monitoring reports aim to use a small number of key indicators to assess the quality

of health care services and measure the effectiveness of the response to HIV [298] [299]. Indicators have different uses. For example, they can serve to evaluate the effectiveness of country-wide programmes by assessing increases in ART coverage. Within ART programmes, they can be used to track patient status over time, to detect immediate problems including increased mortality rates and to inform resource allocation choices. For donors, indicators assess compliance with their guidelines, ensure accountability for funds and serve to guide further programme funding decisions.

The number of stakeholders involved in various aspects of HIV care, including the WHO, UNAIDS, PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), has resulted in a plethora of guidelines, recommendations, glossaries, tools and frameworks on how best to monitor HIV programmes, and the generation of a wealth of similar yet slightly different monitoring indicators in LMIC [300] [300] [301] [299] [302] [303] [304] [305] [306] [69, 307, 308]. Further, early warning indicators (EWI) exist to monitor how well sites are performing in relation to minimising the risk of HIV drug resistance (HIVDR) [300]. However, there is little consensus on priority indicators recommended by international agencies. Table 6.1 shows indicators relating to outcomes on ART, recommended by major international funders of ART programmes (PEPFAR and the GFATM) and by the WHO in 2008 [69, 307, 308]. However, only one indicator specific to the outcome of patients in ART care is commonly recommended: *the proportion alive and on treatment 12 months after ART initiation* and even this is subtly different for the three organisations. Indicators relating to, for example, on-time drug pick-up, concurrent prophylaxis, morbidities, and screening and treatment for Tuberculosis (TB), are prioritised differently by international organisations. A multitude of

Table 6.1 Comparison of indicators recommended to monitor ART care in LMIC as at end 2008 (similar indicators are across the same rows)

WHO	Global Fund	PEPFAR
Survival at 6,12,24 months after initiation of ART	Percentage of adults & children known to be on treatment after 12 months on ART	Percentage of persons still alive after 6,12,24 months on ART
		Percentage of deaths attributable to HIV
Percentage of patients lost to follow-up after 12 months on ART		
Percentage of persons starting first-line ART who are still on a recommended first-line ART regimen 12 months later		
Distribution of reasons for drug substitution, regimen switching, termination/interruption, & poor adherence		
Percentage of persons who attended all appointments during a year		
Percentage of individuals who demonstrate ≥90% pill count adherence		

WHO	Global Fund	PEPFAR
Percentage of persons picking up all prescribed drugs on time during a quarter	Number and percentage of facilities offering ART that meet national targets for ART patient on-time drug pick-ups	
Percentage of quarters in which there were no drug stock outages	Number and percentage of health facilities dispensing ART that experienced stock-outs in the last 12months	
Percentage of patients on ART whose functional status is working at 6,12,24months		
Median CD4 increase & percentage with CD4 count ≥200 cells/mm^3 at 6,12 months on ART		
Percentage with side-effects, OIs, other problems		Percentage of patients on ART with AIDS related morbidity

WHO	Global Fund	PEPFAR
		Percentage of chronically ill patients with severe pain & symptoms who report that their pain & symptoms were controlled Quality of live for PLWHA
Number of patients on Cotrimoxazole (CTX), Fluconazole, Isoniazid prophylaxis at end of month	Number and percentage of HIV positive TB patients who received CTX preventive therapy	Percentage of HIV positive patients who are given CTX preventive therapy
Number and percentage attending HIV treatment and care services screened for TB symptoms and diagnosed with TB	Number and percentage receiving HIV treatment and care services screened for TB symptoms	Percentage of clients attending HIV testing and counseling who test positive and are screened for TB
Number and percentage of ART patients simultaneously on TB treatment within last year	Number and percentage of HIV positive incident TB cases that received treatment for TB and HIV	Percentage of HIV-positive incident TB cases that receive treatment for TB and HIV

additional indicators (not shown) are recommended to report on the number of patients accessing ART and the number of additional services provided to patients on ART (e.g. the GFATM requests the number and percentage of health facilities which offer ART and also provide psychosocial support services, while PEPFAR request reporting on the number of individuals receiving ART with evidence of severe malnutrition who receive food and nutritional supplementation). These indicators, too, are prioritised differently by different organisations. In attempts to consolidate the plethora of indicators, UNAIDS created an online indicator registry. In 2008, this contained over 200 indicators from various funders and international health bodies relating to HIV care, including 55 specific to ART care [309]. Clinic staff members at the forefront of care find themselves burdened with a complex matrix of monitoring reports, particularly when programmes are supported by multiple funders [72]. The difference in recommendations highlights an uncertainty regarding which indicators are most useful for routine monitoring.

Recognising the complexity of HIV programme monitoring, international organisations and national governments have committed to developing a common monitoring and evaluation system throughout a country with appropriate mechanisms to assess progress [310] [311]. In 2006, guidelines were published by the WHO for monitoring patients on ART, and templates made available online of standardised tools to collect and report such data [69]. Further work has included the publication by UNGASS in 2008 of 25 Core and 15 Recommended Indicators for HIV care, two of which relate to assessing the health of patients on ART [295, 309]. This has been the most comprehensive step in ART monitoring standardisation to date.

Given the increasing labour-intensiveness of monitoring systems, it is vital that only the most relevant indicators are collected. It is important, therefore, to understand what data are currently collected in HIV programmes in LMIC. Therefore, firstly, having previously reviewed the different outcomes reported by individual studies on patients in ART treatment cohorts (Chapter 2), I aimed to conduct a review of the literature to identify comparisons of which indicators or outcome data are reported nationally in LMIC. I also aimed to review which indicators are recommended to be reported by authors in published literature. Finally, I undertook a cross-sectional study to compare the implementation of the WHO and UNGASS recommended monitoring tools used to assess the health of the treated population in four LMIC.

6.2 Review

The main aim of the review was to synthesise the information from studies comparing which indicators or outcome data are reported to national MoH in LMIC ART programmes. A secondary aim was to synthesise recommendations in published articles on which indicators are useful to collect to assess the health of the treated population.

6.2.1 Search strategy

My search strategy involved two stages. Firstly, I used broad search criteria to identify English language studies published since the advent of ART in 1996 which compared or commented on monitoring outcomes or indicators used to assess the health of the population in ART care in LMIC. I searched Medline through PubMed. The search was last updated on 16-11-2013. I used the following search terms resulting in the number of references noted to capture programmatic monitoring of patients in HIV care:

i) terms related to HIV or AIDS: HIV or AIDS or HIV/AIDS (147, 692 references)

ii) combined with terms relating to monitoring: quality indicators, health system indicators, epidemiological monitoring (1,178 references)

Having read the 1,178 titles, I excluded titles that described monitoring of or indicators used: in HIV prevention programmes; to assess the quality of services provided; titles which described patient monitoring techniques (e.g. telephone appointments versus face-to-face appointments), or titles which described indicators used the patient-level (e.g. to measure quality of life, to predict infections, or predictors of adherence).

Thirty-six titles remained. Having read these abstracts, I selected articles which described or commented on indicators or monitoring strategies for the population of patients in ART care, and were not related to indicators or outcomes used in clinical trials, were not specific to certain population groups (e.g. prisoners, or patients on methadone), and did not describe indicators for use at the patient-level (e.g. indicators of quality of life). Four articles remained, 3 in English, 1 in Spanish (Table 6.2) [312-315]. I was unable to access the full text of the Spanish article thus the review is based on data extracted from the abstract.

6.2.2 Review results

At the time of the updated literature search, no comparison of national monitoring tools used in ART programmes in LMIC was identified. One of the identified articles proposed a series of indicators derived after conducting a literature review of opinion articles. The article which I was unable to retrieve described an expert panel review and proposed a set of indicators. One article described a study

Table 6.2 Articles recommending ART programme monitoring tools or indicators

Author	Article aim	Methods	Results
Catumbela [312]	to identify a core set of indicators for assessment of HIV/AIDS patients	literature review of organisations and authors proposing HIV care indicators	65 indicators identified, including 15 relating to outcomes in care, 16 to monitoring, 12 to therapy indicators
van Wichmann (GESIDA) [313]*	to design quality of care indicators to be used in HIV units to identify results and introduce improvement measures	committee of health professionals discussion, review by external reviewers, invited on public website for comments	66 indicators discussed, reduced to final 22: a number relating to results in HIV care, of which a number relate to the follow-up of patients on ART and mortality rates. Justifications were given for selected indicators as a measure of quality, dimension evaluated, calculation methods, standard to be achieved and commentary on the validity
Liu [314]	to test a hypothesis that incrementally setting quantitative targets for key M & E indicators would facilitate AIDS policy implementation in	core indicators were developed and implemented '07 - '09, with incrementally-derived targets	Indicators relating to being on ART were: number on ART with follow-up visits, proportion with CD4 count monitoring, proportion with viral load monitoring. Setting targets for core indicators facilitated implementation of national AIDS programme

Author	Article aim	Methods	Results
	China		
Hong [315]	to assess whether 5 of the WHO EWI HIVDR should be monitored in Namibia	data of 5 WHO EWI HIVDR were extracted from 9 sites	Supports monitoring of the following 3/5 WHO EWI HIVDR: proportion of sites initiating 100% of patients on first-line regimen, proportion of sites with ≤20% LTFU, proportion of sites with 0% switched to second-line. Patient retention on first-line at 12 months, on-time drug pick-up and continuity of ART drug-supply were not deemed to be feasible to report

Note: * abstract only retrievable

evaluating the feasibility of collecting some of the WHO early warning indicators (EWI) of HIV drug resistance (HIVDR) in Namibia, and the final article described the use of indicators with quantitative targets as a measure of assessing ART roll-out in China.

Similarities or commonalities of proposed indicators were seen in the following three areas:

Retention in care

i) Percentage of patients initiating ART at the site who are still on ART after 12 months; and whose initial ART regimen was changed during the first 12 months to a regimen with a different drug class (target: 0%),

ii) Proportion of patients on anti-retroviral treatment who survived and remained in treatment for 12 months

iii) Follow-up of patients on ART; mortality of patients on ART (abstract article)

Viral suppression

i) Proportion of ART-naıve patients whose viral load was suppressed during the first 6 – 12 months of treatment

ii) Undetectable HIV viral load at 48 treatment weeks

Continuity of care

i) Percentage of patients initiating ART at the site who are LTFU during the 12 months after starting ART (target: <20%),

ii) Proportion of patients with continued care

The following additional indicators were recommended by individual articles:

i) Percentage of patients initiating ART at the site who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen (target: 100%)

ii) Proportion of patients receiving ART who have been monitored for viral load at least once a year to monitor treatment failure

iii) Proportion of patients receiving ART monitored for CD4 cell count at least once a year to determine treatment effectiveness

iv) Proportion of patients with previous ART regimen change for whom reason for change in regime is documented

v) Proportion of patients on ART with at least 95% (good) reported adherence on last visit

vi) Proportion of patients on Cotrimoxazole prophylaxis with at least 95% reported adherence on last visit

vii) Proportion of HIV-positive patients in HIV care or treatment (pre-ART or ART) who started TB treatment

viii) Proportion of HIV-positive clients given treatment for latent TB Infection

6.2.3 Review discussion

Few articles were available for this review and the full text was not available for retrieval from one of the articles recommending a list of indicators. This compromises the ability to establish clear recommendations to monitor ART care. However, even among expert panels, there remains little consensus on which data are important to collect from ART programmes. Moreover, no articles compared across LMIC the indicators which are reported to national MoH. Despite international recommendations, the priorities of LMIC national ministries of health remain unclear. This is an important area of research as it is ultimately national

MoH who are responsible for the patients in their countries. Therefore, I designed a cross-sectional study to compare outcomes requested by national MoH to assess ART programmes in four LMIC.

6.3 Aim, objectives and outline

The aim of this study was to compare the degree to which internationally recommended monitoring tools and indicators used to assess the health of the ART treated population had been incorporated into national monitoring systems by the MoH in Malawi, Uganda, the Ukraine and Tanzania. The secondary aim was to discuss challenges arising from monitoring the health of the HIV-infected population on ART using these currently recommended or collected indicators. The objectives were to:

• compare across the four countries the implementation in 2008 and 2010 and frequency of use of the WHO and UNAIDS recommended ART programme monitoring tools in national monitoring systems,
• compare the consensus with the international recommendations on the type of data collected in MoH reports and the inclusion of data required to calculate the UNGASS indicators,
• compare the concordance with the four countries of additional data collected, focusing on the use at end 2010,
• compare the age stratification used in reports, and to
• discuss the internal, external, content and context validity and the predictive value over time of key indicators which were collected in the national monitoring reports.

This work will provide a summary to national MoH and international researchers of similarities and differences in current practice relating to the monitoring of the

health of patients in ART care. Commonalities across countries will highlight which indicators are perceived by national MoH to be the most important.

6.4 Methods

6.4.1 Settings and tools to be compared

National monitoring tools were compared from countries selected by convenience sampling. This was based on countries with partner organisations within the EfA collaboration who had staff capacity to support this study. Therefore, this study compared monitoring systems recommended by the MoH in Malawi, Uganda, the Ukraine and Tanzania.

I compared the implementation of the WHO template tools recommended in 2006 and the UNGASS Core and Recommended Indicators, proposed by organisations working through UNAIDS in 2008. The tools and indicators were accessible online to MoH in LMIC and were the most up-to-date international recommendations for monitoring the health of the treated population. I did not examine the use of indicators recommended by individual donors (e.g. PEPFAR or GFATM) as these requirements are in addition to national MoH requirements, and would only apply to programmes funded by certain donors.

Comparisons with the recommended tools and indicators were conducted with tools designed for use in ART programmes by the MoH in each country. I compared the recommended tools with MoH tools in use in 2008 and 2010. These times were selected to follow on from the announcement of the WHO tools in 2006 and the UNAIDS recommendations in 2008 and for national systems to have incorporated the tools and indicators.

6.4.2 Gathering monitoring tools

During visits to each country, I met the ART programme Monitoring and Evaluation (M & E) officer representatives of the MoH: Andreas Jahn (Malawi), Wilford Kirungi and Norah Namuwenge (Uganda), the heads of Odessa and Donestk regional AIDS centres (the Ukraine), and had electronic communications with Geoffrey Somi (Tanzania) due to travel logistics. I discussed the rationale for and the aims and objectives of the study and sought and obtained consent from the MoH for their monitoring tools to be compared. From each MoH representative, I obtained copies, as available of: individual treatment cards, ART registers, and cross-sectional and cohort monitoring reports. I gathered copies of the data-collection and reporting tools which were in use in national ART programmes at the end of 2008 and 2010.

I obtained copies of the international monitoring tools and indicators by internet download from the HIV M & E sections on the websites of the WHO and UNAIDS [69, 316].

6.4.3 Analytical methods

Firstly, I examined the frequency of requested reporting by each MoH and whether or not the MoH was implementing the internationally recommended monitoring tools. Secondly, for each tool, using tables created in Microsoft Excel, I examined the consensus with the international recommendations on the type of data collected in the MoH reports, and the inclusion of data required to calculate the UNGASS indicators. I grouped data items for comparisons into categories broadly representing patient status at ART initiation, outcomes on therapy and treatment received. I compared the tools used in the four countries at the end of 2008 and 2010. Thirdly, for each tool, I compared the concordance with the four countries of

additional data collected, focusing on the use at the time of data-collection at the end of 2010. As no template tool was available for the cross-sectional reports, I examined the collection of UNGASS-related data in the MoH cross-sectional reports and compared data items collected across the countries. Where additional data-items were collected by a country without being recommended in the international tools, this was noted. Finally, I compared the age stratification used in reports.

I discuss the implications of using key indicators which were collected in the national monitoring reports requested by the MoH in the four countries. I focus the discussion on the internal, external, content and context validity of monitoring indicators and their predictive value over time.

6.5 Results

6.5.1 Recommended and available monitoring tools

To monitor the health of the population on ART, the WHO 2006 guidelines recommended the use of the following tools:

i) individual treatment cards to gather information on patients in care,

ii) ART registers to gather information of the patient-population in care,

iii) cross-sectional monitoring reports to report aggregated information on the population in care, and

iv) cohort monitoring reports to report aggregated information on reporting cohorts of patients in care

Template tools for a patient treatment card, ART register and cohort monitoring report were accessible from the website of the WHO. No template was available for cross-sectional reporting, despite this being recommended in the WHO guidelines [69].

The following UNGASS indicators were the only two that specifically related to the health of patients in ART care: survival at 12 months (defined by UNGASS as the percentage of adults and children with HIV known to be on treatment 12 months after initiation of ART); TB incidence (percentage of estimated HIV positive incident TB cases that received treatment for TB and HIV).

For all four countries, I accessed patient monitoring cards, ART registers, and cross-sectional and cohort reports, with the exception of the 2008 Malawian ART register which was not available.

6.5.2 Implementation of recommended monitoring tools

In 2008, Malawi, Uganda and Tanzania were using all the tools recommended in the 2006 guidelines to monitor the health of patients on ART. The Ukraine was using only a patient master card and a cross-sectional report. While all four countries were using a cross-sectional monitoring report, reporting frequency varied between quarterly reporting in Malawi to the more labour-intensive monthly reporting in the Ukraine and Uganda. Tanzania reported both quarterly and at monthly intervals. Malawi collected reports on the health of treated cohorts at 12-monthly intervals while Uganda and Tanzania reported cohort outcomes at 6 months, then 12-monthly.

By 2010, all four countries were using all four types of ART programme data collection and reporting tools. The frequency of cross-sectional reporting was standardised, with reports completed quarterly, rather than monthly, in all countries. However, the frequency of cohort reporting continued to vary, with the Ukraine reporting at the same 12 month frequency as Malawi, while the frequency of cohort reporting in Uganda and Tanzania remained unchanged.

6.5.3 Concordance in the number of recommended data collected and reported

Table 6.3 shows the number of data items recommended for collection in the international template tools. Twenty-nine items were recommended to be collected in the patient master card and 14 items were recommended for collection in each of the ART register and cohort report. Table 6.3 also shows the discordance between the number of items recommended and the number collected and reported across the four countries. The proportion of the template data collected in each country ranged from 24% to 100% in 2008, and from 36% to 97% in 2010. For example, the template ART register recommends 14 data-items, but in 2010, Malawi collected only 6 (43%) of the items recommended in the template.

Across all the tools, by 2010, Uganda, the Ukraine and Tanzania collected individually between 71% and 97% of recommended data. However, common use across all the countries of the same recommended data was low both in 2008 and 2010, with the exception of the 2008 ART register. The available 2008 ART registers from Uganda and Tanzania showed a high degree of concordance in recommended data in and across the two countries. However, in the 2008 master cards and cohort reports, only 10% and 21% of the recommended data were commonly collected in all four countries. Across all the registers with available templates, despite progress towards collecting standardised data by 2010, less than half of the recommended data remained commonly collected in all four countries: 48% in the patient master card, 29% in the ART register and 29% in the cohort reports.

Table 6.3 Number of data-items in internationally recommended template tools, number (%) of recommended data-items collected in Malawi, Uganda, the Ukraine and Tanzania (2008, 2010), and number (%) of recommended template data-items commonly collected

		2008	2010	2008	2010	2008	2010	2008	2010
Data-collector	**Number of data-items collected**	**Patient master card**		**ART register**		**Cross-sectional report**		**Cohort report**	
Recommended template tool	**Total number of data-items**	29		14		Template not available		14	
Malawi	**Number (proportion) of template data-items collected**	12 (41%)	20 (69%)	Data not available	6 (43%)	-	-	5 (36%)	5(36%)
Uganda	**Number (proportion) of template data-items collected**	27 (93%)	28 (97%)	13 (93%)	12 (86%)	-	-	13 (93%)	10 (71%)
Ukraine	**Number (proportion) of template data-items collected**	7 (24%)	22 (76%)	Tool not in use (0)	10 (71%)	-	-	Tool not in use (0)	10 (71%)
Tanzania	**Number (proportion) of template data-items collected**	21 (72%)	24 (83%)	14 (100%)	12 (86%)	-	-	12 (86%)	13(93%)
All countries	**Number (proportion) of template data-items commonly collected in all countries**	3 (10%)	14 (48%)	13 (93%)*	4 (29%)	3	1	3 (21%)^	4 (29%)

*2009 Malawi unavailable & Ukraine not using register therefore 2-country consensus comparison;^No cohort reporting done in Ukraine 2008 therefore 3-country comparison

6.5.4 Concordance in type of data recommended with those collected and reported

Table 6.4 shows the concordance between types of data relating to ART care recommended in the Template Master Card (TM) and Template ART Register (TR) with items in the equivalent MoH tools in 2008 and 2010. Table 6.5 shows the concordance between types of data relating to ART care recommended in the Template Cohort (TC) reporting tool with data collected in the MoH cohort reporting tools, and additionally shows data collected in MoH Cross-Sectional Monitoring Reports (CS) in 2008 and 2010.

In the master cards in 2008, there was much discordance between recommended data and those used nationally. The only commonly collected template data were patient demographics, weight (and height for children), and WHO stage or CD4 count at enrolment into care. By 2010, though many data at enrolment were not recorded by all countries, a far larger degree of consensus was observed. Of note, key recommended primary outcome data relating to deaths, transfers-out and treatment interruptions and switches were commonly collected across all countries. Many secondary outcomes were also commonly reported by 2010, including for example information on TB status at each appointment, ART adherence and OI prophylaxis and diagnosis.

Within the ART register, in 2008 Uganda and Tanzania, the only countries with available data or using the tool, collected all the recommended data relating to ART initiation, outcome and treatments, with the exception of Isoniazid prophylaxis (IPT) which was not collected in Tanzania at the time. By 2010, all four countries were collecting the recommended ART initiation data on demographics, ART start date

Table 6.4 Concordance between types of data-items recommended in Template Master Card (TM) and Template ART Register (TR) data-collection tools with data-items used in Malawi (Mw), Uganda (Ug), the Ukraine(Ur) and Tanzania (Tz), (2008, 2010)

	2008	2010	2008	2010
Type of data-item	**Patient master card**		**ART register**	
Enrolment information				
*Patient demographics (sex, age) **TM, TR**	Ur, Mw, Ug, Tz	Ur, Mw, Ug, Tz	Ug, Tz	Ur, Mw, Ug, Tz
Transfer-in status **TM, TR**	Mw, Ug, Tz	Mw, Ug, Tz	Ug, Tz	Mw, Ug, Tz
Prior ART exposure **TM**	Ug, Tz	Mw, Ug, Tz	-	-
Date confirmed HIV positive, date enrolled to care **TM**	Ug, Tz	Ug, Tz, Mw	-	-
HIV status of family members **TM**	Ug	Ug	-	-
Date eligible for ART, date ready to start ART **TM**	Ug, Tz	Ur, Ug, Tz	-	-
Reason for ART eligibility **TR**	-	-	Ug, Tz	Mw, Tz
*ART start date **TM, TR**	Mw, Ug, Tz	Ur, Mw, Ug, Tz	Ug, Tz	Ur, Mw, Ug, Tz
ART type **TM, TR**	Ur, Mw, Ug	Ur, Mw, Ug	Ug, Tz	Ur, Mw, Ug, Tz
Weight & height (children) **TM, TR**	Ur, Mw, Ug, Tz	Ur, Mw, Ug, Tz	Ug, Tz	Ur, Ug, Tz
WHO stage or CD4 count **TM, TR**	Ur, Mw, Ug, Tz	Ur, Mw, Ug, Tz	Ug, Tz	Ur, Ug, Tz
Functional status **TM, TR**	Ug, Tz	Tz	Ug, Tz	Ug, Tz
Primary Outcomes				
*Death + date **TM**	Mw, Ug	Ur, Mw, Ug, Tz	-	-
*Discharge/transfer-out and date **TM**	Mw, Ug	Ur, Mw, Ug, Tz	-	-
*Regimen interruption/stopped ARVs and date **TM**	Mw, Ug, Tz	Ur, Mw, Ug, Tz	-	-
Regimen switch/change and date **TM, TR**	Mw, Ug	Ur, Mw, Ug, Tz	Ug, Tz	Ur, Mw, Ug, Tz
*Lost **TM**	Mw, Ug	Mw, Ug, Tz	-	-
Appointment information				
Weight, height (for children) **TM**	Mw, Ug, Tz	Ur, Mw, Ug, Tz	**-**	**-**
*TB status **TM**	Ug, Tz	Ur, Mw, Ug, Tz	**-**	**-**
Adherence **TM**	Mw, Ug, Tz	Ur, Mw, Ug, Tz	**-**	**-**
OI diagnosis, treatment **TM**	Ug, Tz	Ur, Mw, Ug, Tz	-	-
OI prophylaxis **TM, TR**	Mw, Ug, Tz	Ur, Mw, Ug, Tz	Ug, Tz	Ur, Ug, Tz
INH prophylaxis/treatment **TR**	-	-	Tz	Ug, Tz
TB treatment **TR**	-	-	Ug, Tz	Ur, Ug, Tz
WHO stage **TM**	Ur, Ug, Tz	Ur, Ug, Tz	**-**	**-**
CD4 count or percent **TM, TR**	Ur, Ug, Tz	Ur, Ug, Tz	Ug, Tz	Ur, Ug
Functional status **TM, TR**	Ug, Tz	Ur, Ug, Tz	Ug, Tz	Ur
Regimen type **TM**	Ur, Tz	Ur, Mw, Ug, Tz	**-**	**-**
Pregnancy status **TM, TR**	Ug, Tz	Ur, Ug, Tz	Ug, Tz	Ur, Ug, Tz
PMTCT **TM**		Ur, Ug	**-**	**-**
Duration of time on ART **TM**	Ug	Ur, Ug	**-**	**-**
Side –effects **TM**	Ug, Tz	Mw, Ug	**-**	**-**

*items used to calculate UNGASS indicators relating to the number alive at 12 months and TB status

Table 6.5 Concordance between types of data-items recommended with data-items used in Template Cohort Report (TC) and in Cross-Sectional Monitoring Reports (CS) in Malawi (Mw), Uganda (Ug), the Ukraine(Ur) and Tanzania (Tz), (2008, 2010)

	2008	2010	2008	2010
Type of data-item	**Cohort report**		**Cross-sectional report**	
ART initiation				
*Number registered for ART care (cumulative & this quarter)	-	-	-	Mw
*Number started on ART: in the original cohort **(TC)** : at beginning & at end of quarter : this quarter : cumulative : excluding transfer-ins	Mw, Ug, Tz - 	Mw, Ug, Ur, Tz - 	- Ug, Ur, Tz Ug, Ur, Mw Mw Tz	- Ug, Tz Ug, Mw Mw Tz
Number of transfers-in from another facility **(TC)**	Ug, Tz	Ug, Ur, Tz		
Number transferred-in on ART (cumulative and/this quarter)			-	Mw, Tz
Number of Transfers-out from this cohort **(TC)**	Mw, Ug, Tz	Mw, Ug, Ur, Tz		
Net current cohort **(TC)**	Ug, Tz	Ug, Ur, Tz		
Number restarted on ART (this quarter & cumulative)			Ug	Mw
Number starting ART by reason: WHO stage/CD4 count (cumulative & this quarter)			Mw	Mw
Number started on ART with TB (cumulative & this quarter)			Mw	Mw
Number started on ART with KS (cumulative & this quarter)			-	Mw
Number of baseline CD4 counts done (and median CD4) for person started on ART in last month			Ug	
Number on any first-line/second-line regimen (this quarter)			-	Tz
Primary outcomes				
*Current number on ART at end of reporting period : by sex and age : by sex, age and funder			Mw, Tz, Ug	Mw Tz, Ug Ur
*Number not on ART at end of quarter due to death/ default/transfer-out/ stopping ART (cumulative)			Mw, Ug, Ur	Mw, Tz
*Number/percentage of cohort alive and on ART **(TC)**	Mw, Tz, Ug	Mw, Ur, Ug, Tz		
*Number dead; stopped treatment **(TC)**	Mw, Ug	Mw, Ug, Ur, Tz		
*Number lost to follow-up **(TC)**	Mw, Ug	Mw, Ug, Tz		
Number died within 1/2/3/>3 months of ART (cumulative)			Mw	Mw
Number in need of ART and receiving/ not yet receiving ART				Ur
Secondary outcomes				

Number on original first-line regimen **(TC)**	Tz, Ug	Ug, Ur, Tz		
Number on alternative first-line regimen **(TC)**	Tz	Ur, Tz	Mw	Mw, Ur
Number on second-line **(TC)**	Tz, Ug	Ug, Ur, Tz		
Number on any/specific first-line regimen; on any/specific second line regimen (by sex and age) (by sex, age and by funder)			Mw, Ug, Tz Tz, Ug Ug	Tz, Ur/Mw, Ug Ug Ur
Total on any non-standard regimen			-	Mw, Ur
Number who switched			Ur	
CD4 median or proportion=>200 (optional) **(TC)**	Tz, Ug	Ug, Tz		
Functional status **(TC)**	Tz, Ug	Ur, Tz		
Number with side-effects (cumulative)			Mw	Mw
*Number with TB: assessed (this quarter) : confirmed (cumulative/this quarter) : on treatment (cumulative/this quarter)			-	Ug Mw, Ur Mw, Ug
Number of IDUs and number with hepatitis				Ur
Adherence: number picking up ART 6/6 months **(TC)** : number picking up ART12/12 months **(TC)** : based on drug pick-up in previous months : based on missed doses this quarter	Tz, Ug Tz, Ug	Tz -	 Ug Mw	 Mw

*items used to calculate the UNGASS indicators relating to the number alive at 12 months and TB status

and regimen type. Remaining recommendations at initiation on WHO clinical stage or CD4 count, weight, height for children and functional status and recommended data at follow-up were recorded to varying degrees.

In the 2008 cohort reports, recommended primary outcome data which are essential to calculate the 'survival' indicator as accurately as possible data were not commonly reported. Only in 2010 did the three African countries report the percentage of the original cohort alive and on ART, distinguishing between patients who had died, stopped treatment or become lost to follow-up. The Ukraine did not report on losses to follow-up when calculating this key indicator. Further differences were observed in the reporting on secondary outcomes such as drug switches and adherence.

No template was available for the cross-sectional reports and the variability in data collected in the reports, both in 2008 and 2010, was high. Variation was in part due to reporting being done on the cumulative number of patients in care or on the current group of patients in care. Furthermore, while data on, for example the number of patients alive and on ART at the end of the reporting period, were recorded in all countries, they were not commonly disaggregated by sex and age. While the number of patients still on a first-line regimen was recorded in all countries, only Malawi and the Ukraine additionally reported the number on alternative first-line or non-standard regimens. Data on adherence was reported in Malawi and Uganda, but it was calculated differently in the two countries, based on missed doses in Malawi and drug pick-up in Uganda.

6.5.5 Concordance with additional data-items

Table 6.6 shows the types of data, additional to those items recommended in the

Table 6.6 Discordance in additional data-items not specifically recommended but used in master card (MC), ART register (AR) and cohort report (CR) in Malawi (Mw), Uganda (Ug), the Ukraine(Ur) and Tanzania (Tz), (2008, 2010)

	2008	2010
Type of data-item	**All reports**	
Enrolment information		
ART funding source **(MC)**	Ur, Ug	Ur
TB identification number **(MC)**		Tz
Route of transmission **(MC)**	Ur	
ART initiation		
Date eligible for ART, date ready to start ART **(AR)**		Ur
First-time initiation/Re-initiation/prior ART exposure **(AR)**	Tz	Mw, Tz
Occupation **(AR)**		Mw
Free drugs or paying for drugs/funding source **(AR)**	Ug	Ur
CD4 count or percent **(MC)**	Ur, Ug, Tz	Ur, Mw, Ug, Tz
Viral load **(MC)**	Ur	Ur
TB & KS status **(MC, AR)**	Mw **(MC)**	Mw **(MC),** Mw **(AR)**
KS status **(MC)**	Mw	Mw
Pregnancy status **(MC, AR)**	-	Mw **(MC),** Ug **(MC),** Mw **(AR)**
Absolute lymphocyte count **(MC)**	Ur, Ug, Tz	-
PMTCT **(MC)**	Mw	-
Number on 1st line regimen at beginning of period (including subs) **(CR)** Number on 2nd line regimen at beginning of period (inc switch) **(CR)** Fraction of patients with CD4=>150cells **(CR)** Median CD4 at beginning of period **(CR)** Number with CD4% not classified as severe at beginning of period **(CR)**	-	Ug
Primary Outcomes		
*Adverse outcome: death **(AR)**	Ug, Tz	Ur, Mw, Ug
Death within 1/2/3/>3 months of ART **(AR)**		Mw
*Lost to follow-up/default **(AR)**	Ug, Tz	Ur, Mw, Ug
*Stopped ART **(AR)**	Ug, Tz	Ur, Mw, Ug
*Transferred out **(AR)**	Tz	Ur, Mw, Ug
Appointment information		
Number of times restarting ART after default/stop> 2 months while at this site: 1st, 2nd, 3rd, 4th restart **(AR)**		Mw
Clinical stage **(AR)**		Ug
Number with CD4 count done **(CR)**	-	Ur
Number/proportion of adults with CD4 count equal to or above threshold **(CR)**	Tz (>200 cells) Ug (>200cells)	Ur (>350cells) Ug (>250 cells) Tz (>200 cells)
Number of infants, young children and children with CD4 above threshold /not classified as severe **(CR)**	Ug	Ur, Ug
*TB status **(AR)**		Ur, Ug

TB prophylaxis **(MC)**	Tz	Tz
Diflucan / Fluconazole **(AR)**	Tz	Ug
Heamoglobin **(MC)**	Tz	Ur, Tz
Viral load **(MC, AR)**	Ur **(MC)**	Ur **(MC),** Ur **(AR)**
Number with viral load done and number with VL < 75 copies/ml **(CR)**	-	Ur
Child MUAC **(MC)**		Ug
Weight, child height **(AR)**	Tz	Ur, Ug
Exposed infants: feeding practices at 2 months, CPT started by 2 months, HIV result **(MC)**		Ug
Nutritional status, supplements needed/given **(MC)**	Tz	Tz
IDU status & Hepatitis status **(MC, AR)**		Ur **(MC),** Ur **(AR)**
Adherence: missed drug pick-up **(AR)** : missed appointment **(AR, CR)** : not specified **(AR)** : good, moderate, poor **(CR)**	Ug Tz **(AR)**	Ug Ug **(AR),** Ug **(CR)** Ur Ur
Number who regularly and promptly received ARV **(CR)**		Ur

templates, collected and reported in MoH monitoring tools, and their discordant use across the countries. For example, in the 2010 patient master card, data relating to TB status in Malawi and to viral load in the Ukraine were collected at ART initiation although these were not the template data and were not recorded elsewhere. At follow-up appointments, data were collected in the master card in Uganda on child's mid-upper arm circumference and in the Ukraine on intravenous drug use status. Similarly, in the 2010 cohort reports, Uganda, the Ukraine and Tanzania report on the proportion of adults with CD4 count above a certain threshold. However, the threshold in all three countries was different, from 200 cells in Tanzania, to 250 cells in Uganda, to 350 cells/mm^3 in the Ukraine. Malawi recorded information specifically on the time since ART when deaths occurred, though this was not recorded elsewhere.

6.5.6 Consensus on paediatric age groupings

In the absence of ART outcome indicators specific to paediatric populations, the tools used to report on those in care captured data for the combined clinic population and the population disaggregated by age. However, different age bands were used across the tools. For example, when reporting on the number of patients on ART in the 2010 cross-sectional reports, infants were categorised as those aged less than 17 months in Malawi, less than 12 months in Uganda and Tanzania, and aged 0 – 3 years in the Ukraine. Children were categorised broadly as 18 months – 14 years in Malawi, as 1 – 4 years and 5 – 14 years in Uganda and Tanzania, and as 4 – 10 and 11 – 14 years in the Ukraine. Within the same cross-sectional reports, data on the number on first and second-line regimens were disaggregated into broad categories of 'children' in Malawi and those aged 0 –14 years on Uganda, Tanzania and the Ukraine. The cohort reports were disaggregated less by age.

In Malawi, a separate cohort survival analysis for all children aged less than 15 years was reported at 12 months but at no other time, while Tanzania did not disaggregate the cohort reports by age. Uganda reported on the baseline and follow-up median CD4% for children less than 5 years of age at all cohort reporting times while the Ukraine reported on the number with CD4% above specified thresholds for children aged 0 - 12 months, 12 - 35 months and 36 months and above.

6.6 Discussing challenges with ART programme monitoring tools

This section discusses the challenges arising from monitoring the health of the HIV-infected population on ART using the observed recommended or collected indicators. Key challenges of certain indicators are described in Table 6.7. I discuss these challenges in more detail below.

6.6.1 Internal validity

Programme managers need to be able to rely on monitoring indicators to make correct inferences about the health of the treated population to inform patient care. However, data inaccuracies will compromise this ability. For example, an audit of routinely reported data in Malawi indicated that 28% of sites inaccurately reported the *cumulative number of patients alive on ART* or the *number on first line regimen at end of quarter*. This resulted in a 5% and 12% undercount of the number of patients on ART, and on first line regimen, respectively [297]. Furthermore, an examination of ART databases in LMIC found nearly 11% of missing data for key variables, which would contribute to inaccurate indicators [317]. Manual monitoring systems used to report on ART care in LMIC are susceptible to incomplete data and data entry errors and the cohort monitoring system may be particularly at risk of data errors [72, 297, 317]. Cohort monitoring requires the creation, as patients initiate ART, of new reporting cohorts within an ART programme at specified

Table 6.7 Indicators commonly collected to monitor the health status of the treated population within HIV treatment and care programmes

ART programme indicator	Construct being measured	Validity
Number initiating ART at beginning of reporting period	Total number of patients newly initiating ART in a clinic during a specific reporting period	Fails to account for drug-experienced patients transferring, overestimating those in care and underestimating survival
Proportion of treated population alive and known to be on ART 6, 12, 24 months after ART initiation	Survival of treated population	Measures retention in care. High numbers of transfers out may underestimate country-wide retention. Absence of person-time denominator compromises details of length of survival after initiation. Absence of information on vital status for patients not returning for care biases survival estimates. Cross-programme comparisons highly susceptible to misinterpretation.

ART programme indicator	Construct being measured	Validity
Proportion of patients lost to follow-up 6 months after ART initiation	Retention in care	Resources available to trace the vital status of those lost to follow up vary between programmes making comparisons inappropriate.
Median CD4 cell count or percentage increase 6 months after ART initiation	Improvement in immunological status of treated population	Fails to take into account those no longer in care, who may have lower CD4 cell counts, overinflating population CD4 cell counts Complex numerical calculations routinely produced from paper-based systems may lead to data inaccuracies.
Proportion demonstrating >90% adherence by self-report	Adherence to treatment regimen	May be influenced by expectation of socially desirable answer. Challenging to measure in infants using liquid formulations.

intervals, for example, quarterly. With the numbers of patients accessing ART increasing, creating new cohorts routinely will result in growing numbers of cohorts to be reported on over time. As reporting is required on the health of patients in each cohort throughout the time for which any patient remains in care, this will lead to an ever-increasing level of data to be collected and reported. And the number of data items required to compute some of the indicators can be vast, far exceeding the number of indicators themselves. For staff working in busy ART facilities, manually computing multiple indicators at frequent intervals is time-consuming and impacts on the completeness and accuracy of reports [317], [297], [72]. Ultimately, the scope for error in generating monitoring reports will depend on competing priorities for clinic staff.

In the absence of universal electronic record systems, further challenges to the current paper-based systems include extracting and deriving data for reports from records stored in different sections of health centres, e.g. antenatal care, tuberculosis treatment wards and ART clinics. Commonly, registers kept in each department are unlinked and unique patient identifiers which are common across the departments are rare [93]. This may lead to over-counting of patients. For example, some patients initiate Cotrimoxazole Preventive Therapy (CPT) in an antenatal clinic but also go on to register in the pre-ART register when initiating HIV care. This register is likely to have a tick-box column asking if the patient has been initiated on CPT. Reporting on the number of patients initiated on CPT using data from both the antennal clinic and the pre-ART register, in the absence of unique patient identifier common to both clinics, not surprisingly results in double-counting of patients and an overestimation of the indicator.

6.6.2 Construct validity

Programme managers must be able to rely on indicators to measure the theoretical construct they intend to measure to obtain robust estimates of the size and health of the population in care. However, a number of fundamental indicators may not measure what they intend to measure.

The ability of the denominator used for most indicators, *number initiating ART at the beginning of the reporting period*, to represent correctly those in care is questionable. The cohort grouping, rarely, if ever, distinguishes between patients newly initiating therapy and drug-experienced patients transferring in from another clinic. Yet the number of patients transferring between clinics can be high. In Malawi, for example, 12% of patients who registered in the national ART programme during the second quarter in 2009 had transferred from another clinic [318]. Failure to capture these details will considerably inflate the reported number of new ART initiators. For donors who use information on the number of patients enrolling for ART to provide accountability for spending, a slight over-count in the number of persons provided with ART may have limited consequence, or indeed may appear good for the donor. However, for programme managers aiming to understand the survival of patients since they initiate ART, the cohort will contain patients who have remained alive on ART for a number of months already and are likely to be healthier than new initiators. Furthermore, the inflated number of new initiators, used by programme managers as the denominator for most indicators, will fundamentally bias reported indicators. For example, in a hypothetical scenario, if 360 new ART initiators die by 12 months, the proportion of new initiators to have died will appear to be 18% if a cohort has 2000 patients. However, assuming transfers-in accounted for 12% of the cohort (as per the Malawi

data), the true number of new initiators would be 1785 patients and the same number of cases would result in the proportion (20%) of patients to have died being higher. The more prevalent the outcome of interest, the more extreme the bias will be. Moreover, for the MoH or researchers, monitoring patient survival after ART initiation, this will be underestimated as cohorts which fail to take into account transfers-in will include some patients who have been on ART for longer than the time registered in the clinic.

Understanding survival on ART in LMIC has further challenges. In survival analysis, patients contribute different durations of follow-up until an event, (in this case death). However, in LMIC, as many clinics lack the infrastructure to capture patient data electronically or the statistical software for complicated computations, calculating 'survival' is not practical. Therefore, as seen in the literature review, facilities create reporting cohorts and attempt to capture 'survival' by reporting the number of patients on ART at the beginning and end of a discrete time period. This indicator, in reality, captures the proportion retained in care of those who enrolled for therapy. There is no person-time denominator and the important detail of how long people are alive after starting therapy is lost.

Moreover, the status of patients not returning for ART is captured as died, lost to follow-up (LTFU), stopped ART or transferred-out. Yet, accurately estimating each of these indicators themselves is complicated and failure to distinguish between them will bias retention and survival estimates. For example, a review of 17 studies in LMIC demonstrated that 40% of patients recorded as LTFU whose outcome could be ascertained through active follow-up had died [319]. Failure to account for the fact that some patients who are recorded as LTFU will have died will lead to an

overestimation of survival. Conversely, it is likely that some patients who are recorded as LTFU will have transferred unofficially and be receiving ART elsewhere. Failure to account for these patients, or to account for patients who transfer-out officially and follow-up their transfer, will negatively bias survival estimates and underestimate true retention in a country-aggregated monitoring system. For example, in northern Malawi, 90% of patients who were recorded as having transferred-out from ART-clinics were alive and on ART elsewhere, while the remaining 10% were not [320]. However, assuming all patients who transfer-out will follow-up on the transfer is likely to be over optimistic. The ability to capture data accurately on deaths and transfers will greatly influence interpretation of survival and retention on ART.

It has been demonstrated, among southern African IeDEA cohorts that the competing risk of death may bias standard analyses of LTFU by as much as 6.4% [91]. Similarly, adjustments to correct mortality estimates for LTFU have been proposed. One method derives a correction factor (from the percentage of patients LTFU and an estimated ratio of mortality among patients lost and not lost) and applies it to estimated mortality among patients not lost from care, and was proposed by members of the IeDEA collaboration [92]. Other methods involve imputing data based on mortality estimates from studies which traced patients LTFU, or using combinations of imputed data and linkages to vital registers [93] [90]. Using these three methods, programme mortality estimates which fail to account for mortality among patients LTFU were estimated, respectively, to be biased by nearly 10%, between 27 - 73%, and by over 100% [92] [90, 93]. As expected, bias in mortality estimates has been noted in studies reporting high LTFU [92].

Treating HIV as a chronic condition means that managers must maximise retention in care because patients who interrupt ART risk ongoing HIV transmission, incomplete virological suppression, immunological decline, opportunistic infections and death [298]. However, programme performance must not be assessed using 'retention' as a stand-alone indicator as this gives equal weight to the number of patients who have died as to those transferring-out or stopping ART [321]. Programme managers and funders must base human-resource planning and clinical care decisions on data relating to retention, survival, deaths, LTFU and transfers-out with extreme caution.

Further examples of indicators representing complex constructs that are difficult to observe directly include measures of patient satisfaction and adherence to ART, which may capture a perceived socially-desirable answer rather than the true one. Furthermore, assessing the progress of an ART programme based on patients retained in care may overstate performance. For example, evaluating a programme on the *median CD4 count increase after 6 months* fails to take account of those no longer in care who are expected to be sicker than those retained in follow-up [322].

6.6.3 Content validity

It is vital that the data content of an indicator represents what the indicator aims to measure. For example, the indicator *proportion of a cohort whose functional status is working* aims to measure increased productivity, and thus successful ART [69]. Therefore, the data classifying a patient's functional status as *working, ambulatory or bedridden* must truly represent productivity and health status. However, a patient's functional status may change, due to necessity, without an associated health improvement. Furthermore, interpreting functional status classifications may differ. One site may record patients actively employed, while another records all

patients able to work but not necessarily employed. Moreover, functional status is often poorly completed on patient treatment cards (*personal communication A Jahn December 2009*) and, as such, programmes may inaccurately estimate productivity changes.

Certain indicators are recommended to be collected as proxies to monitor the development of HIV drug resistance within a treated population. However, these indicators may not represent the constructs they intend to. For example, in a study in Namibia, 100% of surveyed sites met the target of 100% of patients initiated on an appropriate first-line regimen, yet only 67% of sites met the target of 0% switched to a second-line regimen [315]. Both indicators cannot purport to measure how well a site is doing to prevent HIVDR when there is a difference of more than 30% in their estimates.

Recently, assessments of pharmacy refill adherence have been shown to be as accurate as CD4 counts for detecting patients at high or low risk of virological failure [258]. However, while measures such as pharmacy refill or weight gain may indicate improved immunological or virological status at the patient level, producing it routinely from paper-based systems may result in poor quality data used to calculate even a sound indicator [323, 324]. The validity of using such manually-derived aggregates to assess the health of the treated population has never been examined.

6.6.4 External validity

As indicators are used to learn from more 'successful' programmes to improve patient care, and to compare programmes' performance to inform resource-allocation decisions, indicators must make correct inferences about different

populations.

A programme's mortality and retention indicators, cautiously interpreted within the programme's context, can provide vital information to managers to ensure high quality of care. However, using these indicators to assess performance across programmes is problematic, particularly if different inclusion criteria have been used. For example, enrolling patients based on demonstrated good prophylaxis adherence and an absence of alcohol problems may result in a programme 'out-performing' another which has no selection criteria [325].

Furthermore, some sites trace patients LTFU to encourage them back into care. By ascertaining the vital status of those LTFU, a site may report a high number of deaths. Increased reporting of deaths is also likely if sites adjust their survival estimates using correction factors or imputed data for patients LTFU [92] [84, 90, 93]. Comparing these indicator estimates to programmes without the ability to trace patients or adjust estimates is clearly inappropriate.

Stratifying indicators by age groups is important within a programme to evaluate the effectiveness of ART for infants, children, adolescents and adults. However, subtle differences in age stratifications in different programmes make cross-programme comparisons challenging. Moreover, reporting the same indicators for adults, children and adolescents may be inappropriate. For example, indicators report the *proportion of patients demonstrating >90% adherence*. However, in infants, given that their medication is a liquid formulation, measuring adherence is particularly challenging [326]. And, adolescents, a substantial epidemic of whom is emerging in sub-Saharan Africa [327], experience particular issues as a result of

long-term infection, including stunting, puberty delay and histories of chronic ill health [328]. Specific indicators to monitor their progress are required.

6.6.5 Predictive value over time

As directly assessing long-term progress on ART is problematic in LMIC, it is imperative that routine indicators can be used to predict longer-term outcome in terms of survival and treatment failure. For example, in LMIC, both the incidence of TB and mortality among HIV-infected patients attending ART programmes are higher during the first few months on ART than later months [329] [182]. An indicator measuring the proportion of a population with active TB, for example, 3 months after ART initiation may closely predict the survival of the treated population 12 months after ART initiation. Knowledge of the value of an indicator, for example *more than 20% of a cohort with active TB at 3 months*, corresponding to the poor outcome of a programme, should enable managers to respond to predictors of failure early. However, the ability of early indicators to predict longer-term survival has never been evaluated.

Furthermore, in the context of life-long ART care and cohort reporting, defining clear endpoints on indicators will reduce the reporting burden. For example, UNAIDS encourage annual reporting on survival. However, the most appropriate time-points at which to collect indicators have never been evaluated. An understanding of the risk of death and morbidity over time will help inform the decision on the optimal time-points for indicator reporting. For example, given that children under 5 years of age appear to have a more rapid disease progression compared to young adults, more frequent monitoring, specifically shortly following therapy initiation, may be necessary in paediatric programmes [35].

6.7 Discussion

This study compared tools prioritised by national MoH to monitor the health of the population in ART care, and discussed challenges with monitoring in this way. Understanding which indicators are commonly collected across LMIC provides programme funders and organisations responsible for designing ART programme data-capture tools with information on what data are perceived to be most relevant. Furthermore, understanding the gaps between what data are recommended to be collected by international organisations and what are requested by national systems highlights differences in perceived priorities.

This study, however, has some limitations. Firstly, the lack of availability of the WHO template cross-sectional monitoring report impeded the ability to assess the influence of international recommendations in all monitoring tools. However, this study highlighted discordance in the data reported in cross-sectional reports across the four countries, suggesting that having a template tool available was useful for national MoH.

A further limitation of this study is that I assessed only the uptake of WHO recommended tools and indicators. I did not consider in detail indicators recommended by international agencies, such as PEPFAR and the GFATM. These agencies require funder-specific monitoring reports from programmes which they fund to justify their expenditure. Yet, these funder reports are additional to reports to national MoH, and represent the priorities of funder. By assessing the implementation of the WHO recommendations it was feasible to assess national priorities, before considering any funder indicators that countries are compelled to include.

A further limitation of this study is that I compared the uptake of WHO recommended tools and indicators in four countries, each of which has its own distinct HIV epidemic, most notably in the Ukraine. However, the inclusion of different countries allowed the comparison, against universal monitoring recommendations, of priorities in countries facing different challenges in responding to HIV. As such, this study highlighted the influence of nationally perceived priorities.

Despite these limitations, this study starkly highlighted, even by 2010, the lack of common use of recommended data in national tools used to monitor the clinical progress of the treated population. Additionally, I observed the collection of items not recommended in the templates or used to calculate UNGASS indicators, such as the number in a cohort picking up drugs for 6 out of 6 months, which closely resembled indicators recommended by international donors such as the GFATM [308]. Some data items collected in 2008 were no longer collected in 2010, while others recommended in the templates were not taken up by any of the four countries. Sometimes data were country-epidemic-specific such as on injecting drug use in the Ukraine. It is thus clear that national monitoring systems are designed not solely based upon one set of international recommendations but also include indicators from other funders or organisations and are based on national experiences of which indicators are feasible and useful to collect.

While the monitoring of HIV programmes can be used to identify a 'good' programme, enabling lessons to be learnt from one programme to improve the performance of others, the variety of indicators and age stratifications used make comparisons across programmes challenging. Moreover, this lack of consensus in

number and type of priority data collected and reported across the range of monitoring tools highlights the uncertainty regarding which data collected at the patient-level, and which reported indicators are, in fact, most useful to assess the health of the treated population. Even recent international indicator selection processes for monitoring ART care have been based on assessing a variety of factors including technical merit and feasibility of use rather than any scientific evaluation of the indicators themselves [330] [296].

ART programme monitoring reports aim to use indicators to assess the quality of health care services and measure the effectiveness of the response to HIV [298] [299]. To assist the interpretation of indicators, emphasis must be placed on explaining how numerators and denominators in reported data are derived. Information must be provided on whether or not transfers-in were included in the cohort denominator and explanations should be given of whether any tracing of LTFU to ascertain vital status has taken place or whether any correction factor has been applied to deaths and LTFU estimates. Only by capturing accurate information on deaths and transfers, can a true picture of country-wide retention in ART programmes and survival on ART in LMIC be drawn. New monitoring systems have been proposed for LMIC to increase reporting accuracy, including the use of web-based technologies [331]. However, given the lack of infrastructure, the wide-spread implementation of such systems seems unlikely in the short-term and the current system seems likely to remain in place.

It is vital therefore to understand which data currently reported by sites, are actually useful in assessing the performance of a treatment programme. It would be of value to know for example, if the data on the number on ART at end of a

reporting period shown in Table 6.5, common to all four countries, are enough to monitor the progress of the treated population within ART programmes. However, as the internal, external, construct validity and predictive value of current indicators have never been evaluated, it is not known whether fundamental indicators, including survival, capture the construct they intend to measure or accurately reflect the health of the treated population [244]. This compromises the ability of programme managers to monitor their population in care. Furthermore, as it is not known which indicators can predict the longer-term outcome of the patient population, it is not known which key indicator(s) can enable managers to respond to potential predictors of failure early. It is not known, moreover, how accurately currently-used monitoring indicators reflect the welfare of those in care [20] [68] [56]. Therefore, until there is a better evidence for these monitoring indicators, conclusions drawn about the overall quality of performance of a programme based on one set of indicators are susceptible to misinterpretation.

Valid indicator estimates are essential to furnish programme managers with the information necessary to provide the best treatment to the patients entrusted in their care. Resources within health facilities are being stretched in order to provide the data for monitoring indicators. There is, therefore, an obligation to ensure that the effort is worthwhile, and the reported data adequately reflect the welfare of the treated population. There must be a balance between indicators that are useful to compute, and the feasibility of data collection by clinic staff. For example, in practice, paper-based 'survival' is likely to remain the mainstay for ART programme reporting for years to come.

I recommend, therefore, as priority, a scientific study to evaluate the validity and

predictive value of indicators currently collected at the programme level, against the survival and retention of patients within the treated population. I present the design of such a study in the next chapter. This will provide the evidence base through which indicators can be refined and will guide decisions on which constructs and indicators should be selected to monitor ART programmes.

Chapter 7 Validating programmatic indicators

This chapter represents the main recommendation of my thesis regarding research needed to establish how best to monitor the health of patient populations treated within ART programmes. Only by having a more accurate understanding of the health of patients in care can improvements in services be provided and, ultimately, longer survival with HIV achieved. This chapter describes a study I designed to examine the ability of reported programmatic indicators to represent the health status and predict the longer-term outcome of the population treated within ART programmes in LMIC. The study includes a retrospective and a prospective component within ART programmes in LMIC.

7.1 Background

Between 2004 - 2005, with the support of international donors, the wide-scale roll-out of free ART commenced in many LMIC. Most ART care in LMIC is delivered through a combination of NGOs and public sector services, many partly funded by the national MoH in combination with international organisations such as PEPFAR or the GFATM. Currently, our understanding of the success of ART programmes in LMIC is based on indicators from routine monitoring reports compiled for programme funders, national MoH, international agencies or scientific journals. ART programme indicators are used to monitor performance, measure achievements and determine accountability [332]. The WHO Early Warning Indicators (WHO EWI) of HIV Drug resistance are used to assess how optimally clinics are performing to minimise the development of HIV drug resistance (HIVDR) [300]. ART programmes which have been delivering ART for a minimum of 12 months are requested to compile the WHO EWI. All ART programmes, whether with high,

medium or low patient number burden, in rural or urban settings, resourced with specific data-collection staff or simply nurses, using electronic data-capture systems or paper-based systems requiring manual manipulation, are required to compile the same indicators for monitoring reports for the MoH.

The number of patients seen, however, in health centres varies considerably. By 2012 in Malawi, for example, 651 static health centres were providing ART to 404,905 patients [333]. Of the Malawi health centres, 28 (4%), 55 (8%) and 568 (87%) were considered to be high, medium and low patient burden centres with the number of patients varying accordingly. Since free ART began in Malawi, high, medium and low burden health centres have initiated cumulatively > 5000 patients (average >625 per year), 2000-5000 patients (average 250 - 625 per year), and <2000 patients (average <250 per year) on ART, respectively [333]. As health centres have become more familiar with ART distribution, the number of patients seen annually has increased. However, as the demands of health centres of different sizes differ, monitoring indicators may be calculated differently according to the size of the health clinic and the resources available for report compiling.

Moreover, while a plethora of indicators have been recommended by funders, international organisations and researchers, ART programme monitoring indicators have never been evaluated programmatically. It is, therefore, not known which, if any, most accurately reflect the health of the treated population, or whether their ability to reflect this is equal in different types of health centres with differing amounts of resources [244]. Even recent indicator selection processes by UNAIDS for monitoring ART care have been based on assessing a variety of factors including technical merit and feasibility of use rather than any scientific evaluation of the

indicators themselves [330] [296]. Until there is better evidence for these monitoring indicators, conclusions drawn about the overall performance of a programme based on one set of indicators are susceptible to misinterpretation. As guidelines change to recommend ART initiation earlier in the course of HIV infection and more individuals become eligible for therapy, accurately monitoring the longitudinal health of patients in ART programmes becomes ever more crucial to inform best practice of treatment roll-out. It is vital, therefore, to evaluate the ability of commonly-used indicators to assess the health of the population in care.

I, therefore, designed the study described in this chapter. I received scientific and logistical advice from colleagues at the MRC CTU (Abdel Babiker), University College London (Deenan Pillay) and MRC UVRI (Pontiano Kaleebu) and in particular, from the MoH in Malawi (Andreas Jahn) and Uganda (Wilford Kirungi).

7.1.1 Preparation

To raise awareness of this study and to invite collaboration with key stakeholders involved in designing ART monitoring tools, I have sought to inform from an early stage the WHO, UNAIDS, UNICEF, UK DfID, the International Union Against Tuberculosis and Lung Disease (the Union), the GFATM and PEPFAR. I did this through a series of face-to-face meetings with the following representatives from each organisation: the WHO (Yves Souteyrand, Chika Hayashi), UNAIDS (Mathew Warner Smith), UNICEF (Nina Ferick, Ruslan Malyuta), UK DfID (Malcolm McNeil, Sue Kinn), the Union (Anthony Harries) and the GFATM (Rifat Atun). I was unable to meet in person a representative from PEPFAR but liaised electronically Gillie Arthur and Stefan Wiktor. Additionally, I held telephone discussions with representatives from the UNAIDS Monitoring and Evaluation Reference Group (MERG) (Liza Tong at the HIV/AIDS alliance, UK and Roger Drew, the DfID

representative on the MERG). In addition to international organisatons, I had the opportunity to have meetings with a representative from the national Ministry of Health Uganda (Wilford Kirungi) and Malawi (Erik Shoulten), to discuss the objectives of this study and to ensure this study would be relevant in LMICs.

During these meetings and telephone conversations, I presented the issues that I had identified when comparing the monitoring indicators used by national MoH in Malawi, Tanzania, Uganda, and the Ukraine (Chapter 6) and I highlighted the need for a stronger evidence-base behind monitoring indicators. The importance of the issues was confirmed by all individuals during this consultation process.

7.2 Aim, objectives and outline

The study aims to evaluate the ability of monitoring indicators collated through ART treatment programmes to capture the construct they intend to measure and their ability to predict the longer-term outcome of the treated population. The study also aims to identify appropriate easy-to-generate indicators to monitor the health of ART-treated populations in LMIC.

The objectives are to:

- estimate the long-term clinical response to ART and risk of death over time following therapy initiation to guide optimal time points at which indicators should be compiled,
- estimate the immunological and virological response to ART (including development of drug resistance at 12 and 24 months),
- evaluate the ability of current survival and resistance indicators to reflect individual level data accurately,

- evaluate the ability of current indicators to predict the longer-term survival of the treated population,
- evaluate the ability of the WHO EWI of HIVDR to predict the development of HIV drug resistance, and
- identify appropriate easy-to-generate indicators to monitor the health of individuals treated within HIV programmes

In this study I will gather data collected routinely in a variety of ART treatment programmes across multiple countries to enable the examination of the performance of monitoring indicators in a variety of settings. The study will involve a retrospective component and as well as a prospective component. Retrospective data will allow me to estimate long-term survival and to evaluate indicators used to measure the clinical progress of patients in care over the three year period prior to the commencement of the study. Prospective data will allow me to gather additional data, specifically from blood samples to estimate the rate of HIVDR 12 and 24 months after ART initiation, and to evaluate the WHO EWI HIVDR.

This work is intended to provide an evidence-base to identify which indicator(s), collected at which time-points, best reflect the welfare of the treated population and thus should be used to assess health within HIV treatment programmes.

7.3 Methods

7.3.1 Survival and resistance indicator components: study countries

In order to assess how well the indicators perform across LMIC geographical regions, the retrospective and prospective components of this study will each take place in multiple countries. The study countries included will reflect the estimated number of people living with HIV across the following geographical regions: sub-

Saharan Africa (25,000,000), South and South East Asia (3,900,000), Latin America (1,500,000), Eastern Europe and Central Asia (1,300,000), East Asia (880,000) and the Caribbean (250,000) [95]. For example, as sub-Saharan Africa has the greatest number of people living with HIV, it will contribute the greatest number of countries to the study, and the Caribbean will contribute the least.

As a minimum, ART clinics in Malawi and Uganda will be included, based on previous discussions with the MoH and areas of expertise of the EfA partner organisations and the MoH identified during the study described in Chapter 6. Malawi was selected for the interest and experiences of the Lighthouse Trust and the MoH in attempting to verify the accuracy of data used to monitor clinical outcomes of patients in care. Malawi's MoH routinely send small teams to all ART sites in the 5 main zones of the country to supervise quarterly indicator reporting [334]. Uganda was selected due the role of the MRC UVRI in working with the MoH HIVDR Working Group.

The remaining countries will reflect countries with the highest prevalence of HIV within each region, therefore: sub-Saharan Africa (Lesotho 23%, Botswana 23%, Swaziland 27%), South and South East Asia (Thailand 1.1%, Cambodia 0.8%), Latin America (Guyana 1.3%), Eastern Europe and Central Asia (the Ukraine 0.9%), East Asia (China <0.1%) and the Caribbean (Bahamas 3.3%) [95]. Inclusion will depend on likely interest and engagement in the study of the national MoH.

Having data from a variety of countries will enable an assessment of the performance of monitoring indicators in countries with different rates of HIV prevalence, different programmatic funders, and differing levels of MoH involvement

in data generation.

The methods for the survival indicators and HIV drug resistance indicators components are described separately below.

7.3.2 Survival indicators: study population

In the retrospective component of the study I will collect data from ART treatment programmes on patients who initiated ART as early as 2004, when free ART became widely available in LMIC. All adult, adolescent and child patients who enrolled in clinic ART registers and newly initiated ART since 2004 will be eligible for inclusion. Patients who transfer-in for care and are registered in the ART register as new initiators in the clinic will be enrolled into the study. Where clinic ART registers are not available from 2004, the earliest copy of the ART register will be used and patients will be enrolled into the study from the earliest available date of ART initiation in that clinic. For all patients enrolled in the clinic ART register, longitudinal data of their time in care will be gathered. In order to minimise the effect of survivorship bias on estimates of outcome (i.e. from the inclusion only of patients currently in treatment), I will attempt to include the records of all patients who ever initiated ART, including records for deceased or patients no longer attending ART care who have become lost to follow-up (LTFU).

Clinics will be selected in collaboration with national MoHs. Each health clinic will need to meet the following criteria:

- provides ART within the health centre (patients do not have to transfer elsewhere for ART care),
- has been providing ART for a minimum of 3 years,

- has copies of ART registers, patient files and previously submitted monitoring reports for a minimum of 3 years, and,
- to the best of ability, is a non-research clinic (so that patient outcomes are not influenced by additional resources from research studies).

Health centres will be selected to reflect the distribution of high, medium and low patient-volume burden sites in each country, to account for potential differences in compiling indicators between small and large clinics. For example, based on the proportion of high, medium and low patient-volume burden health centres providing ART in Malawi, 4%, 8% and 87% of study health centres will be selected from high, medium and low burden health centres in Malawi, respectively [333]. The health centres will provide a mix of health centres in urban, peri-urban and rural areas, being funded through the MoH or the MoH in collaboration with external funders, and capturing patient data through paper-based and electronic systems.

Across the countries selected for the study, the number of clinics which will be included will provide a balance between having a high number across which the predictive performance of programmatic monitoring indicators can be assessed and a realistic number from which data from patient files can be gathered. It is recognised that large numbers of patient files will add to data-collection burden and may potentially impact data-cleaning accuracy. Table 7.1 provides scenarios for different number of sites selected per country and the resulting different number of patient files. These scenarios are based on data from Malawi in 2012 [333]. For example, in the scenario where 100 sites are selected in Malawi (15% of Malawi's 661 sites), this will mean indicator performance can be assessed in 100 health centres, and I will be able to conduct survival analyses on data from around

Table 7.1 Scenarios for the number of patient files available for data-collection, by different numbers of health centres, based on Malawi 2012

Health centres by size	**Number of health centres (country total=661 sites)**			
	25 (4% of total sites)	50 (8% of total sites)	100 (15% of total sites)	200 (30% of total sites)
High burden				
Number of sites (4%)	1	2	4	8
Number of patient files (based on >5,000 cumulative/site)	>5,000	>10,000	>20,000	>40,000
Medium burden				
Number of sites (8%)	2	4	8	16
Number of patient files (based on 2 -5,000 cumulative/site)	4,000 – 10,000	8,000 – 20,000	16,000 – 40,000	32,000 – 80,000
Low burden				
Number of sites (87%)	22	44	87	174
Number of patient files (based on <2,000 cumulative/site)	<44,000	<88,000	<174,000	<348,000
Total patient files	53,000 – 59,000	106,000 - 118,000	210,000- 234,000	420,000 - 468,000

210,000 – 234,000 patient files in Malawi. The number of clinics in the remaining countries will be determined once the total number of ART providing clinics, their break down by high, medium or low patient-volume burden, and the cumulative number of patients ever initiated has been established, and consent from the individual national MoH has been obtained.

7.3.3 Survival indicators: data collection

For included patients, all previously-recorded patient-level clinical data will be gathered. These data are currently recorded in ART registers and individual patient longitudinal treatment cards. As a minimum, the following data will be gathered from ART registers:

Demographics	unique identification number, sex, date of birth, age at initiation of ART
Clinical	date of ART initiation, CD4 percentage/CD4 count or WHO stage at initiation of ART, date last seen in ART clinic, and, if available, reason for dropping out of care (e.g. death, transferring-out, becoming lost to follow-up)

Additional information (as collected in current MoH patient treatment cards) will be gathered from patients who remain in care for at least one follow-up appointment. As I demonstrated in Chapter 6, the data collected in patient treatment cards are different in each country. I will gather the following data, which were commonly collected in the four countries examined in Chapter 6:

dates seen in clinic, WHO stage at appointment or CD4 count if available, ART regimen, regimen switch or substitution, ART interruption, ART adherence, diagnosis of opportunistic infections at appointment, hospitalisations, and important clinical events (e.g. new WHO stage IV events including TB, Kaposi Sarcoma).

Only data that are currently recorded in ART registers or patient treatment cards will be collected. No new data items will be sought from individual patient notebooks. However, because LTFU rates are likely to be high in some sites, field staff will be recruited to ascertain the vital status of patients LTFU.

In addition to patient-level data, for each clinic, I will gather ART-programme monitoring data previously reported to the MoH in the cross-sectional and quarterly reports. I will collect the indicator data that were routinely compiled in the reports for the 3-year period prior to the beginning of the study. As a minimum, this will include the indicators which are recommended by the MoH, WHO, UNAIDS/UNGASS, PEPFAR or the GFATM and which are used in Malawi (Table 7.2) [301, 305, 308, 316, 335]. Additional indicator data reported to national MoH will be gathered respectively for each included country.

7.3.4 HIV drug resistance indicators: study population

In the prospective component of this study examining the WHO EWI of HIVDR, all adult and adolescent patients newly initiating ART in selected treatment programmes in LMIC will be invited to participate. Patients transferring-in, having initiated ART earlier elsewhere, will not be eligible for inclusion.

Table 7.2 Indicators measuring the outcome of patients treated within ART programmes, recommended by PEPFAR, the GFATM, the WHO, UNGASS or national MoH and collected in Malawi

Indicators
• Proportion still alive and known to be on treatment 6, 12, 24 etc. months after initiation of ART
• Proportion on first-line regimen after 6, 12, 24 etc. months from initiation on ART
• Proportion whose plasma RNA viral load is <1000 copies/ml after 12 months of first-line ART
• Median CD4 cell count and/or CD4 percentage increase, or lowering of WHO clinical staging, at 6, 12, 24 etc. months compared to baseline
• Proportion with ART toxicities and proportion with ART switch due to toxicities or drug failure
• Proportion with severe pain and symptoms who report their symptoms were controlled
• Proportion whose functional status is 'working' at 6, 12, 24 etc. months
• Proportion with AIDS defining event(s) following treatment initiation
• Proportion of all deaths attributable to HIV
• Proportion with severe malnutrition receiving food supplementation
• Proportion demonstrating >90% adherence by self-reported/pill count
• Proportion picking up appropriate prescribed regimen and/or attending all clinic appointments on time
• Proportion who received ART for entire time period (e.g. 6 out of 6 months)
• Proportion whose regimen was stopped, modified or incompletely dispensed due to ART stock-outs during a time period

Sample size calculations were based on available literature from Senegal, Côte d'Ivoire and Uganda, and a systematic review of HIVDR in sub-Saharan Africa. This literature suggests that HIV drug resistance will develop among 10 – 47% of patients who remain in care at 12 months, with the Lamivudine-associated M184V mutation the most commonly seen mutation [24, 73, 336, 337]. In this study, I have assumed HIVDR of around 30% (the mid-point estimate between 10 - 47%). Table 7.3 depicts the precision which would be given according to different sample size scenarios, which can be used to determine study budget. For example, recruiting 1,000 patients will enable the detection of resistance at 12 months in 30% of those who initiated ART with a 95% confidence interval between 27% and 33%, whereas recruiting 5,000 patients will enable the detection of resistance among 30% of those who initiated ART with a 95% confidence interval between 29% and 31%.

The number of patients to be recruited from any country, and from any one clinic within that will be relative to the total number of patients initiating ART in the country and in individual clinics. For example, Malawi newly initiated around 100,000 patients onto ART in 2012 (4 x 24,168 patients initiated during 4th quarter), whereas the Ukraine newly initiated just under 5,000 patients during 2011 [333] [338]. Further, in Malawi, I calculated that an average of >625, 250 – 625, and <250 patients initiate ART per year in high, medium and low burden sites, respectively [333]. Countries with higher numbers of patients initiating ART will recruit respectively higher number of patients to the resistance study, while high patient-volume burden clinics will recruit at least three times as many patients as low burden clinics. Patients will be invited to participate by consecutive sampling until the required sample size is reached.

Table 7.3 Study precision (Confidence Interval, CI) given by different sample size scenarios for the Resistance study, assuming 90% power and resistance at 12 months is detected in 10%, 30% and 47% of original sample size

Sample size	500	1000	1500	2000	3000	5000	10000
10%							
Lower CI	7.9%	8.5%	8.8%	8.9%	9.1%	9.3%	9.5%
Upper CI	12.5%	11.7%	11.4%	11.1%	10.9%	10.7%	10.5%
30%							
Lower CI	26.6%	27.6%	28.1%	28.3%	28.6%	28.9%	29.2%
Upper CI	33.6%	32.5%	32.0%	31.7%	31.4%	31.1%	30.8%
47%							
Lower CI	43.2%	44.4%	44.9%	45.1%	45.5%	45.8%	46.2%
Upper CI	50.8%	50.0%	49.2%	48.9%	48.5%	48.2%	47.8%

As the size of clinics and workload burden on staff may influence how the HIVDR EWI are computed, the study will recruit patients initiating ART from a variety of health clinics using the same methods for site selection as described in the survival indicators component. This will enable an assessment of the performance of the drug resistance indicators in various settings. The overall number of included clinics will provide a mix of high, medium and low patient-volume burden clinics, from rural, peri-urban and urban settings. The specific clinics will be selected in collaboration with the MoH and each clinic will meet the following criteria:

- has provided ART for a minimum of 12 months (WHO criteria for use of HIVDR EWI),
- is able to recruit the required sample size, and
- is geographically close to the location of where virology tests will take place for ease of transport logistics for stored blood samples.

7.3.5 Resistance indicators: data collection

For all study participants, at ART initiation, a spot of blood will be taken by finger prick and stored as Dried Blood Spots (DBS). For study participants who remain in care 12 and 24 months after ART initiation, a further DBS will be extracted. The DBS samples will be used to measure the presence of transmitted drug resistance at baseline and acquired resistance 12 and 24 months after initiation of ART. The DBS will be collected on filter papers (Guthrie cards), and provide a good alternative substrate for plasma for resistance testing. This is useful as transporting and maintaining the temperature of plasma samples in the warm African environment can be challenging. Although DBS must be stored at -20° C to prevent degradation of RNA, once dried they are considered non-infectious and can be transported at ambient temperature up to a number of days and then stored [339] [340]. The

technique of DBS for measuring drug resistance has been shown both in the UK and LMIC to be appropriate [340, 341].

Viral load quantification will be done on all 12 month DBS samples and, if viral load exceeds 1,000 copies/ml, genotypic resistance testing will be undertaken. If evidence of resistance is present at 12 months, genotypic testing will be undertaken on the participant's stored baseline sample. This will allow an assessment of whether the patient presented with resistance before treatment initiation, or developed resistance after ART initiation. Viral load testing will also be done on the 24 month DBS samples of all patients remaining in care. If viral load exceeds 1000 copies/ml, resistance testing will be undertaken on the 24 month sample.

In addition, a sub-sample of all the DBS samples taken at ART initiation will be tested for resistance. This is because participants who initiate ART with TDR may be less responsive to treatment, either dying or dropping out of care before 12 months, which would lead to a bias in available samples for testing at 12 and 24 months and could result in an underestimate of TDR at ART initiation. The samples for TDR testing will be sequentially selected, based on the size of the sub-sample. Sample size scenarios are presented in Table 7.4. These scenarios are based on evidence from the DART trial, which was conducted in routine ART clinics in Uganda and Zimbabwe, and which estimated the presence of TDR in around 10% of those initiating ART [342]. For example, a sub-sample of 1,000 DBS (20% of a hypothetical 5,000 patients in the resistance study) would enable the detection of TDR among 10% of patients at ART initiation with 90% power, with a 95% confidence interval between 8.5% - 11.7%, whereas a sub-sample of 2,500 DBS (50% of a hypothetical 5,000 patients at ART initiation) would enable the detection

Table 7.4 Precision (Confidence Interval, CI) given by different sample size scenarios for the Transmitted Drug Resistance sub-sample, assuming 90% power and TDR is detected in 10% of ART initiators, based on a hypothetical 5,000 patients in the resistance study

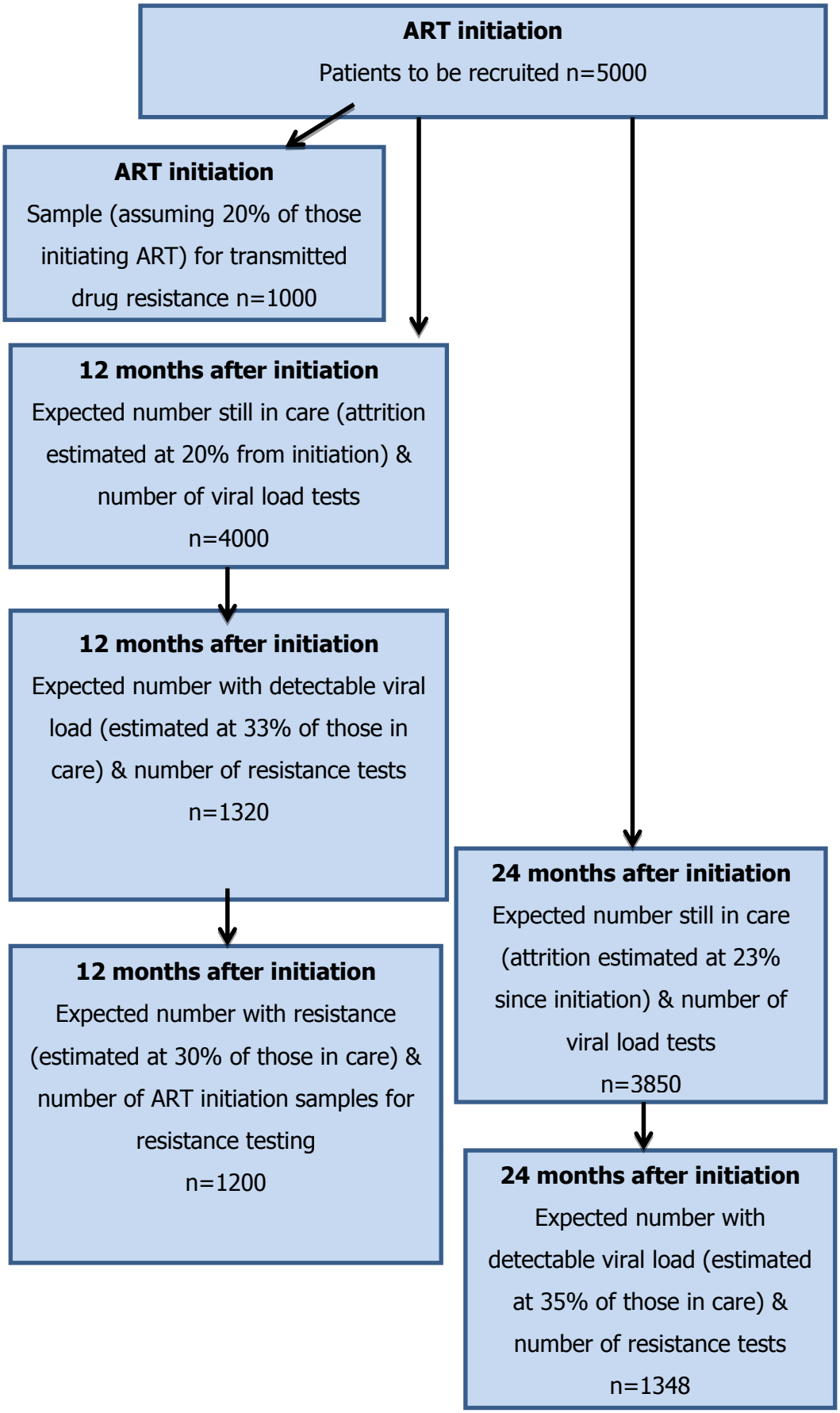
Percent of samples at ART initiation	10%	20%	30%	50%
Sub-sample size	500	1000	1500	2,500
Lower CI	7.9%	8.5%	8.8%	9.0%
Upper CI	12.5%	11.7%	11.4%	11.0%

of TDR among 10% of patients at ART initiation with 90% power, with a confidence interval between 9.0% - 11.0%.

The number of viral load and resistance tests to be carried out will be based on the number of study participants, an estimate of attrition and the number of participants expected to remain in care at 12 and 24 months, and an estimate of the proportion with detectable viral load and the proportion with resistance at each time-point. Twelve months after the initiation of ART, attrition is assumed to be 20% and 23% by 24 months, based on the findings from my literature review, presented in Chapter 2. The proportion with detectable viral load at 12 and 24 months is expected to be 33% and 35% respectively, of those remaining in care, based on the systematic review of African studies [74]. Resistance is estimated to be 30% at 12 months.

Figure 7.1 provides the example scenario if 5,000 patients are recruited to the study. For example, 1,000 DBS samples will be tested for TDR (20% of all ART initiators). No further testing will be conducted on samples found to harbour TDR. After allowing for attrition, it is anticipated that 4000 patients will remain in care at 12 months. Viral load testing will be conducted on the 12 month DBS sample of these 4000 patients. Of these, it is anticipated that 1320 will have detectable viral load. Resistance tests will be conducted on these samples. It is estimated that 1200 participants will have resistance at 12 months. For these participants, resistance tests will be conducted on their baseline DBS samples. At 24 months, it is anticipated that 3850 participants will remain in care. Viral load tests will be conducted on the DBS samples from all 3850 participants at 24 months. Of these, 1348 are expected to have detectable viral load, on whom resistance tests will be

Figure 7.1 Flowchart depicting number of viral load and resistance tests to be conducted for a given sample size of 5000 patients



conducted.

Clinic-level data on all resistance study participants in Uganda will be gathered from patient treatment cards. The resistance component of the study will evaluate the WHO EWI HIVDR, as shown in Table 7.5. Therefore, data from monthly and quarterly indicator reports that are routinely compiled throughout the 24 month study period will also be collated.

7.4 Analysis plan: survival and resistance components

I will estimate long-term survival and the probability of developing HIVDR. I will compare the derived survival and resistance estimates with reported information on survival and resistance indicators. The survival and resistance components are described separately.

7.4.1 Estimating long-term survival

I will use Kaplan-Meier and Cox proportional hazards models to estimate long-term survival of the treated population, accounting for factors at baseline known to influence survival (e.g. immune status and age). I will include all retrospective data, regardless of subsequent outcome (e.g. whether a patient has died, become lost to follow-up or is still attending the clinic), in order to minimise the risk of survivorship bias in estimating survival (i.e. including only those who lived long enough to reach a certain time period). I will assess the available data for completeness by comparing the data on those who register to initiate ART with the data available from the full patient files. If this highlights the preferential inclusion of currently alive patients (e.g. if a site has records only for those currently under

Table 7.5 WHO Early Warning Indicators of HIV drug resistance

WHO Early Warning Indicator of HIV drug resistance
• Proportion still alive and known to be on treatment 6, 12, 24 etc. months after initiation of antiretroviral therapy • Proportion on first-line regimen after 6, 12, 24 etc. months from initiation on ART • Proportion whose plasma RNA viral load is <1000 copies/ml after 12 months of first-line ART • Proportion demonstrating >90% adherence by self-reported/pill count • Proportion picking up appropriate prescribed regimen and/or attending all clinic appointments on time • Proportion whose regimen was stopped, modified or incompletely dispensed due to ARV stock-outs during a time period

follow-up), I will use appropriate statistical methods in the analyses, which allow for left-truncation of data by "late entry" into the risk set [343, 344].

For sensitivity analyses, I will collect information on how complete the active ascertainment of vital status was by the study staff, so that the appropriate "right-censoring" strategies can be used in analyses [344]. Where field workers have not been able to trace patients LTFU and information on patients vital status remains unknown, I will impute estimates of mortality among patients LTFU, based on strategies published in literature to deal with informative censoring [319]. This will be done in two ways. Firstly, I will assume mortality among patients LTFU is 40%, based on the combined estimate from a published literature review (scenario A); secondly, I will assume there is an inverse relationship between the rate of LTFU and mortality among those LTFU, as observed in the literature review (scenario B). In scenario B, I will use, for example, the following associations, as observed in the review: if LTFU is 5%, I will use an estimate of mortality among LTFU of 60% and if LTFU is 45% I will use an estimate of mortality among LTFU of 20%.

Data from patients who transferred-in having initiated ART elsewhere will not be used in the overall survival estimates as their date of ART initiation may be uncertain.

7.4.2 Estimating HIV drug resistance

All nucleotide sequences, generated electronically, will be interpreted using the Stanford programmes HIVdb (for treated patients) and Calibrated Population Resistance programme (for the baseline samples of untreated patients, primary drug resistance) [345]. The study will use a new algorithm for surveillance of

transmitted HIV drug resistance, in conjunction with the WHO HIV Drug Resistance Surveillance Network distinguishing between mutations emerging on therapy, such as those identified in the widely used IAS-USA algorithms, with those associated with transmission [345]. This will enable the study to avoid mis-allocating "baseline" resistance, which developed before entering ART treatment programmes due to prior antiretroviral experience, from transmitted resistance. It appears that resistance due to either transmission or prior therapy can be distinguished by the nature, and number of mutations (unpublished data from the DART trial). The DART trial identified 10% baseline resistance, comprising a range of mutations inferring prior exposure to therapy [342].

7.4.3 Comparing derived versus reported information: survival and resistance components

I will compare derived versus reported information on all indicators by using the patient-level data to compute currently collected indicators. These derived data will be compared with the data recorded in quarterly indicator reports submitted over the three years prior to the commencement of the study. This will enable an assessment of how accurately the reported data reflect actual patient data. Furthermore, this comparison will help highlight whether feasible, simpler, non-computational methods of reporting indicators are adequate in the absence of computerised technology.

7.4.4 Assessing correlation between indicators and outcome

I will assess the ability of the indicators to predict longer-term outcome, in terms of survival and HIVDR.

i) *Assessing Correlation:* for each indicator, the Pearson correlation coefficient will be estimated, assessing the linear dependence of each indicator against survival. For example, for the indicator 'proportion of the population with > 90% adherence', a clinic may report that 80% of the population have > 90% adherence. The survival analyses may, however, estimate that 70% of the population survives to 24 months. The Pearson correlation coefficient will be used to describe how positively or negatively correlated the indicator 'proportion with > 90% adherence' is with the gold-standard of long-term survival. Similarly, the linear dependence of the WHO HIVDR EWI will be assessed against the gold-standard of presence of drug resistance at 12 months.

ii) *Estimating sensitivity and specificity of indicators:* sensitivity and specificity tables will be constructed for each indicator with type I and II errors for each. For example, for the indicator 'proportion with > 90% adherence to ART', each individual will be classified as a success (if they are > 90% adherent) or failure (if they are ≤90% adherent) and compared to the gold standard of being alive at 24 months. The sensitivity and specificity analyses will allow the calculation and assessment of each indicator's positive predictive value, e.g. the proportion that the indicator correctly deems to be alive at 24 months post ART initiation. Receiver Operating Characteristic (ROC) curves will be used to guide overall indicator performance by assessing the most suitable "cut-off" points for an indicator. For example, ROC curves will be used to estimate what

proportion of patients with > 90% adherence, and at which time points, best correspond with 24-month survival.

The analyses will use as the estimate for overall survival, that derived when using scenario B to estimate mortality among patients LTFU. I will stratify the retrospective analyses by calendar period, as the inclusion of retrospective data is likely to introduce a calendar-time effect (i.e. an improvement in programme performance over time).

Data from patients who transferred-in having initiated ART elsewhere during an earlier reporting quarter will be included in the comparisons of how accurately the compiled indicators reflect the data from ART registers. This is because the denominator used for survival indicators in cohort reports is based on the number of patients enrolling in the ART register in a given month or quarter (e.g. January – March), and they do not distinguish between new initiators and patients transferring-in for care.

If it transpires that research is being conducted in any of the included clinics, any data provided by the research site will be used as comparators when assessing the correlation between indicators and survival/resistance. For example, I will evaluate if indicators in research sites are significantly better at predicting survival than indicators compiled in sites without additional research resources. This will enable an assessment of whether the ability of the indicator to predict outcome is dependent on the quality of the data available to the individual compiling the monitoring report.

7.4.5 Assessing indicators in paediatric populations

By including a large number of clinics with paediatric populations, and by extracting individual level data on patient age, the study will evaluate the ability of currently reported indicators to assess outcome in the paediatric populations. All indicators will be evaluated for children who are less than 15 years old when initiating therapy. Additional potential indicators will be evaluated, assessed through the ROC curves, suitable for paediatric patients such as use of height and weight measures, if recorded in patient files, given that malnutrition is known to predict a child's prognosis [35]. This study will also examine a potential indicator relating to the presence of anaemia, using data on mean haemoglobin levels (if available), as these data have been shown to predict survival in observational studies [339].

7.4.6 Estimating risk of mortality and morbidity over time

From the prospective data, the study will enable an assessment of mortality risk over time. Although mortality rates are expected to decrease steeply following therapy initiation, the subsequent rate is unlikely to be as rapid while the patient is maintained on first-line therapy. Currently, however, the frequency of scheduled clinic visits is fairly uniform, whether therapy has just been initiated (when appointments tend to be monthly) or the patient has been stable for 2 years or more (when appointments may be 2 – 3 months apart). The risk of death and morbidity over time following therapy initiation will be estimated using Poisson regression by using number of events and corresponding person-years at risk. These data will be helpful in determining the optimal frequency of follow-up of treated individuals and can inform the decision on the optimal time points on which indicators should be based. For example, if the rate of death is 3 times as high in

the first 12 months as the second 12 months, it would be advisable to have more frequent monitoring in the first 12 months.

7.5 Logistic and budgetary considerations

Resistance tests will be carried out locally, where WHO approved laboratories exist. Where local laboratory facilities are not WHO approved, the DBS samples will be sent to UCL, London. Testing on these samples will be done by UCL staff, working in tandem with local staff, to provide capacity building. Routinely-collected paper-based data from ART registers, patient treatment cards and monitoring reports will be entered onto an electronic data-base. Currently, data-scanning technology exists in Malawi to undertake scanning of data from ART programmes with paper-based record systems, through the NGO BAOBAB Health [346]. This study will use similar methods. To do this, a member of staff will travel to clinics, scan the paper-based data and upload them, using the electronic ART programme data-base at the Lighthouse Trust, Malawi as the basis for data-collection. Each country in the study will be responsible for a data-base housed in a link institution (e.g. Lighthouse Trust Malawi, MRC UVRI Uganda). The data will be extracted from each country's database and a dataset will be pooled centrally at the MRC CTU, cleaned, queried and archived in London. The pooled dataset in London will contain no information that could lead to the identification of ART patients. Ethical clearance will be sought for this study from the appropriate local and international science and ethics committees.

The budget for this study will need to take into account the following: staffing costs in each country (nurses for blood draws, a part-time laboratory technician to conduct the virology and resistance tests, a local study coordinator to scan and collate the patient and programme data, field-tracers to ascertain the outcomes of

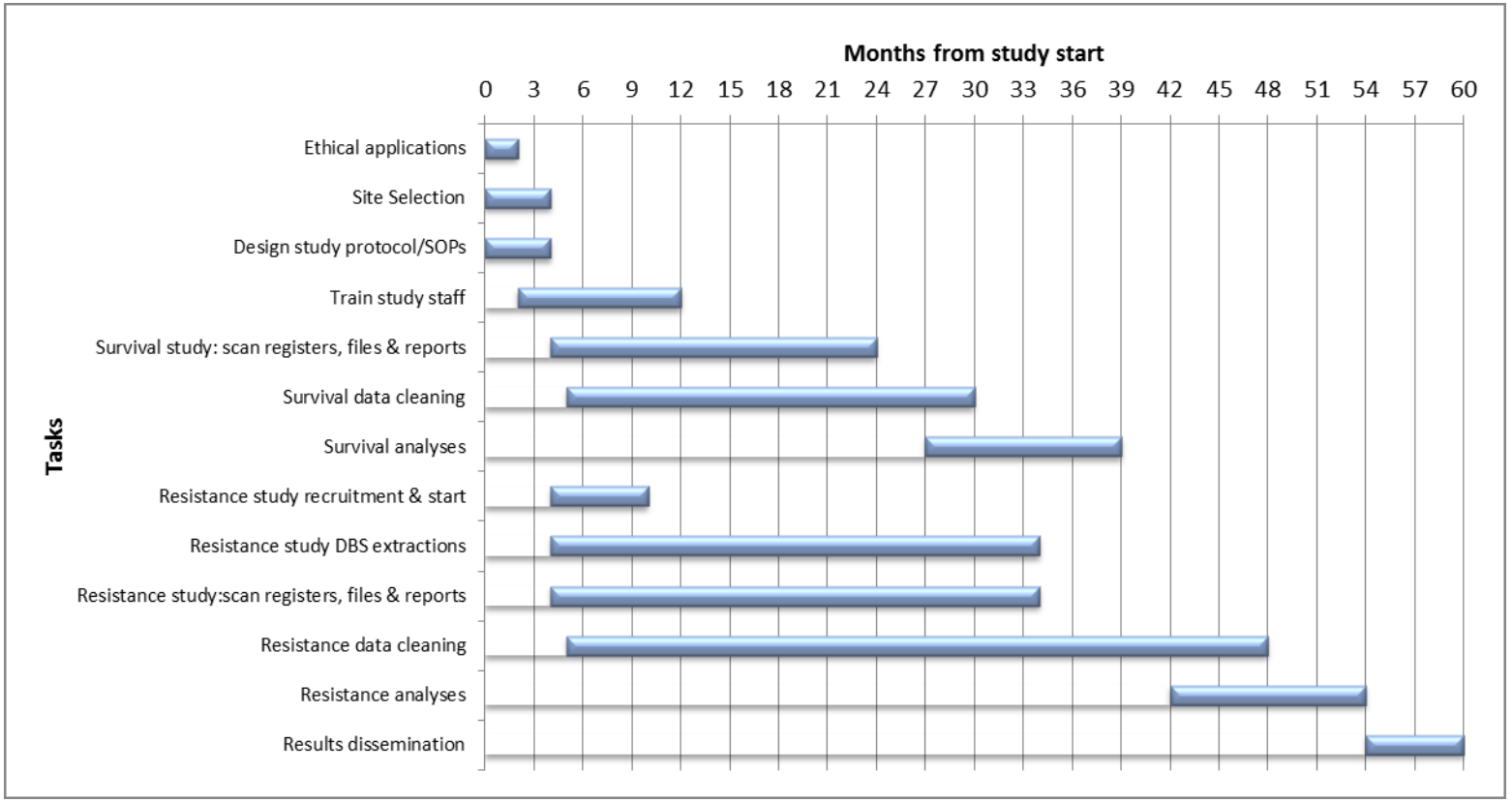
patients who become LTFU), and an epidemiologist based in London to liaise with the teams responsible for the scanning equipment and electronic data-bases, for analyses and to oversee the study; travel costs to ensure the electronic data-bases meet the study requirements and to oversee the data-collection; and funds for the laboratory tests. The selected sample size for the retrospective and prospective components will determine the final costs.

After an initial period of ethical applications, site selection, protocol writing, staff training and pilot visits to sites to ensure retrospective data are available, the data collection for the retrospective component is expected to take around 2 months per site, based on my experience from the CTX study, including patient tracing, with smaller sites requiring less time and larger sites more. An 18-month period is estimated for the retrospective data-collection for the survival indicators. Depending on the target sample-size and number of clinics involved, recruitment to the HIVDR prospective study is expected to take 6 months. The extraction of DBS at initiation, 12 and 24 months and the prospective data-collection is expected to take 30 months. Figure 7.2 shows a Gantt chart depicting a time-line for this study. The study is expected to take 5 years from ethical approval applications to the dissemination of study findings.

7.6 Discussion

ART programme monitoring indicators and the WHO EWI HIVDR have never been evaluated programmatically and the importance of this work has been recognised by representatives from key stakeholders in ART care (WHO, UNAIDS, UNGASS, PEPFAR, GFATM, DfID). Furthermore, by using retrospective data available in most clinics, which should include data from 2004, follow-up information will be available

Figure 7.2 Gantt chart depicting a 5-year time-line from ethical approval applications through to results dissemination



up to nearly 10 years post initiation of ART. This will enable the estimation of up to 10-year survival of patients on ART. Such a long-term estimate of patients on ART in routine care settings in LMIC has never been reported. However, by relying on routinely-collected ART programme data, this study has some limitations.

Firstly, data completeness of ART registers and patient files may vary between health centres. However, by using routinely-collected data, this study will show how well reported indicators reflect the data that are used by staff in health centres for patient and programme management, and how well, according to these data, the indicators reflect the health of patients in care.

Secondly, ascertainment of vital status of the patient population will be dependent on the ability of each clinic to ascertain vital status for their patients who have become LTFU. This can lead to lower survival estimates at clinics able to ascertain that patients no longer seen at the clinic have, in fact, died. LTFU status is unlikely to be random. Data from Malawi recently showed that 65% of patients lost to follow-up had actually died or stopped ART and 90% of patients who transfer out have in fact, transferred in elsewhere and show good survival outcomes, and a recent systematic review reported deaths among patients LTFU ranging from 12 – 87% [319, 320, 347]. The employment of patient tracers to establish the status of patients no longer in care will minimise the number of patients for whom this information is unknown. Where this information is not retrieved by the patient tracers, the use of different scenarios for the vital status of patients LTFU, along with appropriate statistical techniques to account for right censoring will provide a range of estimates for unknown outcomes.

Thirdly, accounting for patients transferring in for care who previously initiated ART elsewhere but who do not inform staff is challenging. The estimates of TDR at ART initiation should provide an understanding of what proportion of ART initiators have had prior drug exposure and have transferred-in unofficially.

Finally, while all efforts will be made to include only non-research health clinics, I recognise that given the multiple stakeholders involved in ART delivery, many health centres in Africa have been involved in research. This is particularly true for large health centres, making it difficult to know if differences from smaller health centres are due to size or engagement in research. The inclusion of sites involved in research will allow me to compare the performance of clinics against optimal ones.

This study will further our knowledge regarding which data reported by sites are actually useful in assessing the performance of a treatment programme. The study will provide the evidence-base through which indicators can be refined, enabling decisions to be made on which indicators should be selected to monitor HIV programmes. Refining indicators will reduce the reporting burden on clinics as indicators with poor performance are dropped, and, with fewer data to collect, should encourage better accuracy of reported indicators. With continuous interactions throughout the duration of this study with the representatives from the WHO, UNAIDS, UNGASS, PEPFAR, the GFATM and national MoH, it is intended that the results will feed into national and international recommendations for indicators used to monitor the health of the treated population. This work will ensure that indicators capture the construct they purport to measure enabling fair programme comparisons to be made and facilitating donor reporting standardisation. Refined indicators can be used to predict longer-term outcome of the patients in care

enabling managers to respond to predictors of failure early. This work is key to effective monitoring of programmes.

Chapter 8 Conclusion

This chapter synthesises the findings addressing the research aims of this thesis, to provide an improved understanding of key aspects of the treatment and health of patients accessing HIV-care programmes in LMIC and to evaluate the ways in which these aspects are measured, as follows:

- one in five and nearly one in four patients are no longer in care 12 and 24 months after ART initiation, respectively. Retention of the treated population over the longer-term is even lower. Furthermore, little published literature reports after 24 months making understanding longer-term outcomes of treated populations challenging. Given that ART has been scaled-up in LMIC since 2004, there is a need for more data on longer-term outcomes on ART.
- national MoHs collect data in cohort reports on the proportion of patients in care for longer periods than the initial 12 months, meaning data are available over the longer-term. Publishing such data would inform stakeholders about the longer-term health of patients on ART.
- published literature on the outcomes of treated populations are heavily weighted towards literature from sub-Saharan Africa and understanding the outcomes of treated populations in other geographical areas is challenging. As the number of patients accessing care programmes in LMIC geographical regions outside of sub-Saharan Africa continues to grow, publishing on the

outcomes of patients treated in these ART programmes will provide a wider understanding of the health of treated populations.

- just over half (47/83) the studies in the literature review reported on retention in care, while only 33 reported on reasons for attrition from care, 32 on immunological outcomes, 16 on virological outcomes and fewer still on other clinical outcomes (including AIDS-defining illnesses such as Tuberculosis, IRIS or hospitalisations), highlighting the uncertainty around how best to report on the health of treated populations.
- capturing and addressing reasons for attrition from care is essential if improvements in retention are to be made. The accuracy of such data when produced from paper-based systems must, however, be considered.

- the probability of CPT initiation after HIV diagnosis was low in Uganda and Tanzania and the proportion of time interrupting CPT was high, 5 years after international recommendations for the routine use of CPT were published.
- monitoring tools used to assess access to CPT are inadequate as reporting numbers diagnosed and numbers initiating CPT leads to assumptions that it is the same individuals starting CPT in the reporting period as were diagnosed. Furthermore, there is no reporting on access to CPT while in care.
- capturing data on the number of days-worth of CPT tablets prescribed for an appointment interval, the number of days-worth CPT is short by if it is prescribed with a shortfall, the number of days by which a patient attends an appointment late, and the number of occasions when CPT is dispensed from pharmacy with a shortfall will highlight the magnitude of supply-chain

or patient-led problems. Revised CPT monitoring reports are needed to reflect these data.

- 7% of patients in Uganda were diagnosed with a CMD and 11% with GPD.
- being able to identify patients at risk of these disorders is vital, yet identifying risk factors from routinely-collected data is currently not possible.
- the validity of K10 and CESD was extremely poor against M.I.N.I. diagnoses and these commonly-used screening tools vastly overestimate the prevalence of mental health disorders. For patients in HIV care in LMIC, where financial and staffing resources are scarce and the scope for mental health interventions is limited, the use of invalid mental health assessments risks targeting scarce resources incorrectly.
- new screening tools for common mental disorders that can be used in LMIC are needed as the use of the K-10 and CES-D in Ugandan HIV outpatient clinics cannot be recommended based on findings from this thesis. More research is needed to identify appropriate tools which can be used within busy HIV care clinics in LMIC.

- wide variations exist in the tools and indicators used by MoHs in Malawi, Uganda, the Ukraine and Tanzania, highlighting a lack of consensus on how best to monitor the health of the treated population. Furthermore, the internal, external, content and construct validity of indicators is questionable and has never been evaluated.
- ART programme monitoring indicators need to be evaluated scientifically in order to identify how best to monitor the health of the treated population.

Following on from the limitations discussed in each chapter, I would add a number of recommendations from the experience I derived from this work, as these may be of benefit to others undertaking similar work in the future.

While the main literature review in chapter 2 was never intended to be a systematic review or meta-analysis, the inclusion of other search engines (e.g. Embase, Global Health) would have allowed for a wider selection of studies to be included. Moreover, in a similar way to the data I included from cohorts reporting to UNAIDS, the inclusion of data from cohorts reporting to the GFATM and PEPFAR would have provided additional data not subject to the potential biases of including only information from cohorts published in peer-reviewed journals. Finally, an evaluation of the quality of studies before deciding on their inclusion would have minimised the influence of cohorts with a weak study design on summary estimates.

The Cotrimoxazole study described in chapters 3 and 4 was challenging as it used retrospective data which resulted in many missing data, particularly on the date of CPT initiation in the pre-ART register. There were also many missing data in patient files relating to the number of pills prescribed or the number of days-worth of pills prescribed to patients. A prospective study may have allowed for better data capture on these key outcome measures.

The mental health study described in chapter 5 which was undertaken in 2 clinics in Uganda would have benefitted from the inclusion of more clinics. The interviews would have benefited from being reversed (having the screening tool assessments before the diagnostic interview) in order to minimise any bias on the part of participants. It would have been interesting to examine the results derived for the

AUROC against a clinically-relevant value rather than choosing values which maximised sensitivity and specificity.

The comparison of MoH indicators described in chapter 6 could have benefited from being undertaken across a wider range of countries, particularly outside of sub-Saharan Africa, for example in Asia, Latin America and more in Eastern Europe. This would have allowed a comparison with the priorities of the Ministry of Health in countries experiencing challenges associated with HIV care different to those experienced in sub-Saharan Africa.

The study described in chapter 7 may benefit from the inclusion of a third component, examining indicators which predict viral suppression among patients in care, given the clinical importance of controlled viraemia for patients in care. A further expansion to this study design would have been the inclusion of ART programmes in areas of civil conflict where the burden of refugees and internally displaced persons is vast. This would allow the examination of which indicators are most appropriate to monitor the health of patients accessing ART programmes in areas where ensuring the regular supply of medications and retaining patients in care is particularly challenging [348, 349].

8.1 Dissemination plans and recommendations for future research

I plan to disseminate the results of the Cotrimoxazole and mental health studies to representatives from the MoH, who approved the work in their countries. Thereafter, I hope to publish the following manuscripts:

- A review of the long-term health of populations treated in ART programmes in LMIC

- Access to and ongoing use of CPT after HIV diagnosis and associated factors in Uganda and Tanzania
- Validity of measurement tools used to diagnose mental disorders among HIV-infected patients in Uganda

I have previously published the results of the comparison of national monitoring data and continue to liaise with the representatives from the MoH involved in this work as I attempt to secure funding for the proposed indicators validation study.

This topic is multifaceted and to generate achievable policy changes there is a need for further assessments at the local level. Future research in the following areas can facilitate the attainment of better overall care and monitoring of the health of patients in HIV care:

1. It is important to monitor the welfare of HIV-positive individuals not yet on ART, particularly relating to access to and retention on CPT. Studies are needed to quantify the role of CTX stock-outs and late-appointment attendance on poor outcome.
2. It is important to identify the most appropriate mental health screening tools which can be used quickly by HIV health care workers. A multi-country study is needed in which more evidence can be generated to assess whether any data routinely collected in HIV care can be used to identify at-risk patients, and in which appropriate screening tools can be identified.
3. It is important to assess currently used monitoring indicators scientifically. A study (as recommended in Chapter 7 of this thesis) is needed to evaluate the validity and predictive value of currently collected ART programme monitoring indicators.

8.2 Conclusion

With international recommendations to raise CD4 thresholds to 500 cells/mm^3 for the initiation of ART and the move towards the use of ART for the prevention of HIV transmission, HIV care is now entering an era of further expanded access to ART [350]. It is worth noting that while current evidence suggests that a combination of ART and CPT is better than ART alone in the prevention of mortality and morbidity in children, the role of CPT may become less relevant as ART is initiated earlier in the course of disease [240]. With the new recommendations, as the number of patients accessing ART will increase, so too will the challenges for clinic staff responsible for the health of patients in their care. Primarily, retaining ever-increasing numbers of patients in care with suppressed viraemia will become all the more important. This is likely to be particularly challenging as patients who are less sick at ART initiation may be less adherent to appointments and to ART regimens, increasing the risk of onward viral transmission and the development of drug resistance. Identifying indicators which best capture retention in care and which can reliably predict HIVDR, as proposed in chapter 7, will be crucial. The provision of ART to larger numbers of patients will result in increased and prolonged exposure to ART and an associated need to monitor toxicities and transmitted and acquired drug resistance [350]. Additionally, the provision of ART to pregnant and breastfeeding mothers will increase the need to monitor pregnancy-related toxicities, birth defects, the growth of new-borns and possible developmental delays in infants exposed to ARV drugs [350]. These additional monitoring activities will add to the reporting burden on clinic staff and resources will need to be put in place to ensure that accurate data on all aspects of HIV care are captured, to address the validity issues identified in chapter 6. The study proposed in chapter 7, to identify only the most relevant monitoring indicators, becomes all the more relevant, the

results of which should ensure the burden on clinic staff of reporting requirements is minimal.

In spite of the significant achievements in scaling-up access to ART in LMIC, in practice, this has only offered part of a solution to the long-term management of patients in HIV care. Many areas of health are not being sufficiently addressed, examples of which are given here: the prevention of opportunistic infections and the identification of common mental disorders which are known to affect adherence to care. Furthermore, the benefits of initiating patients on ART may be short-lived, if retention in care is not ensured. Moreover, evidence is needed for ART programme monitoring indicators, to assess which, if any, reflect the health of the populations in care. This is important if health care staff time is to be used efficiently and effectively and if HIV care programmes are to be better evaluated.

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Appendices