Key Social and Behavioural Factors Influencing Clinical Outcomes for People with HIV receiving Antiretroviral Therapy in Diverse Settings

by

James Hamilton McMahon
MB BS, MPH, FRACP

A thesis submitted in fulfilment of the requirements
for the degree of Doctor of Philosophy

Monash University, Melbourne, Australia

April 2013

Addendum

p 33 line 4: delete “the definitive” and replace with “a comprehensive”

p 87 end of para 2 insert:

“Furthermore, multiple techniques to physically trace patients are possible including home visits by community workers, healthcare workers or individuals nominated by patients. The ability to implement these programs in different clinical and social contexts will be dictated by multiple factors including: costs, acceptability to patients, safety for individuals performing physical tracing and ensuring the confidentiality of patients.”

p 87 end of para 3 insert:

“This is particularly relevant considering new 2013 WHO guidelines for management of HIV in adults and adolescents that now recommend viral load testing whenever possible for people receiving ART (1). This will likely lead to increased virological outcome data that will need to be accurately interpreted in the context of previously reported virological outcomes from LMICs such as the summary data presented in this review.”

p 158 para 2 line 6 before “Ultimately” insert:

“In addition significant associations documented in the observational studies in this thesis are potentially subject to unknown confounders that could alter the findings.”

p 159 line 1 before “Findings” insert:

“This review also lays the groundwork to explore different approaches to implement PAMs such as the medication possession ratio in real-time clinic and/or program settings to assess ART adherence, and potentially trigger interventions to maximise adherence”

P 159 para 3 line 3 after “studied”:

“and how prevalent these factors are elsewhere in India.”

Addendum Reference

1. WHO. Consolidated guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recimmendations for a public health approach. June 2013. World Health Organization, 2013.

Table of contents

1 Summary, Declarations and Publications vi

1.1 Abbreviations vii

1.2 Summary 8

1.3 Originality statement 10

1.4 General Declaration of author's contribution 11

1.5 Resultant publications 16

2 Background 19

2.1 Introduction 20

2.2 Social factors influencing clinical outcomes in the United States 23

2.3 The public health model of providing antiretroviral therapy 25

2.4 Summary 29

2.5 Aims of thesis 30

3 Literature Review 31

3.1 Introduction 32

3.2 Effects of patient tracing on estimates of lost to follow-up, mortality and retention in antiretroviral therapy programs in low-middle income countries: A Systematic Review 35

3.2.1 Declaration 35

3.2.2 Paper 37

3.3 Viral Load Outcomes after 12 Months Antiretroviral Therapy in Low to Middle Income Countries: A Systematic Review 50

3.3.1 Declaration 50

3.3.2 Paper 52

3.4 Pharmacy based adherence measures to assess treatment and adherence to antiretroviral therapy. Review of the literature and implications for treatment monitoring 70

3.4.1 Declaration 70

3.4.2 Paper 73

3.5 Summary 88

4 Hunger, Education, and Residential Status Impact Survival in HIV 90

4.1 Declaration 91

4.2 Introduction 93
4.3 Paper 95
5 Repeated assessments of food security predict CD4 change in the setting of antiretroviral therapy 105
5.1 Declaration 106
5.2 Introduction 108
5.3 Paper 110
6 Targets for intervention to improve virological outcomes for patients receiving free antiretroviral therapy in Tamil Nadu, India. 115
6.1 Declaration 116
6.2 Introduction 120
6.3 Paper 122
7 Pharmacy and self-report adherence measures to predict virological outcomes for patients on free antiretroviral therapy in Tamil Nadu, India 141
7.1 Declaration 142
7.2 Introduction 146
7.3 Paper 148
8 General Discussion 156
9 References 162

1 Summary, Declarations and Publications

1.1 Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
HIC	High Income Country
HIV	Human Immunodeficiency Virus
LMIC	Low to Middle Income Country
LTFU	Lost To Follow-Up
NACO	National AIDS Control Organization
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PAM	Pharmacy Adherence Measure
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Protease Inhibitor
PLHIV	People Living with HIV/AIDS
SES	Socioeconomic Status
UNAIDS	Joint United Nations Program on HIV/AIDS
UNGASS	United Nations General Assembly Special Session on AIDS
US	United States
WHO	World Health Organization

1.2 Summary

Since the advent of combination antiretroviral therapy (ART) in 1996 there has been significant reductions in mortality for patients living with HIV where these medications have been available. Despite this advance, socio-behavioural factors such as socioeconomic status (SES) while on ART and adherence to ART can impact outcomes considerably for these individuals. The overarching goal of this thesis was to identify patient specific factors associated with worse clinical outcomes and the identification of methods to better assess adherence to ART in diverse clinical settings. These factors and estimates of adherence can then allow for the implementation of evidence based interventions or the design of targeted interventions that will maximise clinical outcomes for people receiving ART.

The studies that were performed to make up this thesis used multiple techniques to identify assessments of ART adherence and socio-behavioural factors that predict clinical outcomes for patients receiving ART. These include systematic reviews of the literature, analyses of prospective cohorts receiving ART in the North-eastern United States and retrospective cohort studies of a population of HIV-infected individuals receiving ART in Tamil Nadu India.

Major findings from this group of studies include the first systematic summary of how ART adherence assessments using routinely collected pharmacy data predict survival, virological and immunological outcomes for patients in HICs and LMICs. In addition a framework to categorise pharmacy adherence measures (PAMs) and recommendations on how to best select PAMs to predict clinical outcomes in patients receiving ART was established. Further systematic reviews established normative rates of virological suppression for individuals in LMICs after 12-months ART, and documented the impact of tracing patients who become lost to follow-up (LTFU) after initiating ART. In addition a systematic review of the effects of physical tracing of patients who are LTFU describes how physical tracing may lead to increased re-engagement of patients in care, rather than just improved classification of outcomes for patients considered LTFU.

Analyses of a cohort of individuals followed in the North-eastern United States revealed how different markers of SES such as poverty, education level and housing insecurity predict survival despite the use of ART. An additional study identified that individuals assessed as food insecure on even one occasion over multiple years of follow-up was a potent predictor of immunological decline even in the setting of ART.

Studies of a retrospective cohort of HIV-infected individuals initiating free ART in Tamil Nadu, India identified multiple factors predicting virological failure after 12-months of ART. Programmatic factors such as prolonged patient travel time to clinic and individual factors such as patients having busy schedules or reporting a history of alcohol use were identified as factors predicting poor virological outcomes after 12-months ART. Furthermore multiple assessments of adherence to ART using different questions about self-reported adherence or pharmacy data identified that PAMs but not self-report measures were most predictive of virological outcomes in this setting.

This body of work is a significant contribution as multiple socio-behavioural factors and adherence measures that predict poor outcomes for people receiving ART were identified. Importantly this group of studies have been performed in different populations affected by HIV using different models of HIV care. This gives a unique insight into how different social, cultural and behavioural aspects of the lives of people living with HIV can influence clinical care. Furthermore, these novel patient specific factors and mechanisms to assess ART adherence that were found to predict clinical outcomes are important because they are amenable to implementation, in both HICs and LMICs to alleviate morbidity and mortality for patients receiving ART.

1.3 Originality statement

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at Monash University or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at Monash or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

James Hamilton McMahon
April 2013

1.4 General Declaration of author's contribution

PART A: General Declaration

Monash University

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 6 original papers published in peer reviewed journals and 1 unpublished publication. The core theme of the thesis is exploring social and behavioural factors that influence clinical outcomes for people with HIV receiving antiretroviral therapy in higher and lower income settings. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Infectious Diseases at Alfred Health and Monash University, and the Department of Public Health and Community Medicine at Tufts University in Boston under the supervision of Dr Julian Elliott, Professor Sharon Lewin and Professor Christine Wanke.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapter numbers 3, 4, 5, 6 and 7 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
3.2	Pharmacy Adherence Measures to Assess Adherence to Antiretroviral Therapy: Review of the Literature and Implications for Treatment Monitoring	Published	I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript
3.3	Effects of patient tracing on estimates of lost to follow-up, mortality and retention in antiretroviral therapy programs in low-middle income countries: A Systematic Review.	Published	I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript
3.4	Viral Load Outcomes after 12 Months of Antiretroviral Therapy in Low and Middle Income Countries: A Systematic Review	Published	I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript
4	Poverty, Hunger, Education, and Residential Status Impact Survival in HIV	Published	I led the design based on a pre-existing dataset, performed all analyses and wrote the manuscript
5	Repeated Assessments of Food Security Predict CD4 Change in the Setting of Antiretroviral Therapy	Published	I led the design based on a pre-existing dataset, performed all analyses and wrote the manuscript
6	Targets for intervention to improve virological outcomes for patients receiving free antiretroviral therapy in Tamil Nadu, India	Submitted	I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript

7	Pharmacy and self-report adherence measures to predict virological outcomes for patients on free antiretroviral therapy in Tamil Nadu, India	Published	I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript

I have / have not (circle that which applies) renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: [redacted]

Date: 16 APR 2013

I hereby specifically acknowledge the following contributions of other people and organisations to the content of this thesis:

Pharmacy Adherence Measures to Assess Adherence to Antiretroviral Therapy: Review of the Literature and Implications for Treatment Monitoring

My co-authors Michael R. Jordan, Karen Kelley, Silvia Bertagnolio, Sharon R. Lewin, Christine A. Wanke and Julian H. Elliott for contributing to the development of the manuscript. Michael R. Jordan and Julian H. Elliott helped conceive the idea for the review and an approach to review of the literature.

Kenneth Mayer provided advice to develop the discussion of the manuscript

Effects of patient tracing on estimates of lost to follow-up, mortality and retention in antiretroviral therapy programs in low-middle income countries: A Systematic Review.

My co-authors Julian Elliott, Steven Hong, Silvia Bertagnolio and Michael R. Jordan for contributing to the development of the manuscript. Michael R. Jordan helped conceive the idea for the review and also reviewed selected studies if there were any concerns about the initial data abstraction. Michael R. Jordan and Julian H. Elliott

helped devise the protocol to systematically review the literature. Julian H. Elliott was available as a third reviewer in case of conflicting results after data abstraction. Steven Y. Hong, and Silvia Bertagnolio participated in interpreting the results and structuring the manuscript.

Viral Load Outcomes after 12 Months of Antiretroviral Therapy in Low and Middle Income Countries: A Systematic Review

My co-authors Julian H. Elliott Silvia Bertagnolio, Rachel Kubiak and Michael R. Jordan for contributing to the development of the manuscript. Michael R. Jordan helped conceive the idea for the review. Michael R. Jordan and Julian H. Elliott helped devise the protocol to systematically review the literature. Rachel Kubiak assisted with the initial search of published work, reviewed full-text articles and conference abstracts and extracted data from the manuscripts and conference abstracts. Silvia Bertagnolio participated in interpreting the results and structuring the manuscript.

Poverty, Hunger, Education, and Residential Status Impact Survival in HIV

My co-authors Christine Wanke, Norma Terrin, Sally Skinner and Tamsin Knox for contributing to the development of the manuscript. Christine Wanke and Tamsin Knox helped conceive the idea for the analysis and provided advice throughout the process of developing the manuscript. Norma Terrin advised on a statistical plan. Sally Skinner assisted with accessing data from the NFHL dataset and formulating statistical code for the analyses.

Repeated Assessments of Food Security Predict CD4 Change in the Setting of Antiretroviral Therapy

My co-authors Christine Wanke, Julian Elliott, Sally Skinner and Alice Tang for contributing to the development of the manuscript. Christine A. Wanke and Alice Tang helped conceive the idea for the analysis and provided advice throughout the process of performing the analysis and writing the manuscript. Julian H. Elliott contributed to interpreting the results and preparing the manuscript. Sally Skinner assisted with accessing data from the NFHL dataset and formulating statistical code for the analyses.

Targets for intervention to improve virological outcomes for patients receiving free antiretroviral therapy in Tamil Nadu, India

My co-authors Anand Manoharan, Christine Wanke, Shoba Mammen, Hepsibah Jose, Thabeetha Malini, Tony Kadavanu, Michael R. Jordan, Julian H Elliott, Sharon R. Lewin and Dilip Mathai for contributing to the development of the manuscript. Anand Manoharan and Dilip Mathai helped design the study, write the study protocol, interpret the results and oversee study procedures at the study site. Christine Wanke, and Sharon R. Lewin helped conceive the analysis and interpret the study results. Michael R. Jordan, Julian H Elliott helped design the study, conceive the analysis and interpret the study results. Hepsibah Jose, Thabeetha Malini and Tony Kadavanu helped recruit and conduct interviews for study participants. Shoba Mammen established procedures for the performance of viral load tests and interpret viral load data.

Pharmacy and self-report adherence measures to predict virological outcomes for patients on free antiretroviral therapy in Tamil Nadu, India

My co-authors Anand Manoharan, Christine Wanke, Shoba Mammen, Hepsibah Jose, Thabeetha Malini, Tony Kadavanu, Michael R. Jordan, Julian H. Elliott, Sharon R. Lewin and Dilip Mathai for contributing to the development of the manuscript. Anand Manoharan and Dilip Mathai helped design the study, write the study protocol, interpret the results and oversee study procedures at the study site. Christine Wanke, and Sharon R. Lewin helped conceive the analysis and interpret the study results. Michael R. Jordan, Julian H Elliott helped design the study, conceive the analysis and interpret the study results. Hepsibah Jose, Thabeetha Malini and Tony Kadavanu helped recruit and conduct interviews for study participants. Shoba Mammen established procedures for the performance of viral load tests and interpret viral load data.

1.5 Resultant publications

This thesis has resulted in a number of publications, which have been published or are currently under review. The manuscripts that have been accepted for publication are presented as they were published in the respective journals. Publications still under review are presented to fit the thesis format, including consistency of font and referencing, and omission of article abstracts. Bibliographies of references for each of the seven manuscripts included in this thesis, whether published or submitted for publication, are listed at the end of each manuscript. In addition a separate bibliography of references at the end of the thesis contains references that are cited within the remaining text of the thesis.

Published review and opinion articles in refereed journals

McMahon JH, Elliott JH, Kubiak R, Jordan MR. Viral Load Outcomes after 12 Months Antiretroviral Therapy in Low to Middle Income Countries: A Systematic Review. Accepted. Bull WHO. 2013

McMahon JH, Elliott JH, Hong SY, Bertagnolio S, Jordan MR. Effects of patient tracing on estimates of lost to follow-up, mortality and retention in antiretroviral therapy programs in low-middle income countries: A Systematic Review. PLoS One. 2013 Feb;8(2):e54607

McMahon JH, Wanke CA, Elliott JH, Skinner S, Tang AM. Repeated assessments of food security predict CD4 change in the setting of antiretroviral therapy. J Acquir Immune Defic Syndr. 2011 Sep 1;58(1):60-3.

McMahon JH, Jordan M, Kelley K, Bertagnolio S, Lewin SR, Wanke CA, Elliott JH Pharmacy based adherence measures to assess treatment and adherence to antiretroviral therapy. Review of the literature and implications for treatment monitoring. Clin Infect Dis. 2011 Feb;52(4):493-506.

McMahon J, Wanke C, Terrin N, Skinner S, Knox T. Poverty, Hunger, Education, and Residential Status Impact Survival in HIV. AIDS Behav. 2011. Oct;15(7):1503-11.

McMahon JH, Manoharan A, Wanke CA, Mammen S, Jose H, Malini T, Abraham P, Bella A, Kadavanu T, John J, Lewin SR, Jordan MR., Elliott JH, Mathai D. Pharmacy and self-report adherence measures to predict virological outcomes for patients on free antiretroviral therapy in Tamil Nadu, India. Accepted. AIDS Behav 2013

Submitted/for submission to refereed journals

McMahon JH, Manoharan A, Wanke CA, Mammen S, Jose H, Malini T, Abraham P, Bella A, Kadavanu T, John J, Lewin SR, Jordan MR., Elliott JH, Mathai D. Targets for intervention to improve virological outcomes for patients receiving free antiretroviral therapy in Tamil Nadu, India

Conference proceedings

McMahon JH, Elliott JH, Kubiak R, Jordan MR. Viral Load Outcomes after 12 Months Antiretroviral Therapy in Low to Middle Income Countries: A Systematic Review. Abstract WEPE142. 19th International AIDS Conference Washington, D.C., USA. July 2012, and Oral Presentation. Abstract 462. Australasian HIV/AIDS Conference, Melbourne, Australia.

McMahon JH, Manoharan A, Wanke CA, Mammen S, Jose H, Malini T, Abraham P, Bella A, Kadavanu T, John J, Lewin SR, Jordan MR., Elliott JH, Mathai D. Social and clinical factors predicting virological and adherence outcomes for patients receiving free antiretroviral therapy in Tamil Nadu, India. Abstract TUPE073. 19th International AIDS Conference Washington, D.C., USA July 2012.

McMahon JH, Elliott JH, Hong SY, Jordan MR. Effects of patient tracing on estimates of lost to follow-up, mortality and retention in antiretroviral therapy programs in low-middle income countries: A Systematic Review. Oral Abstract MOAC0302. Access to

and Retention of Antiretroviral Treatment Session, 19th International AIDS Conference Washington, D.C., USA. July 2012.
And Oral Abstract 458. Australasian HIV/AIDS Conference, Melbourne, Australia.

McMahon JH, Jordan M, Kelley K, Bertagnolio S, Lewin SR, Wanke CA, Elliott JH Pharmacy and self-report adherence measures to predict clinical outcomes for patients on free antiretroviral therapy in Tamil Nadu, India. Oral Abstract 68, Australian Society for Infectious Diseases Conference, Fremantle, Australia, 2012

McMahon JH, Manoharan A, Wanke CA, Mammen S, Jose H, Malini T, Abraham P, Bella A, Kadavanu T, John J, Lewin SR, Jordan MR., Elliott JH, Mathai D. Social and Clinical Factors Predicting Virological Response in the Public Health Model of HIV care in Tamil Nadu, India. Abstract 354, Australasian HIV/AIDS Conference, Canberra, Australia. 2011.

McMahon JH, Tang AM, Skinner S, Elliott JH, Rubin A, Sprague S, Wanke CA. Associations between history of food security, body mass index and immunological response. Abstract CDC0264. International AIDS Society conference, Austria, 2010

McMahon J, Wanke C, Terrin N, Skinner S, Knox T. Demographic, HIV related and socioeconomic factors and mortality in a cohort of HIV infected patients, Oral Abstract, Australian Society for Infectious Diseases Conference, Hunter Valley, Australia, 2009

2 Background

2.1 Introduction

The most recent estimate of the global burden of the HIV pandemic published by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2012 report that 34 million people are living with HIV/AIDS (PLHIV) and 2.5 million new infections occurred globally by the end of 2011 (1). Since the introduction of antiretroviral therapy (ART) PLHIV have experienced decreasing levels of morbidity and mortality. This was initially observed in high-income and subsequently in low- to middle-income countries (LMICs) as ART became more widely available (2, 3). Initial studies of antiretroviral monotherapy reported reductions in levels of circulating HIV with the first clinical trials of the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine in the late 1980s (4) and subsequently protease inhibitors (PIs) in the mid-1990s (5) Despite these initial observations, subsequent elevations in HIV viral load and the selection of drug resistant strains of HIV (6) were observed in patients receiving monotherapy; leading to the investigation of combination antiretroviral therapy. Randomized clinical trials of different antiretroviral (ARV) combinations reported the virological and clinical superiority of double NRTIs over NRTI monotherapy (7) and subsequently the combination of 3 drugs, including either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI), over double NRTI regimens (8-10) Furthermore, data from an LMIC, Cote d'Ivoire, where double-NRTI regimens were initiated in some patients due to the increased cost of triple ARV regimens, also reported double-NRTI regimens having inferior virological efficacy (11).

The advantages of combination ART using 3 medications as described in these pivotal clinical trials was rapidly translated into reductions in mortality, opportunistic infections and hospital admissions within observational cohorts and routine surveillance systems (2, 12, 13). Reductions in morbidity and mortality have also been seen in LMICs as ART became more widely available in the mid-2000s. However rates of survival in the first 12-months after starting ART were impacted by patients commencing ART with advanced symptomatic disease at lower CD4 T-cell counts (14, 15). Despite these advances the recently published global burden of disease 2010 study reports AIDS-related deaths as still the 6th most common cause of death globally (16) which the executive director of UNAIDS has described as "..a persistent, significant, and egregious burden of avoidable death" (17).

The goal of combination antiretroviral therapy is to achieve virological suppression (18-20). While high rates of virological suppression can be achieved for populations receiving ART in both HICs and LMICs residual levels of mortality and morbidity are still observed for PLHIV receiving ART (21, 22). In addition populations living with HIV can be overrepresented by individuals with characteristics such as low SES, use of intravenous drugs (IDU), cigarette smoking, heavy alcohol consumption, co-morbid psychiatric illnesses and traditional cardiac risk factors such as hypertension, dyslipidaemia and diabetes (23-25). Importantly low SES has also been associated with worse survival and increased numbers of clinical events for diseases such as cancer and cardiovascular disease for people not living with HIV (26-29).

Debate about whether residual elevated morbidity associated with HIV is due to the HIV virus itself or factors overrepresented in populations living with HIV continues with evidence from prospective observational cohorts and mathematical modelling studies supporting the notion that factors not related to the HIV virus itself play an ongoing role in predicting clinical outcomes (22, 30). In addition there is evidence that in populations affected by HIV SES can impact clinical outcomes such as survival, virological failure on ART and the appearance of opportunistic diseases as immune function declines (31-33). These social and behavioural factors that can impact clinical outcomes on ART can be assessed using various methods. For example, SES can be measured using individual, household or ecological measures focussing on issues such as income, education level achieved or access to reliable housing and sources of food (31, 32, 34, 35).

Another important factor affecting outcomes for people receiving ART is adherence to these medications. Consistent suppression of HIV below the levels of detection in commonly used clinical assays requires high levels of adherence, commonly quoted as greater than 95% (36). The inherent capacity of HIV to replicate in the absence of drug pressure, also known as its replicative capacity, means that reductions in adherence will lead to the emergence of drug resistant HIV. This contribution of low adherence to virological rebound and HIV drug resistance is assisted by the error prone nature of HIV replication, its high mutation rate in the presence of drug selective

pressure, and because of the need for lifelong treatment. Subsequently high levels of adherence represent a critical factor in achieving good outcomes for people receiving ART and low adherence has been associated with virological failure, the emergence of drug resistance and worse survival (36-40). Assessments of adherence take multiple forms ranging from self-reported levels of adherence, prescription or pill-based methods, therapeutic drug monitoring and use of electronic devices such as pill bottles that can record opening times or web-enabled pill boxes (40-43). These different methods have different advantages and disadvantages with assessments such as electronic pill bottles or therapeutic drug monitoring being largely confined to research settings (41).

The work presented in this thesis demonstrates how the identification of social factors predicting poor outcomes or individuals with low ART adherence allows for the development of interventions to improve clinical outcomes. This can take the form of interventions that have already been shown to be successful in improving treatment outcomes on ART (44-47). In addition identification of issues that predict poor outcomes can lay the foundations for further research, such as randomised controlled trials, of interventions that are designed to directly address identified barriers to care. Importantly, research to identify the most effective interventions based on studies similar to those in this thesis are warranted due to different barriers to care that occur PLHIV in diverse clinical settings (48).

In conclusion there is a critical need to establish accurate assessments of social factors and ART adherence associated with poor clinical outcomes to build on the significant gains delivered by the introduction of ART. This is particularly important as a greater understanding of these factors will allow for the design of targeted interventions to improve outcomes for people receiving ART. Furthermore this work needs to have a global focus to identify issues specific to settings with different cultural, social and economic pressures and to allow populations in both HICs and LMICs disproportionately affected by the HIV epidemic to maximise the potential of combination ART.

2.2 Social factors influencing clinical outcomes in the United States

The observational Whitehall studies that prospectively studied British civil servants from 1967 reported the landmark findings relating lower socioeconomic status with worse survival. In addition lower social class was linked to an increased likelihood of a range of chronic medical conditions including cardiovascular disease, diabetes mellitus and chronic respiratory illnesses (49, 50). Since these early observations there has been increasing interest in the contribution of SES in predicting shorter life expectancy and the earlier onset of chronic medical illnesses across different populations. Following on from the broader initial Whitehall observations, data linking low SES as measured by poverty and social integration has been associated with increased disease-specific mortality for chronic diseases such as cardiovascular disease, cancer and chronic renal failure, diarrheal disease and respiratory infections (51-56).

In the context of populations living with HIV in HICs, studies since the onset of the HIV epidemic examining associations between different markers of SES and mortality have reported different findings. Before the availability of combination ART an association between lower SES and mortality was not consistently reported yet studies after the widespread use of ART document associations between low SES and increased mortality (32, 33, 57-59). Importantly these studies are often limited by the use of ecological assessments of SES that typically apply suburb or area-level information on median income derived from periodic census data. Individual assessments of SES based on responses to questions about levels of income, current housing status and ability to access food provides more accurate information when attempting to associate these measures with clinical outcomes such as survival. The Nutrition for Healthy Living (NFHL) cohort is a prospective cohort of PLHIV followed in Massachusetts and Rhode Island in the North-eastern United States (60). This study performed individual assessments of SES every 6 months encompassing personal income, education level, housing status and food security status. Repeated assessment of SES on an individual level allows for analyses that allow a more detailed

and potentially more accurate understanding of the relationship between SES and clinical outcomes in PLHIV such as all-cause mortality.

Food insecurity, or the limited or uncertain availability of an adequate food supply, occurs in approximately 50% of North American PLHIV and is roughly five times the rate of food insecurity in the general population (61-64). In HIV-infected populations it has been associated with markers of low SES such as poverty, IDU and co-morbid depression (35, 61, 63). Furthermore, food insecurity has been linked to lower adherence to ART, poor virological outcomes and decreased survival (61, 62, 65). The mechanism by which food security is associated with these clinical outcomes is unclear. Potentially food insecurity is a surrogate for lower SES or there may be a biological mechanism that links poor quality diet to inferior clinical outcomes. Associations of food security with immunological responses have only been reported in cross-section, and studies examining repeated assessments of food security over time are not available. Within the NFHL cohort assessments of food security status occurred every 6 months for individuals enrolled and allowed to examine how multiple assessments of food security could predict treatment response in a HIC setting where ART was widely available. Immunological response, or change in the number of CD4 T-cells is a critical indicator of treatment success as initially demonstrated after the introduction of combination ART from 1996. Rises in CD4 T-cell counts and concomitant reductions in mortality and the incidence of opportunistic infections were seen in Europe and North America (2, 66). In addition higher CD4 T-cell counts for individuals maintained on ART have been associated with a reduced risk of death from serious non-AIDS events such as liver disease, cancer and cardiovascular disease (67).

We examined for associations between food security and CD4 T-cell changes controlling for antiretroviral therapy use and other markers of SES. Furthermore, the presence of repeated food security assessments allowed an analysis of how individual and repeated assessments of individuals as food insecure influenced immunological response over time.

2.3 The public health model of providing antiretroviral therapy

Of the estimated 34 million people living with HIV, lower income countries share a disproportionately high burden of the pandemic. Over 20 million people in sub-Saharan Africa and 5 million people in Asia are living with HIV with next most heavily affected areas being the Caribbean, Eastern Europe and central Asia (1). The first presentations about the use of combination ART that could induce profound and long lasting viral suppression occurred at the 1996 International AIDS conference in Vancouver (68). Soon after this advantages in survival for people living with HIV became clearly apparent (2, 9, 69). As ART became more widely available in HICs the disparities between health outcomes in higher and lower income settings broadened further. The burden of HIV in LMICs continued to grow while ART was leading to dramatic reductions in mortality in HICs the concept of alternate and lower pricing for ART was launched with the UNAIDS Drug Access Initiative in 1997 (70). While the prices of ART negotiated in this initiative were lower than in HICs they were not of an order to allow the widespread uptake of ART in LMICs.

From this beginning and with the assistance of increasing pressure from political groups and community activism a method to provide low-cost reliable ART became an increasingly important focus for all populations living with HIV and other stakeholders associated with HIV care and treatment around the globe. Negotiations with pharmaceutical companies and the generic manufacture of ART in India and Brazil lead to marked reductions in cost. This combined with initiatives such as: a Global Fund to receive donations from UN-member countries for purchase and distribution of generic ART, a declaration on HIV/AIDS by the UN general assembly, the US government's commitment via the President's Emergency Plan for AIDS Relief (PEPFAR) and a commitment by the WHO in 2003 to have 3 million individuals receiving ART by the end of 2005 ("3 by 5" initiative) (71, 72). These activities were critical steps to initiate the scale-up of ART in LMICs which has now reached over 8 million people as of the end of 2011 (1). In addition ART was provided in a public health model that aimed to minimise monitoring of therapy and simplify how treatment is provided while still maximising the advantages of ART. This model was defined by

the WHO as "one that strikes an acceptable balance between the most intensive, individually tailored treatment and laboratory monitoring used in high-income countries and those likely to be most effective, equitable and feasible for treating large numbers of people in resource-constrained settings" (72).

It is estimated that 2.4 million people are living with HIV in India which represents the country with 3rd highest number of PLHIV behind South Africa and Nigeria and the highest burden country in Asia (73). In contrast to sub-Saharan Africa the epidemic is not generalised throughout the country with focussed epidemics affecting different at-risk populations in different regions of the country. Subsequently the prevalence of HIV varies by state and ranges from 0.1 to 1.1%. The state of Tamil Nadu is considered one of the 6 high prevalence states within India and has an estimated prevalence of 0.34% (74, 75). Since 2000, the government of India has provided free ART at government and other supported clinics as part of its national comprehensive HIV national control program (75) and as of January 2012 over 480,000 people are receiving free National AIDS Control Organization (NACO) funded ART (76). However, despite these achievements ART coverage remains a challenge with somewhere between 23 – 55% of eligible patients receiving ART during 2009 (77). The NACO sponsored clinic (ACTFID) at Christian Medical College (CMC) in Vellore, is one of 5 sites providing free government sponsored ART in the Vellore district (population 3.5 million) of Tamil Nadu. This clinic represents one of many public-private partnership sites in India where non-governmental and private organizations collaborate with NACO to provide free clinical care and ART services per NACO treatment guidelines (78).

Data on treatment initiation is available from NACO, but there is limited data on virological outcomes for people receiving ART in India via the public health model of care. Specific cohorts reporting on patients receiving private or a mixture of public and private care have documented rates of virological suppression upwards of 80% for people receiving first line ART (79-82). HIV drug resistance outcomes in these cohorts have also been reported. Data on cohorts exclusively receiving free ART is lacking and a clear gap in our current understanding of ART outcomes in LMIC. Adherence to ART is critical to achieve viral suppression, prevent HIV drug resistance, reduce

HIV related mortality (37) and ensure the maintenance of first-line ART (42). The ability to sustain high levels of adherence to ART it is of particular interest in LMICs where switching to second line therapies may be difficult due to increased cost, complexity, and lack of further treatment options (83). Furthermore monitoring adherence via simple low-cost measures is essential if individuals with low adherence are to be identified so they can benefit from interventions to improve outcomes on ART. Adherence interventions can then be designed based on the identified barriers. These targeted interventions can then be preferable in terms of improving ART adherence and virological outcomes (84-86) compared to more generalized interventions that do not achieve the same adherence and virological benefits (87, 88).

Assessment of adherence can be performed by different modalities, each with their own limitations. The most commonly used method to assess adherence, patient self-report, tends to be specific but not sensitive and is susceptible a social desirability bias where missed doses are underreported (89). The use of electronic pill-bottle caps to record openings is more sensitive for non-adherence, but is expensive, which limits their use in clinical care and can be difficult to work with even in a clinical research setting (90). Therapeutic drug monitoring is specific, but is also influenced by ARV absorption and metabolism leading to unwanted variability in the assessment of adherence. Research on HIV treatment programs in Africa has assessed pharmacy based measures of ART adherence including the measure of 'on-time pill pick-up' (38, 39, 43). These studies used pharmacy claims data to demonstrate that on-time pill pick-up was associated with survival, and predicted virological failure in a linear dose-response fashion, and more accurately then changes in CD4 cell counts after 6- and 12- months ART (38, 39, 43). Notably these data were collected from medical records of patients from sub-Saharan Africa where ART was not available free of charge. Additionally patients in these cohorts utilized more ART regimens and started therapy at higher CD4 counts than occurs in NACO sponsored clinics and countries following World Health Organization (WHO) treatment guidelines (78, 91).

In an effort to optimize ART adherence numerous studies have performed investigations to identify barriers to adherence. The most recent systematic review of barriers to adherence in both HICs and LMICs identified fear of disclosure,

forgetfulness, a lack of understanding of treatment benefits, complicated regimens, and being away from their medications as adherence barriers consistently identified in both HICs and LMICs (48) Once barriers have been identified interventions can be appropriately designed to improve and maintain adherence. A range of successful adherence interventions have been reported and include individual or community based behavioural interventions, pharmacist directed interventions and mobile phone based messaging interventions (46, 47, 92, 93).

ART adherence in India has been assessed by both quantitative and qualitative studies using self-reported measure of adherence and has identified major barriers and facilitators to adherence (94-97). Identified barriers include: stigma, ART side effects, depression, co-morbidities and costs of care. Importantly, these studies were not performed in NACO sponsored clinics and a significant proportion (95, 97) or all the study participants paid for their care (94, 96) which is notable as cost was identified as a barrier to adherence (94, 97). Therefore barriers identified in the available ART adherence literature are not generalizable to clinics using the public health model. In addition to adherence barriers important identified facilitators of adherence included the presence of social supports, having reminders to take medications and perceived benefits of adherence to overall health and management of HIV disease (94, 96).

Therefore we sought to perform studies that would identify factors that predict virological outcomes in a clinic providing free ART in the public health model of care. In addition we wanted to identify factors that could be targeted for intervention that could lead to improved clinical outcomes in this setting. Therefore the focus of the studies in southern India was to identify measures of ART adherence that most accurately predict virological outcomes with a particular focus on adherence measures derived from routinely collected data on ART pick-up. Additionally, we sought to identify barriers and facilitators to ART adherence for people receiving free ART in the public health model that were associated with virological outcomes that could subsequently serve as targets for intervention.

2.4 Summary

This thesis expects to gain a broader understanding of the socio-behavioral factors influencing outcomes for HIV infected patients in both HICs and LMICs. The principal goal of this work is to identify social and behavioural factors, and methods to estimate ART adherence, that are associated with poor clinical outcomes. This will then allow for the implementation of targeted interventions to improve treatment outcomes for populations living with HIV in diverse clinical settings.

To address this goal the studies of this thesis are designed to focus on social and behavioural aspects of people's lives and different methods to estimate ART adherence in clinically diverse settings. This includes the systematic synthesis of evidence of pharmacy adherence measures and recommendations how best to use these measures when monitoring adherence to ART, and the synthesis of evidence specific to LMICs about key clinical outcomes such as virological suppression on ART and retention of PLHIV in ART programs. Additional studies then examine associations between different markers of SES and clinical outcomes such as mortality and immunologic response in patients receiving ART in HIC settings. Subsequent studies then focus on India as a country that provides free ART in a public health model common to most LMIC settings. These studies then identify factors that can be targeted for intervention to improve outcomes. Firstly work to identify social and behavioural factors predicting poor virological outcomes and then work to identify associations between different self-report and pharmacy based adherence measures and HIV viral load of ART adherence identifying individuals at risk of poor outcomes on ART.

In conclusion, this thesis endeavours to understand the relationship between socio-behavioural factors and outcomes on ART in higher and lower income countries. This work can then be used to design interventions to improve outcomes on ART for patients in these clinically diverse settings.

2.5 Aims of thesis

The broad aims of this thesis are:

1. Describe clinical outcomes for individuals receiving ART in diverse settings in different models of HIV care.
2. Examine the associations between measures of socioeconomic status and clinical outcomes in patients receiving ART in a high income country setting
3. To describe socio-behavioural factors associated with virological failure amongst HIV infected patients receiving free ART in a public health model of care
4. Identify different methods to estimate ART adherence associated with virological failure amongst people receiving ART in the public health model of care in Tamil Nadu, India

3 Literature Review

3.1 Introduction

This section comprises three published systematic reviews that address critical issues for individuals receiving ART in higher and lower income country settings. The issues of early mortality and individuals being lost to care are important factors driving outcomes (3, 98) for ART programs in LMICs. For example the risk of death in LMICs has been reported up to 4 times higher than for HIC s in the early months after initiating ART (3) and the proportion of people lost to care has been reported up to 25-50% of those initiating ART after one year (99-102). . Individuals who are considered LTFU have either transferred care to another ART site, died or become disengaged from care. Studies aimed at trying to correct mortality estimates using mathematical models or by tracing patients who are LTFU have shown that true mortality estimates are up to 10% higher when those missing patients that have actually died are included in a mortality outcome (103, 104). Importantly individuals who are adversely affected by a range of social and clinical factors such as low CD4 count at diagnosis and decreased levels of community support are at risk of becoming LTFU or disengaged from ART (105-107). ART site or program managers are frequently required to report estimates of LTFU, mortality, and retention to ministries of health, funders, and international organizations (108-110). Additionally, these stakeholders and researchers in the field routinely report on LTFU, mortality and retention to quantify the extent of this issue in LMICs (111-113).Therefore an understanding of normative outcomes specific to populations receiving ART in the public health model is critical to accurately interpret outcomes in LMICs.

In addition to summarising these outcomes we also investigated the effect of physically tracing individuals who are LTFU to examine how this affected summary estimates of patient retention, LTFU and survival on ART. Tracing individuals who have not attended for clinic appointments by phone or in person is a commonly employed practice in ART clinics to establish the status of individuals with unknown outcomes and facilitate re-engagement of patients back to ART care. While this may be considered a resource intensive intervention, cost-effectiveness studies of tracing interventions do not exist. Furthermore some LMIC studies report successfully tracing patients who are LTFU with peer supporters or people without formal medical qualifications (107, 114) raising the possibility that these interventions are potentially

cost-effective. Therefore we performed a systematic review of evidence to understand how this commonly employed intervention of patient tracing affects estimates of LTFU, mortality and retention in LMIC settings

Virological outcomes are increasingly reported in research or programmatic settings from LMICs. However, summary estimates of virological suppression for the broader population receiving ART in LMICs and are not available using different thresholds of HIV RNA to define viral load suppression (115, 116). As increasing numbers of individuals receive ART in LMICs this summary data is necessary to guide ART program managers on normative levels of population-level virological suppression. These summary estimates are necessary to allow ART program managers to define desirable levels of ART clinic and program performance and set targets of virological suppression. Additionally summary estimates assist researchers when mathematically modelling different strategies of ART provision in LMICs. Therefore in addition to reviewing programmatic data focusing on how physical tracing of patients LTFU affects clinical outcomes we systematically reviewed virological outcomes for people receiving ART in LMICs from programmatic and research settings. The objective was to establish summary estimates of virological suppression using different HIV RNA thresholds to define virological suppression.

The use of prescription or pill-based methods for estimating adherence to antiretroviral therapy (ART), pharmacy adherence measures (PAMs), are objective estimates calculated from routinely collected pharmacy data. Despite the potential advantages of using pre-existing pharmacy data to establish estimates of adherence and the large number of ART adherence reviews already in publication (41, 42, 48, 117, 118), no review has examined pharmacy based measures in detail. PAMs have been widely reported in association with virological and other clinical outcomes for individuals receiving ART but these reports have included a wide range of PAMs constructed in different ways associated with different clinical endpoints. Therefore an important gap in the ART adherence literature was a systematic summary of studies reporting PAMs and their associations with different clinical outcomes. The following systematic review summarises the current state of knowledge regarding pharmacy adherence measures, including their associations with virological failure and clinical progression.

It also identifies research gaps, and proposes an approach to selecting PAMs for monitoring adherence and treatment outcomes. In addition this review places PAMs in the context of the most commonly used method to estimate ART adherence, patient self-report. The review represents the definitive summary of this important and widely used approach to HIV treatment monitoring and details the potential for PAMs to identify individuals at risk for treatment failure.

3.2 Effects of patient tracing on estimates of lost to follow-up, mortality and retention in antiretroviral therapy programs in low-middle income countries: A Systematic Review

3.2.1 Declaration

Declaration for Thesis Chapter 3.2

Declaration by candidate

In the case of Chapter 3.2, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript	80

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors**
Julian H. Elliott	Helped conceive an approach to review the literature, reviewed selected studies and helped develop the manuscript	7.5
Steven Y. Hong	Participated in interpreting the results and developing the manuscript	2.5
Silvia Bertagnolio	Participated in interpreting the results and developing the manuscript	2.5
Michael R. Jordan	Helped develop the manuscript, conceive the idea for the review, assisted with devising the	7.5

	protocol and also reviewed selected studies and independently abstracted data.	

Candidate's Signature	[redacted]	**Date** **16 APR 2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**Alfred Hospital Infectious Diseases Unit, Melbourne**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	JHE	[redacted]		**Date** 16/4/2013
Signature 2	SYH			8/4/2013
Signature 3	SB			10/4/2013
Signature 4	MRJ			10/4/2013

3.2.2 Paper

OPEN ACCESS Freely available online

PLOS ONE

Effects of Physical Tracing on Estimates of Loss to Follow-Up, Mortality and Retention in Low and Middle Income Country Antiretroviral Therapy Programs: A Systematic Review

James H. McMahon[1,2]*, Julian H. Elliott[1,3,4], Steven Y. Hong[2,5], Silvia Bertagnolio[6], Michael R. Jordan[2,5]

1 Infectious Diseases Unit, Alfred Hospital, Melbourne, Victoria, Australia, **2** Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts, United States of America, **3** Department of Medicine, Monash University, Melbourne, Victoria, Australia, **4** Burnet Institute, Melbourne, Victoria, Australia, **5** Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, Massachusetts, United States of America, **6** University College London, London, United Kingdom

Abstract

Background: A large proportion of patients receiving antiretroviral therapy (ART) in low and middle income countries (LMICs) have unknown treatment outcomes and are classified as lost to follow-up (LTFU). Physical tracing of patients classified as LTFU is common; however, effects of tracing on outcomes remains unclear. The objective of this systematic review is to compare estimates of LTFU, mortality and retention in LMIC in cohorts of patients with and without physical tracing.

Methods and Findings: We systematically identified studies in LMIC programmatic settings using MEDLINE (2003–2011) and HIV conference abstracts (2009–2011). Studies reporting the proportion LTFU 12-months after ART initiation were included. Tracing activities were determined from manuscripts or by contacting study authors. Studies were classified as "tracing studies" if physical tracing was available for the majority of patients. Summary estimates from the 2 groups of studies (tracing and non-tracing) for LTFU, mortality, stop of ART, transfers out, and retention on ART were determined. 261 papers and 616 abstracts were identified of which 39 studies comprising 54 separate cohorts (n = 187,666) met inclusion criteria. Of those, physical tracing was available for 46% of cohorts. Treatment programs with physical tracing activities had lower estimated LTFU (7.6% vs. 15.1%; p<.001), higher estimated mortality (10.5% vs. 6.6%; p = .006), higher retention on ART (80.0 vs. 75.8%; p = .04) and higher retention at the original site (80.0% vs. 72.9%; p = .02).

Conclusions: Knowledge of patient tracing is critical when interpreting program outcomes of LTFU, mortality and retention. The reduction of the proportion LTFU in tracing studies was only partially explained by re-classification of unknown outcomes. These data suggest that tracing may lead to increased re-engagement of patients in care, rather than just improved classification of unknown outcomes.

Citation: McMahon JH, Elliott JH, Hong SY, Bertagnolio S, Jordan MR (2013) Effects of Physical Tracing on Estimates of Loss to Follow-Up, Mortality and Retention in Low and Middle Income Country Antiretroviral Therapy Programs: A Systematic Review. PLoS ONE 8(2): e56047. doi:10.1371/journal.pone.0056047

Editor: Michael Alan Polis, National Institute of Allergy and Infectious Diseases, United States of America

Received July 6, 2012; **Accepted** January 8, 2013; **Published** February 12, 2013

Funding: JM was supported by a fellowship from Tufts Medical Center Department of Geographic Medicine and Infectious Diseases, and an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship. MRJ was supported by an National Institutes of Health Career Development Award (5K23AI074423-04). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: ja.mcmahon@alfred.org.au

Introduction

In response to the global HIV epidemic, a public health approach to antiretroviral therapy (ART) has been widely implemented in low- and middle-income countries (LMICs). In 2010, 6.6 million adults and children received ART, representing a 22-fold increase from 2001 [1]. The rapid scale-up of ART is an impressive public health achievement that has led to dramatic declines in HIV related morbidity and mortality [1–4].

Frequently reported outcomes for populations receiving ART include the number of: patients alive and on ART, deaths, patients transferring care from one facility to another ('transfer out'), patients stopping ART (either physician directed or patient initiated) but remaining in care, and patients lost to follow-up (LTFU). [5–8] LTFU is a generic term referring to patients who initiate ART but who have unknown treatment outcomes. These unknown treatment outcomes may be divided into 3 general categories: unreported deaths, unknown transfer of care to a different facility without documentation, and disengagement from care [9].

Patient tracing is a commonly used method to improve retention in care and reduce unknown outcomes. Typically in LMICs, tracing involves contacting patients by telephone (telephone tracing), physically visiting their place of residence (physical tracing), or a combination of both. Tracing patients has two potential benefits: 1) linking patients who are disengaged from

care back into the health care system, and 2) improved classification of unknown outcomes. By minimizing the number of individuals who disengage from care, programs optimize care by maintaining the greatest possible number of patients on ART, thus decreasing mortality [9] and complications of immunodeficiency. Additionally, patients who have disengaged from care are at increased risk of transmitting HIV due to uncontrolled viremia [10] and for the selection of drug resistance by virtue of ART treatment interruptions [11,12]. Maximizing the number of patients alive and receiving ART and minimizing the number of patients with unknown outcomes should become an increasingly important public health priority [1,13,14].

Program managers are frequently required to report estimates of LTFU, mortality, and retention to ministries of health, funders, and international organizations [5–8]. Furthermore, clinicians, program managers and researchers routinely report on LTFU, mortality and retention to quantify the extent of this issue in LMICs [15–17]. Patient tracing may result in the improved classification of unknown outcomes allowing for more accurate estimates of LTFU, mortality, and retention. However, the extent to which patient tracing impacts estimates of LTFU, mortality and retention in LMIC remains uncertain. To the authors' knowledge the only review that stratifies any of these outcomes by tracing status was a mortality estimate from the Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration [18]. All other identified reviews[14,19–21] have synthesized data from multiple studies without incorporating the potential for patient tracing activities to affect estimates of LTFU, mortality or retention.

The proportion of individuals LTFU one year after the initiation of ART has been reported as high as 25–50% in LMICs [22–26]. Reasons for LTFU are multi-factorial and include both program and patient factors. Reported predictors of LTFU include evidence of poor nutrition, low CD4 count at diagnosis, the number of doctors available to treat patients, the ability to contact the patient by telephone and decreased levels of community support. [27–29] Additional factors such as patient refusal to take ART, adverse events or toxicity related to medication or alternative priorities may also lead to disengagement from ART programs. Furthermore, poor data recording and reporting and information systems that do not permit communication between ART clinics may contribute to high levels of reported LTFU. A lack of communication between record keeping systems may be particularly relevant in settings where different systems are used or unique national ART patient identifiers are not available leading to an inability to identify patients who have transferred out or died. Additionally, in many LMICs deaths go unreported to national death registries, if they exist, and ART programs lack a consistent link between death registries and reporting of population level ART outcomes.

The objective of this systematic review is to compare summary estimates of LTFU, mortality and retention in LMIC, in cohorts of patients with and without physical tracing. In settings with tracing, we hypothesized that summary estimates of LTFU would decrease and estimates of mortality and retention would increase.

Methods

The strategy to identify appropriate studies, abstract data from selected studies and an analytic plan was established in a systematic review protocol.

Search Strategy

All searches were performed using Ovid MEDLINE. Searches were limited to studies published in English from January 2003 through May 2011. Studies assessing outcomes in children (<13 years old) were excluded. The search strategy started by combining all sets of terms under the following Medical Subject Headings (MeSH) to identify HIV infected participants receiving ART: "HIV" or "HIV Infections" or "Antiretroviral Therapy, Highly Active" or "Anti-Retroviral Agents". Then to identify studies from LMICs we combined all sets of terms under the following MeSH: "Africa" or "Asia" or "Caribbean region" or "Central America" or "Latin America" or "South America", in addition to the following terms: "resource limited" or "resource constrained" or "developing countries" or "low income countries" or "low and middle income countries" or "Africa" or "Afrika" or "sub Saharan" or "southern Africa" or "Asia" or "Latin America" or "South America". Terms specific to Eastern Europe were not included. The next step combined different combinations of "lost (or loss) to follow up", with the terms: "attrition" or "retention", and all terms under the MeSH "patient dropouts". Finally, items obtained from the searches for: HIV infected participants, LMICs and Loss to follow-up were combined. The exact search strategy is available within the systematic review protocol provided as a supporting document to this manuscript.

The online conference abstract databases for the 2009 International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, the 2010 International AIDS Conference, and the 2009–2011 Conference on Retroviruses and Opportunistic Infections were searched for the terms "lost (or loss) to follow up" and "retention". These more recent years were chosen to capture additional data reported in abstract form that may not have been published in peer reviewed journals. Reference lists from recent reviews assessing patient retention in ART programs in LMICs were also searched [14,19].

Study Selection

Original research studies or abstracts reporting on outcomes of HIV infected patients receiving ART in LMICs were included. Studies were included if they were specifically designed to report on LTFU or in cases where it was a secondary finding. Study designs were either cross-sectional or cohort and either prospective or retrospective. All studies included in the analyses reported rates of LTFU for cohorts of individuals who had received care for 12 months after ART initiation and any definition of LTFU was accepted. If cohort studies only reported a median duration of follow up, they were included only if the duration of follow up ranged from 9 to 15 months. When more than one study reported on the same cohort of patients, only the publication containing the most detailed information was included.

Studies in which the majority of patients were children, patients received mono- or dual-therapy, or that were not performed in LMICs were excluded. Additionally, clinical trials were excluded as the focus of this review was to understand LTFU in service delivery settings. Studies were excluded at one of three steps: after review of the title, the abstract, or the manuscript. The search strategy and study selection is summarized in Figure 1.

Data Abstraction and Management

The following data were abstracted from each study: first author, year of publication, country or countries, healthcare setting (public, private, non-governmental organization), need to pay for ART, dates observed, number of clinics, number of patients receiving ART, baseline demographics (age, gender, CD4 count, clinical stage), ART regimen, ART naive prior to ART

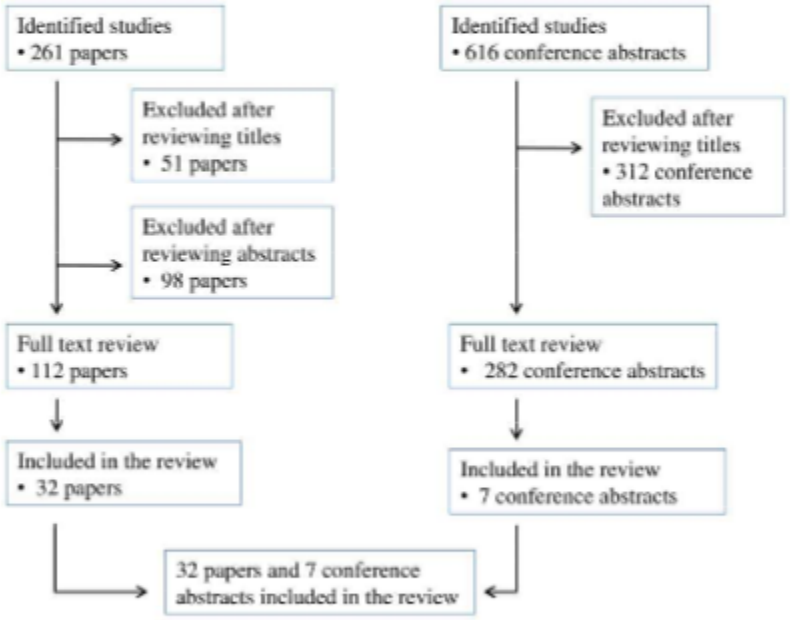


Figure 1. Search strategy and study selection.
doi:10.1371/journal.pone.0056047.g001

initiation, study definition of LTFU and the proportion of patients meeting that definition 12 months after initiation of therapy. If reported, the proportion of subjects who died, transferred care to a different facility, or who stopped ART was abstracted. In addition, details of patient tracing were abstracted, and to minimise reporting bias across selected studies, authors not reporting on patient tracing activities were contacted to establish details about tracing. To provide consistency across all studies the denominator of LTFU estimates included all patients who initiated ART.

Data Analysis

Proportions of patients classified as LTFU, died, stopped ART and transferred to a different facility were derived from text, tables and graphs (if exact values were available) within studies. Data presented as incidence density (e.g. person years) were converted to cumulative incidence using standard formulae [30]. Patient 'retention on ART' was defined as patients alive and receiving ART at the original site plus the group of patients who have 'transferred out'. This assumes that patients who are known to have transferred their care to another site providing ART are retained in care. The proportion retained on ART was determined for studies that reported at least the proportion LTFU and proportion died using the following formula: Retained on ART = 1−LTFU - died - stopped ART. Additionally, the term 'retention at the original site' defines individuals retained on ART and excludes those who have transferred out. Studies also reporting the proportion transferred out were used to estimate the proportion retained at the original site using the formula: Retained at the original site = 1−LTFU−died−stopped ART−transfer out. For the purpose of this review, if transfer out data were not available for a cohort, the estimates of retained on ART and retained at the original site would be the same, an approach consistent with previous reviews focusing on retention in ART treatment programs [14,19]. Summary estimates for tracing and non-tracing studies are reported as medians if the group of estimates was non-normally distributed or as weighted means if data were normally distributed. Weighting of each proportion derived from included studies was by the inverse of its variance [1 / (p x (1-p) / n), where p is the proportion and n is the sample size]. Tracing was deemed to have occurred if the activity involved physical tracing of the patient with unknown outcome to her or his residence and if this tracing activity was performed for at least one half of the study population. Non-physical tracing studies may have reported no tracing activities or phone tracing only. When choosing a method to differentiate tracing from non-tracing studies we elected to compare physical versus non-physical tracing studies due to the potential for the face-to-face interaction associated with attending a place of residence to increase the chances of re-engagement into care.

Summary estimates from the 2 groups of studies (tracing and non-tracing) were compared by the Student's t-test if normally distributed, or the Wilcoxon rank sum test if non-normally distributed for each parameters of interest (LTFU, death, stop of ART, transfer to another facility and retention on ART). A Shapiro-Wilk test p value > 0.05 was used to classify estimates from the tracing and non-tracing groups of studies as normally distributed. No assessment of risk of bias was performed for selected studies. Analyses were conducted using Excel and SAS v9.2 (SAS Institute, Cary, NC).

Results

A total of 261 papers and 616 conference abstracts were identified by the search strategy and of these 39 studies, 32 papers and 7 conference abstracts, met inclusion criteria[4,16,17,22–24,27,31–62] leading to 54 separate cohorts (47 cohorts in 32 papers, and 7 cohorts in 7 abstracts) available for analysis. In 3 papers, data were available for more than one cohort [17,36,57] with 2 of these papers reporting on cohorts with and without physical tracing, [17,57] while the third paper provided data for 2 cohorts that both performed physical tracing [56]. The 39

Table 1. Cohorts with physical tracing.*.

Study (Year)	Country (Cohort or data source)	Type of care	Free ART	Dates observed	Sites (n)	Start ART (n)	Baseline features (Median age, % male, median CD4, WHO clinicalstage)	ART regimens[&]	Time since ART start	Study definition LTFU	LTFU (%)	Died (%)	ART stop (%)	TF out (%)
May et al [56] (2010)	Cote d'Ivoire (Abidjan - CEPREF)	NGO	Yes	Initiated Jan 04–Mar 07	Many	2117	35, 26%, 129, 82% advanced	NR	Mean 11 months	Not attend clinic for > 6 months	11.5	8.7	NR	NR
May et al [56] (2010)	Malawi (Lilongwe)	Public	Yes	Initiated Jan 04–Mar 07	1	3028	36, 41%, 127, 96% advanced	NR	Mean 10 months	Not attend clinic for > 6 months	12.4	8.9	NR	14
Thai et al [46] (2009)	Cambodia (Phnom Penh)	Private (non profit)	Yes	Mar 03–Dec 07	1	1667	35, 49.4%, 61, Stage III 39% Stage IV 46%	100% NNRTI	12 months	Not attended clinic for 6 consecutive months	3.9	7.6	NR	NR
Bedelu et al [57] (2007)	South Africa (Lusikisiki)	Public, NGO	Yes	Initiated Jan–Jun 05. F/U to Jul 06	12	595	NR	NR	Median 12 months	NR	2.2	16.8	NR	NR
Etard et al [40] (2006)	Senegal	Public	Partial	Initiated Aug 98–Apr 02. F/U to Sep 05	≥ 3	404	37, 45%, 128, CDC Stage B 39%, CDC Stage C 55%	42% PI 95% ART naive	12 months	6 months with no contact, or 6 months with no ART if contacted	1.7	11.6	NR	NR
Ferradini et al [41] (2006)	Malawi (Chiradzulu)	Public, NGO	Yes	01–April 04	1	1308	35, 36%, 112, Stage III 55% Stage IV 27%	98% NNRTI 97% ART naïve	12 months	Not attended clinic > 2 months after last scheduled visit	5	19	NR	NR
Marston et al [43] (2007)	Kenya (Kibera)	Public, NGO	Yes	Feb 03–Feb 05	1	283	Mean 36, 30%, 157, Stage III 23% Stage IV 48%	99% NNRTI 1% PI	12 months	No clinic visit in > 3 months	13.0	7.0	NR	NR
Coetzee et al [4] (2004)	Sth Africa (Khayelitsha)	Public, NGO	Yes	Initiated May 01–Dec 02, Censored July 03	3	287	31, 30%, 43, Stage III/IV 100%	99% NNRTI	Median 14 months	Not attended services (clinic or other services) for ≥ 3 months after last scheduled appointment	0.3	13.2	3.1	1.0
Palombi et al [27] (2009)	Mozambique, Malawi. Guinea-Conakry	Public, NGO	Yes	Initiated Feb 02–Jan 06. F/U to Jun 07	5	3749	34, 38%, 192, Stage III/ IV 37%	97% NNRTI 3% 3NRTI	Median 15 months	Not attending clinic for > 3 months	2.8	10.5	NR	NR
DeSilva et al [39] (2009)	Nigeria (Jos)	NGO	Yes	Initiated Dec 04–Apr 06. F/U to Dec 06	1	1552	34, 29%, 112, NR	99% NNRTI 1% PI	Mean 15 months	No clinic records for > 3 months	8.8	6.7	NR	NR
Barth et al [31] (2008)	Sth Africa (Ndlovu)	NGO	Yes	Initiated Sept 03–Apr 06	1	609	35, 29%, 67, Stage III 62% Stage IV 17%	100% NNRTI	12 months	NR	15.0	19.0	NR	NR
Moore et al [44] (2010)	Malawi (Blantyre)	Public	Yes	Initiated 05	1	300	Mean 36, 39%, Mean 157, Stage IV 29%	100% NNRTI	12 months	Failure to attend clinic ≥ 4 weeks after last scheduled appointment	2.7	14.3	5.3	5.3

Table 1. Cont.

Study (Year)	Country (Cohort or data source)	Type of care	Free ART	Dates observed	Sites (n)	Start ART (n)	Baseline features (Median age, % male, median CD4, WHO clinicalstage)	ART regimens[&]	Time since ART start	Study definition LTFU	LTFU (%)	Died (%)	ART stop (%)	TF out (%)
Mutevedzi et al [45] (2010)	Sth Africa (Kwa-Zulu Natal)	Public	Yes	Initiated Oct 04–Sept 07	16	3010	34–37, 22%, 91–128, NR	100% NNRTI	12 months	No clinic visit for ≥ 90 days	3.7	10.9	NR	1.4
Tassie et al [17] (2010)	Kenya (Busia)	NGO	Yes	Initiated Jan–Dec 05	1	860	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	8.5	6.4	3.0	NR
Tassie et al [17] (2010)	Kenya (Homabay)	NGO	Yes	Initiated Jan–Dec 05	1	954	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	10.9	10.6	1.6	NR
Tassie et al [17] (2010)	Kenya (Kibera)	NGO	Yes	Initiated Jan–Dec 05	1	435	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	11.3	5.3	5.7	NR
Tassie et al [17] (2010)	Kenya (Mathare)	NGO	Yes	Initiated Jan–Dec 05	1	549	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	13.5	4.2	5.8	NR
Tassie et al [17] (2010)	Malawi (Thyolo)	NGO	Yes	Initiated Jan–Dec 05	1	1359	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	8.9	12.7	2.4	NR
Tassie et al [17] (2010)	Nigeria (Lagos)	NGO	Yes	Initiated Jan–Dec 05	1	713	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	9.7	5.7	1.7	NR
Tassie et al [17] (2010)	Zambia (Kapiri Kawama)	NGO	Yes	Initiated Jan–Dec 05	1	559	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	3.4	12.0	0.9	NR
Tassie et al [17] (2010)	Zimbabwe (Bulawayo)	NGO	Yes	Initiated Jan–Dec 05	1	222	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	13.5	11.5	0.5	NR
Tassie et al [17] (2010)	Zimbabwe (Connaught)	Public	Yes	Initiated Jan–Dec 05	1	378	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	4.0	6.3	1.6	NR
Culbert et al [38] (2007)	Congo (Bukavu)	NGO	Yes	Initiated May 02–Jan 06	1	494	37, 34%, 123, Stage III 49% Stage IV 34%	100% NNRTI	12 months	NR	5.4	7.9	NR	NR
Johannessen et al [60] (2008)	Tanzania (Manyara)	NGO	Yes	Initiated Oct 03–Nov 06	1	320	35, 30%, NR, Stage III 31% Stage IV 66%	100% NNRTI	Mean 11 months	Missed appointments for ≥ 3 months	9.7	29.7	2.2	10.9
Chi et al [35] (2009)	Zambia (Lusaka)	Public	Yes	Initiated Apr 04–Sept 07	18	37039	35, 39%, 110–132, Stage III 59% Stage IV 10%	100% NNRTI	12 months	NR	13.8	9.9	3.1	NR

*Defined as physical tracing to the patients place of residence and was available to at least half the study population.

[&]All ART naïve at baseline unless stated **Notes:** ART, antiretroviral therapy; WHO, World Health Organization; LTFU, lost to follow up; TF, transfer; NR, not reported; F/U, follow up; NGO, non-governmental organization; NNRTI. Non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; NRTI, nucleoside reverse transcriptase inhibitors;

doi:10.1371/journal.pone.0056047.t001

Table 2. Cohorts without physical tracing.*.

Study (Year)	Country (Cohort or data source)	Type of care	Free ART	Dates observed	Sites (n)	Start ART (n)	Baseline features (Median age, % male, median CD4, WHO clinicalstage)	ART regimens&	Time since ART start	Study definition LTFU	LTFU (%)	Died (%)	ART stop (%)	TF out (%)
Geng et al [16] (2010)	Uganda (Mbarara)	Public	Yes	Initiated Jan 04–Sept 07	1	3628	35,39%, 95, NR	NR	12 months	Not attended clinic for > 6 months	16	1.7	NR	NR
Bisson et al [33] (2008)	Botswana (Gaborone - IDCC)	Public	Yes	Initiated Feb 03–August 03	1	410	37, 40%, 81, NR	97% NNRTI 12% prior ARVs	Median 10 months	Last contact with clinic or pharmacy > 30 days after last scheduled visit	16.6	7.1	NR	NR
Bedelu et al [57] (2007)	South Africa (Lusikisiki)	Public, NGO	Yes	Initiated Jan 05–Jun 05. F/U to Jul 06	1	430	NR	NR	Median 12 months	NR	19.3	13.5	NR	4.0
Wools-Kaloustian et al [24] (2006)	Kenya (Western)	Public	Some paid	Nov 01–Feb 05	8	2059	37, 40%, 86, Stage III 38% Stage IV 17%	95% NNRTI	Median 9 months	Not attended clinic > 3 months	24.5	5.4	NR	NR
Wester et al [48] (2005)	Botswana (Gaborone - IDCC)	Public	Yes	Initiated Apr01–Jan 02. F/U to Nov 03	1	153	36, 41%, 96, Stage III 30% Stage IV 47%	100% NNRTI	12 months	Miss 2 consecutive visits and then not contactable on 2 phone attempts	8.4	15.3	NR	5.2
Charalambous et al [34] (2007)	Sth. Africa	Private (Work)	Yes	Oct 02–Dec 05	69	2262	41, 95%, 158, Stage III 45% Stage IV 27%	"NNRTI"	12 months	"Stopped treatment" = patient request, LTFU or for ART non-adherence	8.3	4.2	See LTFU	5.5
Bisson et al [32] (2006)	Botswana (Gaborone)	Private	Yes	Initiated Dec 99–Jan 04	1	346	37, 42%, 80–113, NR	NR	12 months	No viralload tests after ART start, then not contactable by phone and not picking up ART	12.4	5.2	NR	12.1
Laurent et al [23] (2005)	Cameroon (Douala)	Public/ Private	Yes	Oct 00–Dec 03	19	788	39, 48%, 123, CDC stage B 57% CDC stage C 33%	NR 86% ART naive	Median 13 months	Did not attend in 3 months prior to chart review	25.1	6.6	NR	NR
Karcher et al [42] (2007)	Kenya (Migori)	Public	Yes	Apr 04–Sept 05	1	124	31, 29%, 189, CDC Stage C 46%	"NNRTI"	Median 9 months	Not attended within 4 months after last scheduled appointment	15.3	12.1	NR	NR
Hawkins et al [22] (2007)	Kenya (Nairobi – Saint Mary's)	NGO	Yes	Initiated Sep 04–Aug 06	1	1286	36, 40.9%, 121	99% NNRTI	Median 12 months	Missed clinic visits and failure to collect ART refills for ≥ 3 months	34.8	1.1	NR	4.9
Chung et al [36] (2010)	Kenya (Nairobi - Coptic Center)	NGO	Yes	Initiated Mar 06–Dec 07	1	1231	NR	NR	12 months	Not clinic visit > 30 days after last scheduled pick-up or no clinic visit in 120 days if no pharmacy data	10.0	NR	NR	NR
Toure et al [47] (2008)	Cote d'Ivoire (Abidjan- not CEPREF])	Public/ Private	Partial	Initiated May 04–Feb 07	18	8094#	36, 30%, 123, Stage III 69% Stage IV 12%	94% NNRTI	12 month	Last contact with care center > 3 months and not known to be dead or TF out	18	NR	NR	NR

Table 2. Cont.

Study (Year)	Country (Cohort or data source)	Type of care	Free ART	Dates observed	Sites (n)	Start ART (n)	Baseline features (Median age, % male, median CD4, WHO clinicalstage)	ART regimens[&]	Time since ART start	Study definition LTFU	LTFU (%)	Died (%)	ART stop (%)	TF out (%)
Collini et al [37] (2009)	Ghana (Kumasi)	Public	Partial	Jan 04–Jan 07	1	237	Mean 40, 41%, Mean 120, Stage III/IV 78%	"NNRTI"	12 months	NR	20.3	NR	NR	NR
Assefa et al [61] (2010)	Ethiopia	Public	Yes	Initiated Sept 03–Oct 07	353	60476	NR	100% NNRTI	12 months	Not on ART and not known to have died at 12 months	18.4	8.6	NR	NR
Hong et al [58] (2010)	Namibia	Public	Yes	Initiated after Jan 07	9	1620	NR	100% NNRTI	12 months	Not returned to pharmacy or clinic < 90 days after ART run-out date and have not TF out, stopped, died	17.5	NR	NR	NR
Sharma et al [62] (2010)	India (Delhi - AIIMS)	Public	Yes	Initiated May 05–Oct 06	1	631	Mean 36, 80%, 110, Stage III 51% Stage IV 31%	100% NNRTI	12 months	NR	18.5	13.0	NR	NR
Tassie et al [17] (2010)	Cambodia (Kampong Cham)	NGO	Yes	Initiated Jan–Dec 05	1	606	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	4.4	9.6	4.8	NR
Tassie et al [17] (2010)	Cambodia (Phnom Penh)	NGO	Yes	Initiated Jan–Dec 05	1	610	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	0.8	3.3	8.5	NR
Tassie et al [17] (2010)	Uganda (Arua)	NGO	Yes	Initiated Jan–Dec 05	1	1137	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	13.4	3.9	2.9	NR
Tassie et al [17] (2010)	India (YRG)	Public/ Private	Yes	Initiated Jan–Dec 05	1	767	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	31.9	3.6	6.0	NR
Tassie et al [17] (2010)	Kenya (AMPATH)	Public	Yes	Initiated Jan–Dec 05	1	4111	NR	NR	12 months	No recorded visit for ≥ 90 days from last visit	15.0	6.7	3.8	NR
O'Brien et al [59] (2009)	Congo (Pool)	NGO	Yes	During 07	2	236	37, 31%, 104, Stage III 53%Stage IV 44%	"NNRTI and PI"	Mean 9 months	NR	8.5	12.3	NR	NR
Chinh et al [52] CROI (2010)	Vietnam (Ho Chi Minh City)	Public	Yes	Initiated Sep 05–Dec 07	1	889	30, 77%, 143, Stage III/IV 51%	NR 76% prior ARV	Median 10 months	NR	4.0	5.0	NR	1.2
Cortes et al [51] CROI (2010)	Chile (Chilean AIDS cohort)	Public	Yes	Oct 01 –Sept 08	29	3045	37, 85%, NR, NR	63% NNRTI 15% PI	12 months	NR	2.3	7.1	NR	NR
Auld et al [55] IAS (2010)	Mozambique (National Sample)	Mixed	NR	04–07	30	2596	34, 38%, 153, NR	88% NRTI or NNRTI	1.3 years	NR	22.8	4.3	NR	NR

Table 2. Cont.

Study (Year)	Country (Cohort or data source)	Type of care	Free ART	Dates observed	Sites (n)	Start ART (n)	Baseline features (Median age, % male, median CD4, WHO clinicalstage)	ART regimens[&]	Time since ART start	Study definition LTFU	LTFU (%)	Died (%)	ART stop (%)	TF out (%)
Ehmer et al [50] IAS (2009)	Africa[*] (Solidarmed)	Mixed	Yes	05–08 initiation	8	4362	38, 35%, 121, Stage III/IV 73%	NR	12 months	NR	13.9	10.3	NR	NR
Somi et al [49] CROI (2011)	Tanzania (National Sample)	Public	Yes	Initiated Oct 04–Aug 07	43	2,781	37, 32%, 114, Stage III/IV 77%	NR	12 months	NR	20.0	5.0	5	NR
Bertagnolio et al [53] CROI (2011)	Africa (Multiple countries)	Public	NR	02–10	6	829	NR	NR	12 months	Not returned to pharmacy or clinic < 90 days after ART run-out date and have not TF out, stopped, died	12.9	9.2	0.8	14.5
Balestre et al [54] CROI 2011	leDEA-West Africa	NR	NR	93% of patients after 04	NR	19,131	40, NR, 159, 85% advanced stage	87% NNRTI 85% ART naïve	12 months	NR	32.8	4.3	NR	NR

*Defined as physical tracing to the patient's place of residence and was available to at least half the study population. Note that 7 cohorts [17,32,36,48,52,62] reported phone only tracing was available to a proportion of the study population, and 4 cohorts [34,47,54,58] reported physical tracing for a minority of the study population [&] All ART naïve at baseline unless stated.

[#]Sample size determined via contact with study authors.

Benin, Cote d'Ivoire, Gambia, Mali, Nigeria, Senegal.

[+]Lesotho, Mozambique, Tanzania, Zimbabwe **Notes:** ART, antiretroviral therapy; WHO, World Health Organization; LTFU, lost to follow up; TF, transfer; NR, not reported; F/U, follow up; NGO, non-governmental organization; NNRTI. Non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; NRTI, nucleoside reverse transcriptase inhibitors.

doi:10.1371/journal.pone.0056047.t002

Table 3. Comparison of summary estimates with and without physical tracing.

Outcome of interest	With tracing				Without tracing				P value[b]
	Cohorts (n)	Starting ART (n)	Range of estimates (%)	Summary estimate[a] (%)	Cohorts (n)	Starting ART (n)	Range of estimates (%)	Summary estimate[a] (%)	
LTFU	**25**	**62791**	**0.3–15.0**	**7.6 ± 1.1**	**29**	**124875**	**0.8–34.8**	**15.1 ± 1.7**	**< 0.001**
Mortality	25	62791	4.2–29.7	10.5 (7.0–12.7)	25	113693	1.1–15.3	6.6 (4.3–9.6)	**0.006**
Stopped ART	13	43975	0.5–5.8	2.8 ± 0.2	7	10841	0.8–8.5	3.2 ± 0.8	**0.5**
Transfer out	5	6945	1.0–14.0	2.7 ± 1.9	7	6195	1.2–14.5	3.9 ± 1.3	**0.6**
Retention on ART	25	62791	58.4–88.5	80.0 (76.5–84.5)	25	113693	58.5–91.0	75.8 (70.0–81.2)	**0.04**
Retention at original site	25	62791	47.5–88.5	80.0 (76.0–84.0)	25	113693	58.5–90.6	72.9 (68.5–79.8)	**0.02**

[a]Values represent median (Q1–Q3), or weighted mean ± SE (estimates weighted by the inverse of their variance).
[b]Comparing summary estimates for the 2 groups of studies (tracing and non–tracing) by Wilcoxon rank-sum test for medians or student's t test for weighted means **Notes:** LTFU, lost to follow up; ART, antiretroviral therapy.
doi:10.1371/journal.pone.0056047.t003

included studies reported on 17 countries from sub-Saharan Africa, four multi-country studies from sub-Saharan Africa, three countries from Asia and one from Latin America. Published studies contained information to establish tracing status for 18 of the 54 cohorts included in this review. For the remaining 36 cohorts, tracing status was established by contact with study authors. Table 1 presents data on cohorts with physical tracing and Table 2 on cohorts without physical tracing.

In the 25 cohorts with physical tracing, the weighted mean LTFU was 7.6 % (SE ± 1.1%, range 0.3–15.0%). In the 29 cohorts without physical tracing, the weighted mean LTFU was 15.1% (SE ± 1.7%, range 0.8–34.8%) (Table 3 and Figure 2). The observed difference in summary estimates was statistically significant ($p<0.001$). Definitions of LTFU were different across different studies but 52% of cohorts (28/54) classified patients as LTFU 3–4 months after their last contact with the ART clinic. Five studies required a 6 month period of being lost and seven used a variety of definitions. Estimates of mortality were significantly higher ($p = .006$) in cohorts where physical tracing occurred; median estimate of 10.5% (IQR 7.0–12.7%, range 4.2–29.7%,) compared to 6.6% (IQR 4.3–9.6%, range 1.1–15.3%) in cohorts without physical tracing. Weighted mean estimates of ART stop were 2.8% (SE ± 0.2%, range 0.5–5.8%) in the 13 cohorts with physical tracing compared to 3.2% (SE ± 0.8%, range 0.8–8.5%) in the seven cohorts without physical tracing ($p = 0.5$). The weighted mean estimate of transfer out to another facility was 2.7% (± 1.9%, range 1.0–14.0%) in the five cohorts with tracing and 3.9% (SE ± 1.3%, range 1.2–14.5%) in the seven cohorts without tracing ($p = 0.6$). A median 80.0% of patients were retained on ART in studies reporting physical tracing (IQR 76.5–84.5%, range 58.4–88.5%) versus 75.8% (IQR 70–81.2%, range 58.5–91.0%) in studies without physical tracing. The median of retention in care at the original ART site for cohorts with physical tracing was 80.0% (IQR 76.0–84.0%, range 47.5–88.5%) versus 72.9% (IQR 68.5–79.8%, range 58.5–90.6%) at clinics without physical tracing. Differences in retention were statistically significant, $p = .04$ for retention on ART and $p = .02$ for retention at the original site.

Discussion

This review demonstrates lower estimates of LTFU and higher estimates of mortality in LMIC settings where patients receiving ART attend clinics employing physical tracing. The observed differences may be explained by more accurate classification of patients in studies where physical tracing was performed. Specifically, many patients who had previously been classified as LTFU, once traced, were found to have died, thereby contributing to an apparent increased mortality. It remains uncertain by how much the observed decrease in LTFU within physical tracing cohorts was a result of re-engagement of patients back into care versus re-classification of patients with previously unknown outcomes. However, in addition to the significant reduction in LTFU and increase in mortality, we report a significant improvement in retention at the original site. While it is not unexpected that tracing activities would decrease the proportion LTFU and increase mortality estimates due to improved classification of outcomes, the observed improvement in retention at the original site suggests that tracing may have increased the number of patients re-engaged in care. Although the tracing activity would re-classify patients previously thought to be LTFU as transferred out our having died, this reclassification would not alter the estimate of retention at the original site due to its inclusive definition. Therefore, the improvement in retention at the original

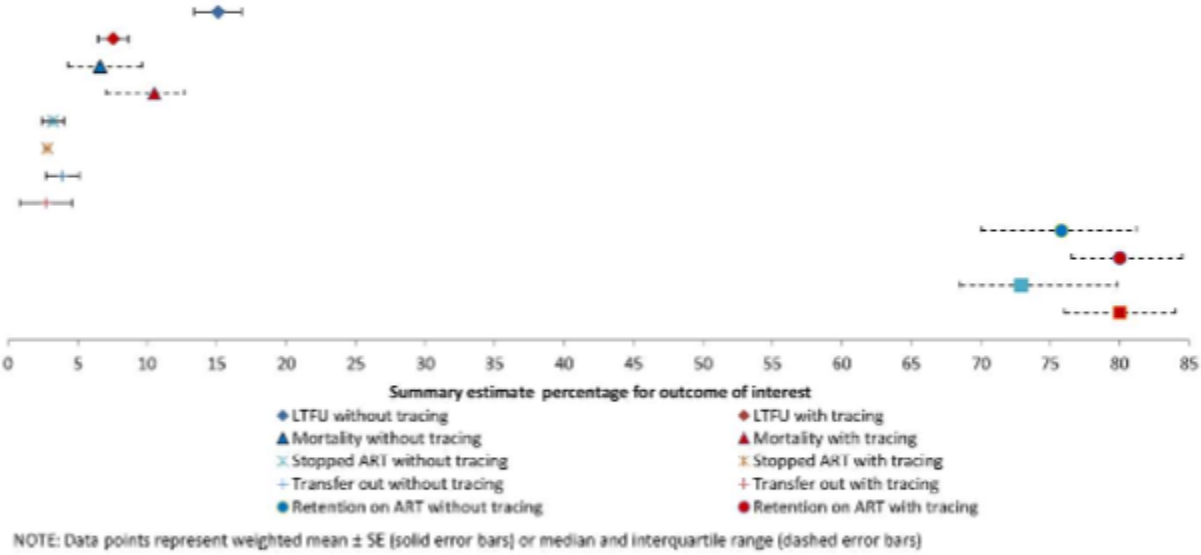


Figure 2. Plot of summary estimates with and without physical tracing.
doi:10.1371/journal.pone.0056047.g002

site is likely not explained by re-classification, but is due to less LTFU, death, or transfers out. Individuals that are re-engaged would have the opportunity to receive the beneficial effects of ART such as improved survival, decreased risk of opportunistic infections, [63] and potentially preventing virological failure and the emergence of HIVDR by limiting treatment interruptions [11,12]. In addition, the maintenance of an increased proportion of individuals in care and receiving ART is likely to benefit the community by decreasing HIV incidence [64–66]. Furthermore, if data on the costs of physical tracing can be obtained, this intervention may potentially be a cost-effective mechanism to re-engage patients into care. Cost-effective analyses of intervention to minimize LTFU and improve survival have been performed but analyses incorporating tracing are not known to the authors at this time. While the qualifications of individuals performing physical tracing is not always reported some included studies did document tracing by peer supporters or people living with HIV without medical qualifications [27,39,57] suggesting that physical tracing may prove cost effective in many settings.

The considerable difference in summary estimates between physical and non-physical tracing emphasizes the importance of knowing whether physical tracing is used within an ART program or at a specific ART clinic when interpreting LTFU, mortality or retention data. Estimates of mortality and LTFU are frequently used to assess level of ART program and clinic performance; [5,6] thus, understanding differences which arise due to physical tracing are important. In addition, the indicator of retention on ART after 12 months of therapy is considered an essential and high impact information when assessing ART program performance [7,8]. Criticising a program that does not achieve targets for mortality but has functioning tracing programs resulting in few patients with unknown outcomes may not be appropriate. Likewise, reinforcing current practice in settings without tracing and reporting low mortality and higher LTFU rates sends an incorrect message. Furthermore, guidance from the literature in this area is limited as only one previous review was identified that stratified a summary estimate by tracing status. This study by Braitstein et al [18] documented 6.4% mortality with physical tracing and 2.3% without in an LMIC setting whereas we report a mortality of 10.5% with tracing and 6.6% without tracing . Additional reviews report higher 12-month mortality estimates that do not take tracing into account; 14% by Gupta et al [20] and a range of 8–26% mortality by Lawn et al [21]. The reasons for differences in these mortality estimates are unclear, but potentially reflect differences in reporting or improved clinical outcomes. For example, the lower estimates of mortality reported by Braitstein et al [18] are obtained from a smaller number of sites within the ART-LINC collaboration. Additional reviews report estimates of 75–80% retention consistent with findings in this review although tracing status was not documented [14,19].

This systematic review has some limitations. Settings where physical tracing is available may have increased resources for patients resulting in improved outcomes. Summarizing the effect of tracing from randomised trials containing tracing interventions may provide a more accurate assessment of the impact of tracing on LTFU, mortality and retention by eliminating potential confounding associated with better resourced sites. The authors are unaware of published randomised trials of this nature but data from this review supports the development of randomised trials to quantify the benefits of different tracing strategies including the cost-effectiveness of these strategies. There is also a potential publication bias for settings more likely to publish on LTFU. For example programs associated with academic institutions may be more likely to prepare manuscripts and these programs may have different outcomes from other non-academic settings less inclined to publish their results. Another limitation of this analysis was variability of definitions of LTFU. The majority of studies used a definition of LTFU consistent with international recommendations, [5] yet it is unclear how our findings would have differed if alternative definitions of LTFU had been used. Furthermore, studies classified as physical tracing studies potentially have differing mechanisms to physically trace patients (e.g. number of attempts) which could have influenced outcomes, although the objective of the review was to compare cohorts with and without physical tracing without focussing on specific subgroups within the physical tracing group of studies. Findings from this review may

also be limited if additional data are available from other biomedical databases or relevant grey literature. If additional unidentified studies have different findings from the 54 cohorts identified through Ovid Medline and the international HIV conference databases, summary findings could be different. Finally, data on transfer out was only available in a minority of studies despite looking for this data in all selected studies. Estimates of retention at the original site could have potentially changed if complete transfer out data were available. For example a potential bias could exist if cohorts with physical tracing had decreased transfers out which was not documented. This could lead to increased estimates of retention at the original site not necessarily explained by increased re-engagement in care. This limitation emphasises the importance of understanding the proportion transferred out when accurately interpreting and comparing estimates of retention.

In conclusion, physical tracing leads to a reduction in unknown outcomes and likely improved re-engagement in care. Findings from the observational data in this review highlight a critical need for randomised controlled trials to support the effectiveness of patient tracing to improve re-engagement of patients on ART and assess the cost-effectiveness of tracing interventions. Programs providing ART in LMICs should consider physically tracing patients who have become disengaged from care as an important intervention to improve individual outcomes and programmatic evaluation of HIV infected populations receiving ART.

Supporting Information

Material S1 Physical tracing effects systematic review protocol
(DOC)

Acknowledgments

Some of the authors are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decision or stated policy of the World Health Organization.

Author Contributions

Performed the experiments: JHM MRJ. Devised the protocol to systematically review the literature: JHM JHE MRJ. Did the initial search of published work, reviewed full-text articles and conference abstracts and extracted data from the manuscripts and conference abstracts: JHM. Reviewed selected studies and independently abstracted data if there were any concerns about the initial data abstraction: MJ. Available as a third reviewer in case of conflicting results after data abstraction: JE. Wrote the first draft of the paper: JHM. Participated in interpreting the results and structuring the manuscript: SYH SB. All authors participated in writing the manuscript and all authors have seen and approved the final version of the manuscript. Conceived and designed the experiments: JHM MRJ. Wrote the paper: JHM SYH SB. Analyzed the data: JHM.

References

1. WHO (2011) Towards universal access : scaling up priority HIV/AIDS interventions in the health sector : progress report 2011. Geneva: World Health Organization.
2. Weidle PJ, Malamba S, Mwebaze R, Sozi C, Rukundo G, et al. (2002) Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. Lancet 360: 34–40.
3. Severe P, Leger P, Charles M, Noel F, Bonhomme G, et al. (2005) Antiretroviral therapy in a thousand patients with AIDS in Haiti. N Engl J Med 353: 2325–2334.
4. Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, et al. (2004) Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS 18: 887–893.
5. WHO (2010) HIV Drug Resistance Early Warning Indicators.World Health Organization indicators to monitor HIV drug resistance prevention at antiretroviral treatment sites. June 2010 Update. Geneva: World Health Organization.
6. WHO (2006) Patient monitoring guidelines for HIV care and antiretroviral therapy. Integrated management of adolescent and adult illness / Integrated management of childhood illness. Geneva: World Health Organization.
7. UNAIDS (2009) Monitoring the Declaration of Commitment on HIV/AIDS : guidelines on construction of core indicators : 2010 reporting. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS).
8. PEPFAR (2009) Next Generation Indicator Reference Guide. Version 1.1. The President's Emergency Plan for AIDS Relief. Department of Health and Human Services. United States Government.
9. Brinkhof MW, Pujades-Rodriguez M, Egger M, Brinkhof MWG, Pujades-Rodriguez M, et al. (2009) Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS ONE [Electronic Resource] 4: e5790.
10. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, et al. (2011) Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 365: 493–505.
11. Parienti JJ, Massari V, Descamps D, Vabret A, Bouvet E, et al. (2004) Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis 38: 1311–1316.
12. Oyugi JH, Byakika-Tusiime J, Ragland K, Laeyendecker O, Mugerwa R, et al. (2007) Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. AIDS 21: 965–971.
13. Harries AD, Zachariah R, Lawn SD, Rosen S (2010) Strategies to improve patient retention on antiretroviral therapy in sub-Saharan Africa. Trop Med Int Health 15 Suppl 1: 70–75.
14. Fox MP, Rosen S (2010) Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Tropical Medicine & International Health 15 Suppl 1: 1–15.
15. Cornell M, Grimsrud A, Fairall L, Fox MP, van Cutsem G, et al. (2010) Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007. AIDS 24: 2263–2270.
16. Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, et al. (2010) Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. Journal of Acquired Immune Deficiency Syndromes: JAIDS 53: 405–411.
17. Tassie J-M, Malateste K, Pujades-Rodriguez M, Poulet E, Bennett D, et al. (2010) Evaluation of three sampling methods to monitor outcomes of antiretroviral treatment programmes in low- and middle-income countries. PLoS ONE [Electronic Resource] 5: e13899.
18. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, et al. (2006) Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 367: 817–824.
19. Rosen S, Fox MP, Gill CJ (2007) Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Medicine / Public Library of Science 4: e298.
20. Gupta A, Nadkarni G, Yang WT, Chandrasekhar A, Gupte N, et al. (2011) Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis. PLoS One 6: e28691.
21. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R (2008) Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS 22: 1897–1908.
22. Hawkins C, Achenbach C, Fryda W, Ngare D, Murphy R (2007) Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. J Acquir Immune Defic Syndr 45: 304–310.
23. Laurent C, Meilo H, Guiard-Schmid JB, Mapoure Y, Noel JM, et al. (2005) Antiretroviral therapy in public and private routine health care clinics in Cameroon: lessons from the Douala antiretroviral (DARVIR) initiative. Clin Infect Dis 41: 108–111.
24. Woelk-Kaloustian K, Kimaiyo S, Diero L, Siika A, Sidle J, et al. (2006) Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya. AIDS 20: 41–48.
25. Hinganekar N, Thorat S, Deshpande A, Rajasekaran S, Chandrasekar C, et al. (2012) Initial virologic response and HIV drug resistance among HIV-1 infected individuals initiating first-line antiretroviral therapy at two clinics in Chennai and Mumbai India. Clin Infect Dis 54: S348–354.
26. Ugbena R, Aberle-Grasse J, Diallo K, Bassey O, Jelpe T, et al. (2012) Virological response and HIV-1 drug resistance 12 months after antiretroviral therapy initiation at two clinics in Nigeria Clin Infect Dis 54: S375–379.
27. Palombi L, Marazzi MC, Guidotti G, Germano P, Buonomo E, et al. (2009) Incidence and predictors of death, retention, and switch to second-line regimens in antiretroviral- treated patients in sub-Saharan African Sites with comprehensive monitoring availability. Clinical Infectious Diseases 48: 115–122.

28. Vella V, Govender T, Dlamini S, Taylor M, Moodley I, et al. (2010) Retrospective study on the critical factors for retaining patients on antiretroviral therapy in KwaZulu-Natal, South Africa. Journal of Acquired Immune Deficiency Syndromes: JAIDS 53: 109–116.
29. Zachariah R, Teck R, Buhendwa L, Fitzerland M, Labana S, et al. (2007) Community support is associated with better antiretroviral treatment outcomes in a resource-limited rural district in Malawi. Trans R Soc Trop Med Hyg 101: 79–84.
30. Oleckno W (2008) Basic Measures of Occurrence in Epidemiology. Epidemiology Concepts and Methods. Long Grove: Waveland Press Inc. 98–99.
31. Barth RE, van der Meer JT, Hoepelman AI, Schrooders PA, van de Vijver DA, et al. (2008) Effectiveness of highly active antiretroviral therapy administered by general practitioners in rural South Africa. Eur J Clin Microbiol Infect Dis 27: 977–984.
32. Bisson GP, Frank I, Gross R, Lo Re V, 3rd, Strom JB, et al. (2006) Out-of-pocket costs of HAART limit HIV treatment responses in Botswana's private sector. AIDS 20: 1333–1336.
33. Bisson GP, Gaolathe T, Gross R, Rollins C, Bellamy S, et al. (2008) Overestimates of survival after HAART: implications for global scale-up efforts. PLoS ONE [Electronic Resource] 3: e1723.
34. Charalambous S, Innes C, Muirhead D, Kumaranayake L, Fielding K, et al. (2007) Evaluation of a workplace HIV treatment programme in South Africa. AIDS 21 Suppl 3: S73–78.
35. Chi BH, Cantrell RA, Zulu I, Mulenga LB, Levy JW, et al. (2009) Adherence to first-line antiretroviral therapy affects non-virologic outcomes among patients on treatment for more than 12 months in Lusaka, Zambia. International Journal of Epidemiology 38: 746–756.
36. Chung MH, Kohler P, Attwa M, Thiga J, John-Stewart GC, et al. (2010) Comparing clinic retention between residents and nonresidents of Kibera, Kenya. Journal of Acquired Immune Deficiency Syndromes: JAIDS 53: 422–424.
37. Collini P, Schwab U, Sarfo S, Obeng-Baah J, Norman B, et al. (2009) Sustained immunological responses to highly active antiretroviral therapy at 36 months in a Ghanaian HIV cohort. Clinical Infectious Diseases 48: 988–991.
38. Culbert H, Tu D, O'Brien DP, Ellman T, Mills C, et al. (2007) HIV treatment in a conflict setting: outcomes and experiences from Bukavu, Democratic Republic of the Congo. PLoS Med 4: e129.
39. DeSilva MB, Merry SP, Fischer PR, Rohrer JE, Isichei CO, et al. (2009) Youth, unemployment, and male gender predict mortality in AIDS patients started on HAART in Nigeria. AIDS Care 21: 70–77.
40. Etard JF, Ndiaye I, Thierry-Mieg M, Gueye NF, Gueye PM, et al. (2006) Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. AIDS 20: 1181–1189.
41. Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, et al. (2006) Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. Lancet 367: 1335–1342.
42. Karcher H, Omondi A, Odera J, Kuntz A, Harms G (2007) Risk factors for treatment denial and loss to follow-up in an antiretroviral treatment cohort in Kenya. Trop Med Int Health 12: 687–694.
43. Marston BJ, Macharia DK, Nga'nga L, Wangai M, Ilako F, et al. (2007) A program to provide antiretroviral therapy to residents of an urban slum in nairobi, kenya. J Int Assoc Physicians AIDS Care (Chic Ill) 6: 106–112.
44. Moore E, Beadsworth MBJ, Chaponda M, Mhango B, Faragher B, et al. (2010) Favourable one-year ART outcomes in adult Malawians with hepatitis B and C co-infection. Journal of Infection 61: 155–163.
45. Mutevedzi PC, Lessells RJ, Heller T, Barnighausen T, Cooke GS, et al. (2010) Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? Bulletin of the World Health Organization 88: 593–600.
46. Thai S, Koole O, Un P, Ros S, De Munter P, et al. (2009) Five-year experience with scaling-up access to antiretroviral treatment in an HIV care programme in Cambodia. Tropical Medicine & International Health 14: 1048–1058.
47. Toure S, Kouadio B, Seyler C, Traore M, Dakoury-Dogbo N, et al. (2008) Rapid scaling-up of antiretroviral therapy in 10,000 adults in Cote d'Ivoire: 2-year outcomes and determinants. AIDS 22: 873–882.
48. Wester CW, Kim S, Bussmann H, Avalos A, Ndwapi N, et al. (2005) Initial response to highly active antiretroviral therapy in HIV-1C-infected adults in a public sector treatment program in Botswana. J Acquir Immune Defic Syndr 40: 336–343.
49. Somi G, Arthur G, Gongo R, Senkoro K, T Kellogg T, et al. (2011) 24-Month Outcomes for Adults in Tanzania's National ART Program from 2004 to 2009: Success Maintained during Scale-up, but Should Services Be More Youth Friendly? CROI 2011 Paper #1019.
50. Ehmer J, Truniger C, Waldegg G, Musa I, Mushi A, et al. (2009) Characteristics and outcomes of HIV-infected patients starting HAART in rural treatment programmes in four sub-Saharan African countries International AIDS Society - Abstract - MOPED045.
51. Cortes C, Beltran C, Wolff M (2010) Rate of Mortality, Loss to Follow-up, Viral Suppression, Immune Recovery, and Maintenance of Initial Antiretroviral Regimen at 4 Years: 3043 Chilean Patients. CROI 2010 Paper #523.
52. Chinh N, Quang V, Thi Tuyet Nhung V, Colby D (2010) First-line ART Outcomes in HIV-infected Adults in Ho Chi Minh City, Vietnam. CROI 2010 Paper #517.
53. Bertagnolio S, Kelley K, Saadani Hassani A, Obeng-Aduasare Y, Jordan M (2011) Surveillance of Transmitted and Acquired HIV Drug Resistance Using WHO Surveys in Resource-limited Settings. CROI 2011 Paper # 52.
54. Balestre E, Lokossue A, Eholié S, Sow P, Charurat M, et al. (2011) Effect of Age on Immunological Response in the First Year of HAART in HIV-1-infected Adults, IeDEA West Africa Collaboration. CROI 2011 Paper # 272.
55. Auld A, Mbofana F, Shiraishi R, Sanchez M, Alfredo C, et al. (2010) Treatment outcomes of Mozambique's adult antiretroviral therapy program - earlier treatment and co-trimoxazole are important. International AIDS Society - Abstract - TUAB0204.
56. May M, Boulle A, Phiri S, Messou E, Myer L, et al. (2010) Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet 376: 449–457.
57. Bedelu M, Ford N, Hilderbrand K, Reuter H, Bedelu M, et al. (2007) Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. Journal of Infectious Diseases 196 Suppl 3: S464–468.
58. Hong SY, Jonas A, Dumeni E, Badi A, Pereko D, et al. (2010) Population-based monitoring of HIV drug resistance in Namibia with early warning indicators. Journal of Acquired Immune Deficiency Syndromes: JAIDS 55: 27–31.
59. O'Brien DP, Mills C, Hamel C, Ford N, Pottie K (2009) Universal access: the benefits and challenges in bringing integrated HIV care to isolated and conflict affected populations in the Republic of Congo. Confl Health 3: 1.
60. Johannessen A, Naman E, Ngowi BJ, Sandvik L, Matee MI, et al. (2008) Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC Infect Dis 8: 52.
61. Assefa Y, Van Damme W, Mariam DH, Kloos H (2010) Toward universal access to HIV counseling and testing and antiretroviral treatment in Ethiopia: looking beyond HIV testing and ART initiation. AIDS Patient Care & Stds 24: 521–525.
62. Sharma SK, Dhooria S, Prasad KT, George N, Ranjan S, et al. (2010) Outcomes of antiretroviral therapy in a northern Indian urban clinic. Bulletin of the World Health Organization 88: 222–226.
63. Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, et al. (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338: 853–860.
64. Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, et al. (2010) Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One 5: e11068.
65. Montaner JS, Wood E, Kerr T, Lima V, Barrios R, et al. (2010) Expanded highly active antiretroviral therapy coverage among HIV-positive drug users to improve individual and public health outcomes. J Acquir Immune Defic Syndr 55 Suppl 1: S5–9.
66. Forgione L, Torzian L (2012) Trends in community viral load, new diagnoses, and estimated incidence of HIV, New York City, 2002–2009. Abstract #1123. CROI. Seattle, USA.

3.3 Viral Load Outcomes after 12 Months Antiretroviral Therapy in Low to Middle Income Countries: A Systematic Review

3.3.1 Declaration

Declaration for Thesis Chapter 3.3

Declaration by candidate

In the case of Chapter 3.3, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript	80

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors**
Julian H. Elliott	Helped conceive the idea for the review, an approach to review the literature and develop the manuscript	7.5
Silvia Bertagnolio	Participated in interpreting the results and developing the manuscript.	2.5
Rachel Kubiak	Assisted with the initial search of published work, reviewed full-text articles and conference abstracts and extracted data from	2.5

	the manuscripts and conference abstracts. Helped develop the manuscript.	
Michael R. Jordan	Helped conceive the idea for the review, devise the protocol and develop the manuscript	7.5

Candidate's Signature	[redacted]	**Date 16 APR 2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**Alfred Hospital Infectious Diseases Unit, Melbourne**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	JHE	[redacted]		**Date** 16/4/2013
Signature 2	SB			10/4/2013
Signature 3	RK			9/4/2013
Signature 4	MRJ			10/4/2013

3.3.2 Paper

Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: a systematic review

James H McMahon,[a] Julian H Elliott,[a] Silvia Bertagnolio,[b] Rachel Kubiak[c] & Michael R Jordan[c]

Objective To estimate the frequency of viral suppression in low- and middle-income countries (LMICs) in patients who received antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection.

Methods Data on viral suppression after 12 months of ART in LMICs were collected from articles published in 2003 to 2011 and from abstracts of conferences held between 2009 and 2011. Pooled proportions for on-treatment and intention-to-treat populations were used as summary estimates. Random-effects models were used for heterogeneous groups of studies ($I^2 > 75\%$).

Findings Overall, 49 studies covering 48 cohorts and 30 016 individuals met the inclusion criteria. With thresholds for suppression between 300 and 500 copies of viral ribonucleic acid (RNA) per ml of plasma, 84.3% (95% confidence interval, CI: 80.4–87.9) of the pooled on-treatment population and 70.5% (95% CI: 65.2–75.6) of the intention-to-treat population showed suppression. Use of different viral RNA thresholds changed the proportions showing suppression: to 84% and 76% of the on-treatment population with thresholds set above 300 and at or below 200 RNA copies per ml, respectively, and to 78%, 71% and 63% of the intention-to-treat population at thresholds set at 1000, 300 to 500, and 200 or fewer copies per ml, respectively.

Conclusion The pooled estimates of viral suppression recorded after 12 months of ART in LMICs provide that other ART programmes can use to set realistic goals and perform predictive modelling. Evidence from this review suggests that the current international target – i.e. viral suppression in > 70% of the intention-to-treat population, with a threshold of 1000 copies per ml – should be revised upwards.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

At the end of 2011, over 8 million people in low- and middle-income countries (LMICs) were receiving antiretroviral therapy (ART).[1] The guidelines of the World Health Organization (WHO) for the treatment of human immunodeficiency virus (HIV) infection recommend that, where possible, the viral loads of individuals receiving ART be measured every 6 months to detect viral replication and confirm treatment failure whenever it occurs.[2] Although viral load tests are currently too costly for routine use in many LMICs, the potential for increased access to such tests exists as costs decrease and countries prioritize this method of patient monitoring.[3]

WHO's guidelines for the treatment of HIV infection recommend that a viral load of > 5000 copies of viral ribonucleic acid (RNA) per ml be taken as indicative of virological failure.[2] According to WHO's strategy for the surveillance and monitoring of HIV drug resistance in LMICs, a viral load of < 1000 RNA copies per ml should be taken as evidence of viral suppression.[4] Guidelines for the treatment of HIV infection in high-income countries stipulate that a viral load of < 50 RNA copies per ml – or a load below the limit of detection of the most sensitive assay available – be taken as evidence of viral suppression,[5–7] and that a load of ≥ 50 RNA copies per ml,[5,7] or one of ≥ 200 viral RNA copies per ml confirmed by repeat testing,[6] be used as evidence of virological failure or rebound.

The proportion of a study cohort showing viral suppression is calculated as the number of patients with viral suppression divided either by the number of patients in the study cohort who began ART (i.e. the intention-to-treat population), or by the number of patients in the cohort who are alive and on treatment (i.e. the on-treatment population). On-treatment analyses reflect the effectiveness of ART for those receiving antiretroviral drugs. Intention-to-treat analyses, which use a denominator that includes individuals who die or are lost to follow-up during the study period, reflect factors at the individual or programme level that influence the risk of death and disengagement from care. Relatively high mortality in the first 6 to 12 months of ART and substantial loss to follow-up, both of which have been widely reported in LMICs, can therefore influence estimates of viral suppression based on intention to treat.[5,9]

Summary estimates of viral suppression (as measured, for example, 12 months after ART initiation) are needed to guide ART programme managers on the normative levels of population-level viral suppression and to define desirable levels of clinic and programme performance. Such estimates are also useful when creating and improving mathematical models of the different strategies that might be followed to provide ART in LMICs. Recent reviews of virological outcomes have focused on sub-Saharan Africa and levels of acquired resistance to antiretroviral drugs.[10,11] Across LMICs, summary estimates of viral suppression based on different HIV-RNA thresholds are lacking. The objective of this systematic review was to establish estimates, based on different viral RNA thresholds, of the percentages of the intention-to-treat and on-treatment populations in LMICs that show viral suppression 12 months after ART initiation.

[a] Infectious Diseases Unit, Alfred Hospital, Level 2 Burnet Tower, 85 Commercial Road, Melbourne, 3004, Australia.
[b] HIV Department, World Health Organization, Geneva, Switzerland.
[c] Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, United States of America.
Correspondence to James H McMahon (e-mail: [redacted]).
(Submitted: 16 September 2012 – Revised version received: 1 January 2013 – Accepted: 21 January 2013 – Published online: 21 February 2013)

Methods

Study selection

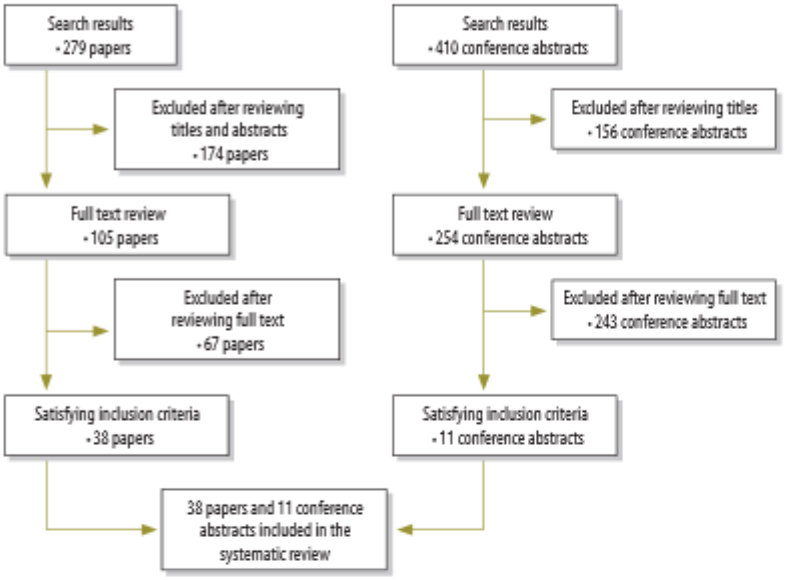
We included publications ("papers") or conference abstracts that reported the proportion of individuals in a study cohort from a LMIC for whom a virological outcome after 12 months of ART was reported, either as a primary or a secondary finding. If only the median duration of follow-up was reported for a study, that study was included in the review provided the median duration was between 9 and 15 months. Any definition of viral suppression (or failure) reporting a proportion of patients below (or above) a defined viral RNA threshold was accepted. If the threshold was not reported, the relevant authors were contacted and asked for details of the threshold that they had used. A study was excluded if (i) the threshold used could not be determined; (ii) only changes in viral RNA loads from the baseline values were reported; (iii) most of the patients were less than 13 years old; (iv) patients received only one or two antiretroviral drugs; or (v) the study was not from a LMIC. All the studies included in the review were published in English and were either clinical trials or cross-sectional or cohort in design.

Search strategy

We searched for relevant articles published between 1 January 2003 and 31 May 2011 through Ovid MEDLINE. Online databases containing the abstracts of presentations made at the International AIDS Society Conferences held in 2009–2010 and at the Conferences on Retroviruses and Opportunistic Infections held in 2009–2011 were also searched.[12,13]

Our search strategy combined the relevant medical subject headings (MeSH) with additional search terms to identify those studies that reported virological outcomes for HIV-infected participants receiving ART. We used other MeSH and search terms to identify studies from LMICs in which outcomes after 12 months of ART were investigated. When more than one article reported data from the same cohort of patients and used the same viral RNA threshold, only the article that contained the most detailed information was selected. Fig. 1 summarizes the search strategy and study selection process. The study protocol provides further details.[14]

Fig. 1. **Search strategy and study selection used in the systematic review**



Note: We excluded duplicate reports, studies on subjects not receiving antiretroviral therapy, studies with patients younger than 13 years or not infected with human immunodeficiency virus or not living in a low- or middle-income country, and reports that provided insufficient information were excluded.

The following data were abstracted from each study: first author, year of publication, study country or countries, health-care setting (i.e. public sector, private sector or nongovernmental organization), whether the study patients had to pay for their ART, dates the patients were observed, number of study sites, number of patients receiving ART, baseline demographics (i.e. age, gender, CD4+ T-lymphocyte count and clinical stage), ART regimen, whether patients were ART-naive at baseline, study definition of virological outcome, and the proportion of patients meeting that definition 12 months after initiating ART. When available, the percentages of subjects who died, transferred out, stopped ART or were lost to follow-up were also abstracted. Whether the proportion of the study cohort reported to have viral suppression was based on an on-treatment or intention-to treat analysis was noted. If intention-to-treat values had not been reported, they were calculated from the raw data (when available). In these calculations, the number of patients who had died or been lost to follow-up at the time of the estimation of virological outcome and, when available, the number that had stopped ART were included in the denominator. Patients who transferred out of the study cohort were excluded from the denominator, consistent with the indicators of retention in care recommended by WHO and the President's Emergency Plan for AIDS Relief (PEPFAR).[15–18]. If only the fraction of patients showing virological failure was reported, we calculated from this figure the proportion with viral suppression.

Data analysis

Proportions (%) of patients meeting the study definition of viral suppression were derived from text, tables or, if they could be accurately determined or estimated in this manner, from published graphs. Summary estimates were determined and categorized as on-treatment or intention-to-treat values. We assessed heterogeneity among proportions by calculating the I^2 statistic. If heterogeneity was high ($I^2 > 75\%$), we pooled proportions using the Freeman–Tukey method with a random-effects model and DerSimonian–Laird weights.[19,20] When possible, we determined summary estimates of viral suppression using different threshold ranges for viral RNA: ≥ 1000, 300–500 and/or ≤ 200 copies per ml. Additionally, we calculated summary estimates separately for studies in which one or two viral load tests were used per patient to define virological outcomes. We performed subgroup analyses to examine the influence of the year of ART initiation and of the time taken to publish the research

findings (i.e. the "time-lag bias") on the summary estimates for the on-treatment populations. Year of ART initiation was defined as the median year of ART initiation and reported as pre-2004, 2004–2005 or post-2005. The time from the median year of ART initiation until publication was categorized as ≤ 3, 4 or ≥ 5 years. Analyses were conducted using Excel (Microsoft, Redmond, United States of America) and version 2.7.9 of the StatsDirect software package (StatsDirect, Altrincham, United Kingdom).

Results

Overall, 49 studies (38 papers[21–58] and 11 conference abstracts[59–69]), together comprising 48 cohorts and 30 016 individuals, were identified for inclusion (Fig. 1). Details of the cohorts from the papers and conference abstracts are presented in Table 1 and Table 2 (available at: http://www.who.int/bulletin/volumes/90/4/12-112946), respectively. Two reports[29,52] described outcomes from the same cohort but made use of two different thresholds to define viral suppression. A further seven reports[26,27,43,44,47,53,55] described outcomes using two or more thresholds of viral suppression. The data from another two papers[24,25] were combined to obtain an estimate of viral suppression in a single cohort. The 48 cohorts in the systematic review comprised 43 single-country cohorts – 37 from sub-Saharan Africa, 3 from Asia and 3 from Latin America or the Caribbean – and 5 multi-country cohorts (of which 4 were from sub-Saharan Africa).

All but one study[48] used a single viral load measurement per patient to define the virological outcome. The ART regimens used were reported for 39 of the studies. In each of 35 (90%) and 29 (74%) of these studies, at least 50% and 95% of the patients, respectively, had received a regimen based on a non-nucleoside reverse-transcriptase inhibitor (NNRTI). Most of the patients in another three studies – a clinical trial studying the efficacy of boosted protease-inhibitor regimens[26] and two studies from regions with high prevalences of HIV-2 infection[35,45] – had received regimens based on a protease inhibitor.

Summary estimates from on-treatment and intention-to-treat analyses are presented – for those studies in which outcomes were defined using a single viral load measurement– in Table 3 and Fig. 2. As high levels of heterogeneity were observed ($I^2 > 90\%$), all summary estimates and 95% confidence intervals (CI) were calculated using a random-effects model.

The summary estimate of the proportion of patients showing viral suppression, for all viral load thresholds in 43 on-treatment analyses, was 84.0% (95% CI: 81.3–86.6; $n = 26\,599$). For the nine cohorts in which viral suppression was defined as < 1000 viral RNA copies per ml, 83.5% (95% CI: 77.8–88.4; $n = 3192$) of the combined on-treatment populations showed suppression. Thresholds ranging from 300 to 500 copies per ml were used for 32 cohorts (a threshold of 400 copies per ml was used for 27 cohorts) and 84.3% (95% CI: 80.4–87.9; $n = 25\,708$) of the combined on-treatment populations of these 32 cohorts showed suppression. The reported outcomes for nine and six cohorts were based on thresholds set at

Table 3. **Summary estimates of the proportions achieving viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries**

Type of analysis and viral load threshold	No. of cohorts[a]	No. of patients starting ART	Patients (%) with viral suppression	
			Range	Pooled (95% CI)[b]
On-treatment				
On-treatment, all thresholds[c]	43	26 599	49–97	84.0 (81.3–86.6)
1000 copies/ml	9	3192	74–94	83.5 (77.8–88.4)[d]
300–500 copies/ml	32	25 708	62–97	84.3 (80.4–87.9)
≤ 200 copies/ml	9	2167	49–93	76.1 (66.8–84.3)
Intention-to-treat				
Intention-to-treat, all thresholds[c]	27	13 134	50–92	71.2 (66.5–75.7)
1000 copies/ml	4	1201	69–87	77.5 (67.6–86.1)
300–500 copies/ml	21	11 528	51–92	70.5 (65.2–75.6)
≤ 200 copies/ml	6	1654	46–77	62.9 (51.2–73.8)

ART, antiretroviral therapy; CI, confidence interval.

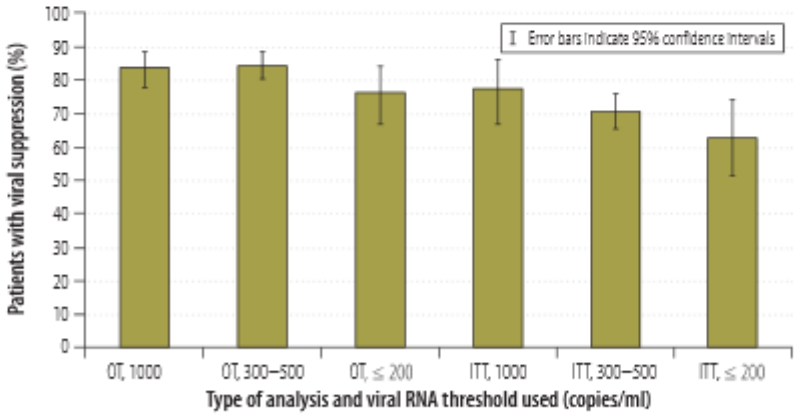
[a] Only includes data from studies in which suppression was detected by one viral load test per patient.

[b] Pooled proportions and CIs were calculated using the Freeman–Tukey method in a random effects model.

[c] When two different thresholds were applied in the study of one cohort, the data for the threshold that was closer to 1000 copies/ml was used.

[d] These values changed to 84.2 (79.1–88.7) when we included in the calculations the data for the study in which two viral load measurements were used, per patient, to define viral suppression (i.e. Scarsi et al.[60] [$n = 2366$]).

Fig. 2. **Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries**



ITT, intention-to-treat; OT, on-treatment; RNA, ribonucleic acid.

Note: The data shown summarizes OT or ITT analyses in which viral suppression was defined by a viral load – measured as copies of human immunodeficiency virus ribonucleic acid (HIV-RNA) per ml of plasma – that fell below a threshold value.

or below 200 and at or below 50 viral RNA copies per ml, respectively. When thresholds set at or below 200 copies per ml were used, 76.1% (95% CI: 66.8–84.3; $n = 2167$) of the combined on-treatment populations showed suppression.

The summary estimate of viral suppression for all 27 cohorts ($n = 13\,134$) in intention-to-treat analyses was 71.2% (95% CI: 66.5–75.7). The corresponding value for the four analyses in which a threshold of 1000 copies per ml was used was 77.5% (95% CI: 67.6–86.1; $n = 1201$). In intention-to-treat analyses of the data from 21 and 19 cohorts, thresholds of 300–500 and 400 copies per ml, respectively, were used. With thresholds that ranged from 300 to 500 copies per ml, 70.5% (95% CI: 65.2–75.6; $n = 11\,528$) of the combined intention-to-treat populations showed viral suppression. Six studies reported the results of intention-to treat analyses based on thresholds set at or below 200 copies per ml – four studies used a threshold set at or below 50 copies per ml – and these produced a summary estimate for the frequency of viral suppression of 62.9% (95% CI: 51.2–73.8; $n = 1654$).

To investigate possible sources of heterogeneity, we performed subgroup analyses exploring the median time of ART initiation and the potential bias introduced by the time taken to publish results: the I^2 values for the subgroups considered were all > 90%. When the median year of ART initiation was pre-2004, 2004–2005 and post-2005, the on-treatment estimates of suppression after 12 months of ART were 80.9% (95% CI: 73.0–87.7), 84.1% (95% CI: 78.3–89.2) and 84.3% (95% CI: 80.0–88.2), respectively. The corresponding values for delays of ≤ 3, 4 and ≥ 5 years between the median year of ART initiation and the year of the publication of results were similar: 83.3% (95% CI: 78.0–88.0), 84.0% (95% CI: 78.7–88.6) and 83.0% (95% CI: 76.9–88.3), respectively.

Discussion

This is the first systematic review to quantify population-level viral suppression 12 months after ART initiation in LMICs, and to stratify estimates by viral RNA thresholds in on-treatment and intention-to-treat analyses. Over 70% of the cohorts included in the review were investigated using thresholds ranging from 300 to 500 viral RNA copies per ml and, after 12 months of ART, viral suppression was noted in 84% (on-treatment) or 71% of patients (intention-to-treat). These summary estimates compare favourably with outcomes reported in high-income countries after 12 months of NNRTI-based ART, such as the 58–73% viral suppression seen in intention-to-treat analyses in early clinical trials and in a meta-analysis at thresholds set from 400 to 500 viral RNA copies per ml.[70–72] Observational data from Canada, the United Kingdom of Great Britain and Northern Ireland and the United States of America also indicate similar frequencies of viral suppression after 12 months of ART. For example, when a viral load threshold of 50 copies per ml was used, 82% of an on-treatment population investigated in the United Kingdom showed viral suppression.[73] In Canada and the United States, in on-treatment analyses based on suppression thresholds between 500 and 1000 copies per ml, 60–63% of individuals initiating ART when they had CD4+ T-lymphocyte counts of < 200 cells per µl were found to have attained viral suppression 12 months later.[74,75]

As anticipated, summary estimates for viral suppression were found to be higher in the on-treatment analyses than in the intention-to-treat analyses and to increase as the viral RNA thresholds used to define suppression increased. Individuals who are lost to follow-up in studies on the efficacy of ART – and included in intention-to-treat analyses but excluded from on-treatment analyses – are defined as not having achieved viral suppression. In addition, as the viral load thresholds for suppression are increased, increasing numbers of patients with low-level viraemia are categorized as cases of viral suppression.

We found no evidence of studies in LMICs that had used viral load thresholds of 10 000 or 5000 copies per ml – as recommended in the ART guidelines published by WHO in 2006[2] and 2010,[76] respectively – to define viral suppression. The reasons for this are unclear. Investigators in LMICs may simply have preferred to use the lower thresholds supported either by the national ART guidelines used in the country where the study was performed or by guidelines not specifically intended for use in a public health model of care.[5–7] They may also have wished to use thresholds based on the lower limit of sensitivity of the viral load assay that they had available.

Only one study[68] reported the frequency of viral suppression based on two viral load measurements per patient. In this case, use of a second test increased the percentage of patients showing viral suppression. A second test is particularly likely to increase the percentage of patients who are virologically suppressed if an intervention to improve adherence to ART occurs after an initial detectable viral load, in a strategy that is recommended by WHO[2] and already followed in several LMICs.[35,77,78] Given that the overwhelming majority of reported outcomes are based on a single viral load measurement per patient, efforts to understand and summarize virological outcomes in LMICs should also be based on a single test result for each patient.

As far as possible, this review used intention-to-treat estimates of viral suppression that, as recommended in the relevant international guidelines,[15–18] excluded individuals who transferred out of the included studies. Individuals were reported to have transferred out of only six cohorts included in the review and, in each case, such individuals were excluded from the intention-to-treat estimate of viral suppression.[21,24,25,28,46,48,49] However, only two of the reports included in the review specifically stated that no patient had transferred out.[44,53] For the other 19 cohorts with intention-to-treat estimates of viral suppression, no data on transfers out were presented. This lack of data left it unclear whether any patients had transferred out and, if so, whether such patients had been incorporated in the denominator used in the final analyses. If any patients who did transfer out were unreported and still included in the denominators used in the final analyses, the intention-to-treat summary estimates generated in this review may be too low.

The summary estimates presented in this systematic review are important for target-setting and benchmarking. They provide guidance to ART clinics and programmes on the mean rates of viral suppression achieved in LMICs (normative referencing). The managers of ART programmes may define adequate levels of programme performance as those that lead to levels of viral suppression that match or exceed the summary estimates (criterion referencing).[79] A combination of normative and criterion referencing methods, incorporating the data summarized in this review, may be used to categorize poor, intermediate and optimal levels of

performance. In its strategy for the surveillance and monitoring of resistance to antiretrovirals, WHO recommends that ART treatment sites achieve viral suppression (as indicated by a viral load of < 1000 copies per ml) in at least 70% of the intention-to-treat population after 12 months of ART.[50] Although data from this review are limited, this target should probably be increased since, in the four reviewed studies that used the same viral load threshold ($n = 1201$), 78% of the intention-to-treat population achieved suppression. Although detectable viral RNA after ART does not prove the presence of resistance to antiretrovirals, individuals who are virologically suppressed on ART have no effective drug resistance. Detectable viral RNA in populations receiving ART is often associated with suboptimal adherence to ART, which is predictive of the emergence of drug-resistant strains of the virus.[65]

The estimates presented in this review may not be truly representative, despite being mean or normative levels of viral suppression. For example, ART programmes or clinics that evaluated and reported viral loads may have greater resources and better clinical outcomes than those where viral loads were not evaluated and/or where virological outcomes were not reported. Additionally, in settings where viral loads were evaluated but where poor virological outcomes were observed, researchers may have chosen not to disseminate the results, and this may have led to publication bias. The summary estimates may therefore overestimate the mean frequency of viral suppression in the broader population receiving ART in LMICs. In addition, high levels of statistical heterogeneity ($I^2 > 90\%$) were observed during the review. Analyses that focused on year of ART initiation and the delays between the recording and publishing of results revealed persistent heterogeneity but no major differences in the proportions achieving viral suppression between the subgroups considered. These findings suggest that other, unidentified factors are potentially contributing to the between-study variation seen in the proportions of viral suppression. Despite these limitations, the systematic method used to identify studies and the statistical methods used to generate summary estimates allow for a reliable estimate of viral suppression rates based on the data available from LMICs. Another potential limitation of the present review is that most of the data investigated came from studies that used thresholds between 300 and 500 copies per ml. Relatively few results from studies based on thresholds set at 1000 or at or below 200 viral RNA copies per ml were available. In the on-treatment analyses, the summary estimate of suppression seen with a threshold of 1000 copies per ml was similar to that seen with thresholds in the range of 300 to 500 copies per ml. However, only nine cohorts were included in the calculation of viral suppression at the high threshold ($n = 3192$), whereas 32 cohorts ($n = 25\,708$) were included in the calculation at the lower thresholds. The summary estimates established at 1000 copies per ml may have been too underpowered to demonstrate a difference with the estimates established at thresholds between 300 and 500 copies per ml.

In conclusion, this is the first systematic review of viral-suppression rates from LMICs after 12 months of ART. It includes summary estimates, at multiple HIV RNA thresholds, based on both on-treatment and intention-to-treat analyses. At the most commonly reported viral RNA thresholds (i.e. 300–500 copies per ml), approximately 71% of the patients in the intention-to-treat analyses and 84% in those in the on-treatment analyses had attained viral suppression 12 months after ART initiation. These proportions compare favourably with outcomes observed in high-income countries and represent a substantial achievement for LMICs, where ART is generally provided under great resource constraints.

The data reported in this review have important public health implications. Researchers and managers of ART programmes in LMICs could use these results to support mathematical models of the effects of ART and set rates of viral suppression as performance targets. Use of these targets would help identify those ART clinics with suboptimal performance that would most benefit from focused interventions to improve service delivery and patient outcomes. ■

Acknowledgements

The authors alone are responsible for the views expressed in this publication, which do not necessarily represent the decisions or stated policies of the World Health Organization. JHM has a dual appointment with the Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, USA. JHE has dual appointments with the Department of Medicine, Monash University, Melbourne, Australia and the Burnet Institute, Melbourne, Australia. MRJ has a dual appointment with the Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, USA

Funding: Authors received support via a Postgraduate Scholarship from the Australian National Health and Medical Research Council (JHM) and from United States National Institutes of Health 5K23AI074423-04 (MRJ.)

Competing interests: None declared.

ملخص

الكبت الفيروسي بعد 12 شهراً من العلاج بمضادات الفيروسات القهقري في البلدان المنخفضة الدخل والبلدان المتوسطة الدخل: استعراض منهجي

الغرض تقييم مستويات الكبت الفيروسي في البلدان المنخفضة الدخل والبلدان المتوسطة الدخل لدى المرضى الذين تتلقى العلاج بمضادات الفيروسات القهقري على العلاج الإصابة بفيروس العوز المناعي البشري.

الطريقة تم جمع البيانات حول الكبت الفيروسي بعد 12 شهراً من العلاج بمضادات الفيروسات القهقري في البلدان المنخفضة الدخل والبلدان المتوسطة الدخل من المقالات التي تم نشرها عام 2009 إلى عام 2011، ومن ملخصات المؤتمرات التي عقدت من عام 2009 إلى عام 2011. وتم استخدام النسب المجموعة للمجموعات السكانية الخاضعة للعلاج والمجموعات السكانية التي تتلقى العلاج لحساب قدرات موجزة وتم استخدام نماذج التأثيرات العشوائية في التحليلات الدراسات التي تتسم بالتغاير [12]

摘要

中低收入国家抗逆转录病毒治疗12 个月后病毒抑制：系统评价

目的 估计中低收入国家（LMIC）接受艾滋病病毒（HIV）感染抗逆转录病毒治疗（ART）的患者的病毒抑制率。

方法 从2003 至2011 年发表的文章以及2009 至2011 年之间举行的会议摘要中收集中低收入国家患者在接受ART 的12 个月之后的病毒抑制数据。使用治疗和意向治疗人群的集合比例作为汇总估计值。对研究（I2 >75%）的异质群体使用随机效应模型。

结果 总体而言，涉及48 个群组和30016 名个人的49 项研究符合纳入标准。在抑制阈值为每毫升血浆病毒核糖核酸（RNA）拷贝数为300 至500 时，84.3%（95% 置信区间，CI：80.4－87.9）的集合治疗人群和70.5%（95% CI：65.2－75.6）的意向治疗人群显示抑制。使用不同的病毒RNA阈值则显示抑制的比例有所变化：阈值为高于每毫升RNA拷贝数300 以上和200 以下的治疗人群抑制率分别变为84%和76%；阈值为每毫升拷贝数1000、300-500 和200 或更少时，意向治疗人群抑制率分别变为78%、71%和63%。

结论 中低收入国家ART治疗12 个月后记录的集合病毒抑制估计可供其他ART计划用来设定现实的目标，并进行预测建模。此评价的证据表明，目前的国际目标（也就是以每毫升拷贝数1000 为阈值，达到70%以上意向治疗人群中的病毒抑制）应向上修正。

Résumé

Suppression virale après 12 mois de traitement antirétroviral dans les pays à revenu faible et intermédiaire: bilan systématique

Objectif Estimer la fréquence de la suppression virale dans les pays à revenu faible et intermédiaire (PRFI) chez des patients ayant reçu un traitement antirétroviral (TAR) contre l'infection due au virus de l'immunodéficience humaine (VIH).

Méthodes Des données sur la suppression virale après 12 mois de TAR dans les PRFI ont été recueillies à partir d'articles publiés entre 2003 et 2011 et de comptes rendus de conférences qui ont eu lieu entre 2009 et 2011. Comme estimations sommaires, on a utilisé des proportions globales pour les populations en cours de traitement et ayant l'intention d'être traitées. On a utilisé des modèles d'effets aléatoires pour les groupes d'études hétérogènes (I2 > 75%).

Résultats Dans l'ensemble, 49 études couvrant 48 cohortes et 30 016 individus respectaient les critères d'inclusion. Avec des seuils de suppression allant de 300 à 500 copies d'acide ribonucléique (ARN) viral par ml de plasma, 84,3% (intervalle de confiance de 95%, IC: 80, 4–87,9) de la population en cours traitement analysée et 70,5% (95% IC: 65,2–75,6) de la population ayant l'intention d'être traitée indiquaient une suppression. L'utilisation de différents seuils d'ARN viral changeait les proportions montrant la suppression: à 84% et 76% de la population en cours de traitement avec des seuils fixés respectivement à plus de 300 et à 200 copies ou moins d'ARN par ml, et à 78%, 71% et 63% de la population ayant l'intention d'être traitée à des seuils fixés respectivement à 1 000, 300 à 500, et à 200 copies ou moins par ml.

Conclusion Les estimations globales de la suppression virale enregistrées après 12 mois de TAR dans les PRFI indiquent que d'autres programmes de TAR peuvent être utilisés pour définir des objectifs réalistes et pour réaliser une modélisation prédictive. Evidence from this review suggests that the current international target – i.e. viral suppression in > 70% of the intention-to-treat population, with a threshold of 1000 copies per ml – should be revised upwards.

Резюме

Вирусная суппрессия после 12 месяцев антиретровирусной терапии в странах с низким и средним уровнем дохода: систематический обзор

Цель Оценка частоты вирусной супрессии в странах с низким и средним уровнем дохода (СНСД) у пациентов, которые прошли антиретровирусную терапию (АРТ) против инфекции вируса иммунодефицита человека (ВИЧ).

Методы Данные о вирусной супрессии через 12 месяцев после начала АРТ в СНСД были собраны из статей, опубликованных в период с 2003 по 2011 годы и тезисов докладов на конференциях, состоявшихся в период с 2009 по 2011 годы. В качестве

сводных данных использовались совокупные пропорции людей, прошедших лечение и начавших лечение. Модели со случайными эффектами были использованы для гетерогенных групп исследований (I2 > 75%).

Результаты В целом, 49 исследований, охватывающих 48 когорт и 30 016 лиц, были признаны соответствующим критериям включения. С порогами супрессии от 300 до 500 копий вирусной рибонуклеиновой кислоты (РНК) на мл плазмы, 84,3% (95% доверительный интервал, ДИ: 80,4-87,9) от совокупной выборки людей, прошедших лечение, и 70,5% (95% ДИ: 65,2-75,6) людей, начавших лечение, проявили признаки супрессии. Использование других порогов содержания вирусных РНК изменило пропорции тех, у кого проявлялись признаки супрессии: до 84% и 76% людей, прошедших лечение, с порогами, установленными выше 300, и на уровне или ниже уровня 200 копий РНК на 1 мл, соответственно, и до 78%, 71% и 63 % от людей, начавших лечение, с порогами, установленными на уровне 1000, от 300 до 500 и 200 или меньшим количеством копий на 1 мл, соответственно.

Вывод Совокупная оценка вирусной супрессии, зафиксированной после 12 месяцев проведения АРТ в СНСД, показывает, что для постановки реалистичных целей и прогнозного моделирования можно использовать другие программы АРТ. Данные из этого обзора позволяют сделать вывод о необходимости пересмотра в сторону увеличения текущих международных целевых показателей, предусматривающих вирусную супрессию у 70% людей, начавших лечение, с порогом 1000 копий на 1 мл.

Resumen

Supresión viral tras 12 meses de terapia con antiretrovirales en países de renta baja y media: una revisión sistemática

Objetivo Calcular la frecuencia de la supresión viral en países de renta baja y media (PRBM) en pacientes que recibieron terapia con antiretrovirales (TAR) para tratar la infección por el virus de inmunodeficiencia humana (VIH).

Métodos Se recabaron datos sobre la supresión viral tras 12 meses de TAR basados en artículos publicados entre 2003 y 2011, así como en resúmenes de conferencias que tuvieron lugar entre 2009 y 2011. Se emplearon proporciones combinadas entre poblaciones en tratamiento y con intención de tratar como estimaciones globales. Se usaron modelos de efectos aleatorios para grupos de estudio heterogéneos (I2 > 75%).

Resultados En líneas generales, 49 estudios que incluían 48 cohortes y 30 016 individuos cumplieron los criterios de inclusión. El 84,3% (intervalo de confianza del 95%, IC: 80,4–87,9) del conjunto de la población en tratamiento y el 70,5% (IC del 95%: 65,2–75,6) de la población con intención de tratar mostraron supresión con umbrales para la supresión de entre 300 y 500 copias de ácido ribonucleico viral (RNA) por ml de plasma. El empleo de diferentes umbrales virales RNA cambió las proporciones que indican supresión: al 84% y 76% de la población en tratamiento con umbrales superiores a 300 y a o por debajo de 200 copias de RNA por ml, respectivamente, y a 78%, 71% y 63% de la población con intención de tratar con umbrales fijados en 1000, 300 a 500 y 200 o menos copias por ml, respectivamente.

Conclusión Las estimaciones combinadas de supresión viral que se registraron tras 12 meses de TAR en PRBM establecen que pueden emplearse otros programas TAR para establecer objetivos realistas y realizar modelos de predicción. Las constataciones de esta revisión sugieren que el objetivo internacional en la actualidad – es decir, la supresión viral en > 70% de la población con intención de tratar, con un umbral de 1000 copias por ml – debe revisarse al alza.

References

1. *Together we will end AIDS*. Geneva: Joint United Nations Programme on HIV/AIDS; 2012.
2. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision*. Geneva: World Health Organization; 2010.
3. Hamers RL, Kityo C, Lange JM, de Wit TF, Mugyenyi P. Global threat from drug resistant HIV in sub-Saharan Africa. *BMJ* 2012;344:e4159. doi:10.1136/bmj.e4159 PMID:22709963
4. Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. *Antivir Ther* 2008;13(Suppl 2):1–13. PMID:18578063
5. Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A et al.; International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2010. Recommendations of the International AIDS Society-USA panel. *JAMA* 2010;304:321–33. doi:10.1001/jama.2010.1004 PMID:20639566
6. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Washington: Department of Health and Human Services; 2012. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf[accessed 12 May 2012].
7. Asboe D, Aitken C, Boffito M, Booth C, Cane P, Fakoya A et al.; BHIVA Guidelines Subcommittee. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. *HIV Med* 2012;13:1–44. doi:10.1111/j.1468-1293.2011.00971.x PMID:22171742
8. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. *Trop Med Int Health* 2010;15(Suppl 1):1–15. doi:10.1111/j.1365-3156.2010.02508.x PMID:20586956
9. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P et al.; Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration; ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006;367:817–24. doi:10.1016/S0140-6736(06)68337-2 PMID:16530575
10. Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. *Lancet Infect Dis* 2010;10:155–66. doi:10.1016/S1473-3099(09)70328-7 PMID:20185094
11. Gupta RK, Hill A, Sawyer AW, Cozzi-Lepri A, von Wyl V, Yerly S et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:409–17. doi:10.1016/S1473-3099(09)70136-7 PMID:19555900
12. International AIDS Society [Internet]. Abstract search. Geneva: IAS; 2012. Available from: http://www.iasociety.org/AbstractSearch.aspx [accessed 12 February 2013].
13. 18th Conference on Retroviruses and Opportunistic Infections [Internet]. Search abstracts. Boston: CROI; 2011. Available from: http://retroconference.org/AbstractSearch/Default.aspx?Conf=20 [accessed 12 February 2013].
14. McMahon JH, Elliott JH, Bertagnolio S, Kubiak R, Jordan M. Protocol for the systematic review of virological outcomes after 12 months of antiretroviral therapy in low and middle income countries. York: University of York; 2011. Available from: http://www.crd.york.ac.uk/PROSPEROFILES/3867_STRATEGY_20130114.pdf [accessed 19 February 2013].
15. *Monitoring the Declaration of Commitment on HIV/AIDS: guidelines on construction of core indicators: 2010 reporting*. Geneva: Joint United Nations Programme on HIV/AIDS; 2009.
16. *Next generation indicator reference guide, version 1.1: the President's Emergency Plan for AIDS Relief*. Washington: US Department of Health and Human Services; 2009.
17. *Monitoring and evaluation toolkit*. 4th ed. Geneva: Global Fund to Fight AIDS,

Tuberculosis and Malaria; 2011.
18. *A guide on indicators for monitoring and reporting on the health sector response to HIV/AIDS*. Geneva: World Health Organization; 2011.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials *Control Clin Trials* 1986;7:177–88. doi:10.1016/j.trstmh.2008.11.007 PMID:19110288
20. Stuart A, Ord JK. *Kendall's advanced theory of statistics*. 6th ed. London: Edward Arnold; 1994.
21. Ahoua L, Guenther G, Pinoges L, Anguzu P, Chaix ML, Le Tiec C et al. Risk factors for virological failure and subtherapeutic antiretroviral drug concentrations in HIV-positive adults treated in rural northwestern Uganda. *BMC Infect Dis* 2009;9:81. doi:10.1186/1471-2334-9-81 PMID:19493344
22. Kelser O, Orrell C, Egger M, Wood R, Brinkhof MW, Furrer H et al. Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared *PLoS Med* 2008;5:e148. doi:10.1186/1471-2334-9-81 PMID:19493344
23. Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS* 2003;17:1369–75. doi:10.1097/00002030-200306130-00011 PMID:12799558
24. Wouters E, Van Damme W, Van Loon F, van Rensburg D, Meulemans H.. Public-sector ART in the Free State Province, South Africa: community support as an important determinant of outcome. *Soc Sci Med* 2009;69:1177–85. doi:10.1016/j.socscimed.2009.07.034 PMID:19692165
25. Wouters E, Van Damme W, van Rensburg D, Meulemans H. Impact of baseline health and community support on antiretroviral treatment outcomes in HIV patients in South Africa. *AIDS* 2008;22:2545–8. doi:10.1097/QAD.0b013e32831c5562 PMID:19005281
26. Ananworanich J, Gayet-Ageron A, Ruxrungtham K, Chetchotisakd P, Prasithsirikul W, Kiertiburanakul S et al.; Staccato Thailand Study Group. Long-term efficacy and safety of first-line therapy with once-daily saquinavir/ritonavir. *Antivir Ther* 2008;13:375–80. PMID:18572750
27. Barth RE, van der Meer JT, Hoepelman AI, Schrooders PA, van de Vijver DA, Geelen SP et al. Effectiveness of highly active antiretroviral therapy administered by general practitioners in rural South Africa. *Eur J Clin Microbiol Infect Dis* 2008;27:977–84. doi:10.1007/s10096-008-0534-2 PMID:18629557
28. Bedelu M, Ford N, Hilderbrand K, Reuter H. Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. *J Infect Dis* 2007;196(Suppl 3):S464–8. doi:10.1086/521114 PMID:18181695
29. Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, Regensberg L et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy *PLoS Med* 2008;5:e109. doi:10.1186/1471-2334-9-81 PMID:19493344
30. Blacher RJ, Muiruri P, Njobvu L, Mutsotso W, Potter D, Ong'ech J et al. How late is too late? Timeliness to scheduled visits as an antiretroviral therapy adherence measure in Nairobi, Kenya and Lusaka, Zambia. *AIDS Care* 2010;22:1323–31. doi:10.1080/09540121003692235 PMID:20711886
31. Bourgeois A, Laurent C, Mougnutou R, Nkoué N, Lactuock B, Ciaffi L et al. Field assessment of generic antiretroviral drugs: a prospective cohort study in Cameroon. *Antivir Ther* 2005;10:335–41. PMID:15865228
32. Bussmann H, Wester CW, Ndwapi N, Grundmann N, Gaolathe T, Puvimanasinghe J et al. Five-year outcomes of initial patients treated in Botswana's National Antiretroviral Treatment Program. *AIDS* 2008;22:2303–11. doi:10.1097/QAD.0b013e3283129db0 PMID:18981769
33. Bussmann H, Wester CW, Thomas A, Novitsky V, Okezie R, Muzenda T et al. Response to zidovudine/didanosine-containing combination antiretroviral therapy among HIV-1 subtype C-infected adults in Botswana: two-year outcomes from a randomized clinical trial. *J Acquir Immune Defic Syndr* 2009;51:37–46. doi:10.1097/QAI.0b013e3181ff102 PMID:19282782
34. Charles M, Noel F, Leger P, Severe P, Riviere C, Beauharnais CA et al. Survival, plasma HIV-1 RNA concentrations and drug resistance in HIV-1-infected Haitian adolescents and young adults on antiretrovirals. *Bull World Health Organ* 2008;86:970–7. doi:10.2471/BLT.07.050120 PMID:19142298
35. Djomand G, Roels T, Ellerbrock T, Hanson D, Diomande F, Monga B et al. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Côte d'Ivoire. *AIDS* 2003;17(Suppl 3):S5–15. doi:10.1097/00002030-200317003-00002 PMID:14565604
36. Fatti G, Grimwood A, Bock P. Better antiretroviral therapy outcomes at primary healthcare facilities: an evaluation of three tiers of ART services in four South African provinces. *PLoS One* 2010;5:e12888. doi:10.1371/journal.pone.0012888 PMID:20877631
37. Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambo L et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. *Lancet* 2006;367:1335–42. doi:10.1016/S0140-6736(06)68580-2 PMID:16631912
38. Fielding KL, Charalambous S, Stenson AL, Pemba LF, Martin DJ, Wood R et al. Risk factors for poor virological outcome at 12 months in a workplace-based antiretroviral therapy programme in South Africa: a cohort study. *BMC Infect Dis* 2008;8:93. doi:10.1186/1471-2334-8-93 PMID:18631397
39. Gandhi NR, Moll AP, Lalloo U, Pawinski R, Zeller K, Moodley P et al.; Tugela Ferry Care and Research (TFCaRes) Collaboration. Successful integration of tuberculosis and HIV treatment in rural South Africa: the Sizong'oba study. *J Acquir Immune Defic Syndr* 2009;50:37–43. doi:10.1097/QAI.0b013e31818ce6c4 PMID:19295333
40. Garrido C, Zahonero N, Fernándes D, Serrano D, Silva AR, Ferraria N et al. Subtype variability, virological response and drug resistance assessed on dried blood spots collected from HIV patients on antiretroviral therapy in Angola. *J Antimicrob Chemother* 2008;61:694–8. doi:10.1093/jac/dkm515 PMID:18218644
41. Hegazi A, Bailey RL, Ahadzie B, Alabi A, Peterson K. Literacy, education and adherence to antiretroviral therapy in The Gambia. *AIDS Care* 2010;22:1340–5. doi:10.1080/09540121003693514 PMID:20711888
42. Kamya MR, Mayanja-Kizza H, Kambugu A, Bakeera-Kitaka S, Semitala F, Mwebaze-Songa P et al.; Academic Alliance for AIDS Care and Prevention in Africa. Predictors of long-term viral failure among Ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007;46:187–93. doi:10.1097/QAI.0b013e31814278c0 PMID:17693883
43. Kouanfack C, Montavon C, Laurent C, Aghokeng A, Kenfack A, Bourgeois A et al. Low levels of antiretroviral-resistant HIV infection in a routine clinic in Cameroon that uses the World Health Organization (WHO) public health approach to monitor antiretroviral treatment and adequacy with the WHO recommendation for second-line treatment. *Clin Infect Dis* 2009;48:1318–22. doi:10.1086/597779 PMID:19320592
44. Landman R, Poupard M, Diallo M, Ngom Gueye NF, Diakhate N, Ndiaye B et al. Tenofovir-emtricitabine-efavirenz in HIV-1-infected adults in Senegal: a 96-week pilot trial in treatment-naive patients. *J Int Assoc Physicians AIDS Care (Chic)* 2009;8:379–84. doi:10.1177/1545109709344352 PMID:19755618
45. Laurent C, Ngom Gueye NF, Ndour CT, Gueye PM, Diouf M, Diakhaté N et al.; ANRS 1215/1290 Study Group. Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1-infected adults. *J Acquir Immune Defic Syndr* 2005;38:14–7. doi:10.1097/00126334-200501010-00003 PMID:15608518
46. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet* 2010;376:1838–45. doi:10.1016/S0140-6736(10)61997-6 PMID:21071074
47. Lyagoba F, Dunn DT, Pillay D, Kityo C, Robertson V, Tugume S et al.; DART Virology and Trial Team. Evolution of drug resistance during 48 weeks of zidovudine/lamivudine/tenofovir in the absence of real-time viral load monitoring. *J Acquir Immune Defic Syndr* 2010;55:277–83. doi:10.1097/QAI.0b013e3181ea0df8 PMID:20686411
48. Moore E, Beadsworth MBJ, Chaponda M, Mhango B, Faragher B, Njala J et al. Favourable one-year ART outcomes in adult Malawians with hepatitis B and C co-infection. *J Infect* 2010;61:155–63. doi:10.1016/j.jinf.2010.04.009 PMID:20470823
49. Mujugira A, Wester CW, Kim S, Bussmann H, Gaolathe T et al. Patients with advanced HIV type 1 infection initiating antiretroviral therapy in Botswana: treatment response and mortality. *AIDS Res Hum Retroviruses* 2009;25:127–33. doi:10.1089/aid.2008.0172 PMID:19239353
50. Mutevedzi PC, Lessells RJ, Heller T, Bärnighausen T, Cooke GS, Newell M-L. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? *Bull World Health Organ* 2010;88:593–600. doi:10.2471/BLT.09.069419 PMID:20680124
51. Nachega JB, Chaisson RE, Goliath R, Efron A, Chaudhary MA, Ram M et al. Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy. *AIDS* 2010;24:1273–80. PMID:20453627
52. Nachega JB, Hislop M, Nguyen H, Dowdy DW, Chaisson RE, Regensberg L et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. *J Acquir Immune Defic Syndr* 2009;51:65–71. doi:10.1097/QAI.0b013e318199072e PMID:19282780

53. Ndembi N, Goodall RL, Dunn DT, McCormick A, Burke A, Lyagoba F et al.; Development of Antiretroviral Treatment in Africa Virology Group and Trial Team. Viral rebound and emergence of drug resistance in the absence of viral load testing: a randomized comparison between zidovudine-lamivudine plus nevirapine and zidovudine-lamivudine plus abacavir. *J Infect Dis* 2010;201:106–13. doi:10.1086/648590 PMID:19938977
54. Oyomopito R, Lee MP, Phanuphak P, Lim PL, Ditangco R, Zhou J et al.; TREAT Asia HIV Observational Database. Measures of site resourcing predict virologic suppression, immunologic response and HIV disease progression following highly active antiretroviral therapy (HAART) in the TREAT Asia HIV Observational Database (TAHOD). *HIV Med* 2010;11:519–29. PMID:20345881
55. Ramadhani HO, Thielman NM, Landman KZ, Ndosi EM, Gao F, Kirchherr JL et al. Predictors of incomplete adherence, virologic failure, and antiviral drug resistance among HIV-infected adults receiving antiretroviral therapy in Tanzania. *Clin Infect Dis* 2007;45:1492–8. doi:10.1086/522991 PMID:17990233
56. Sarna A, Luchters S, Geibel S, Chersich MF, Munyao P, Kaai S et al. Short- and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial. *J Acquir Immune Defic Syndr* 2008;48:611–9. doi:10.1097/QAI.0b013e3181806bf1 PMID:18645509
57. Seyler C, Anglaret X, Dakoury-Dogbo N, Messou E, Touré S, Danel C et al.; ANRS 1203 Study Group. Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Côte d'Ivoire. *Antivir Ther* 2003;8:385–93. PMID:14640385
58. Vanni T, Morejón KM, Santana RC, Melo Ld, Ferrão SB, Amorim AP et al. Comparison of the effectiveness of initial combined antiretroviral therapy with nelfinavir or efavirenz at a university-based outpatient service in Brazil. *Braz J Med Biol Res* 2007;40:963–9. doi:10.1590/S0100-879X2007000700011 PMID:17653450
59. Bertagnolio S, Kelley K, Saadani Hassani A, Obeng-Aduasare Y, Jordan M. Surveillance of transmitted and acquired HIV drug resistance using WHO surveys in resource-limited settings. In: *Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections, 27 February to 2 March 2011, Boston, United States of America*. Alexandria: CROI; 2011. Available from: http://www.retroconference.org/2011/Abstracts/41940.htm [accessed 24 January 2013].
60. Calmy A, Balestre E, Boulle A, Thiébaut R, Bonnet F, Sprinz E et al. *Prediction of CD4 cell count slope in patients with virological failure to first-line of antiretroviral combinations in resource-limited settings*. Geneva: International AIDS Society 2010 (abstract CDB081 2009 11/23/2010). Available from: http://www.iasociety.org/Default.aspx?pageId=11&abstractId=200722018 [accessed 24 January 2013].
61. Chang L, Kagaayi J, Nakigozi G, Ssempijja V, Serwadda D, Packer A et al. *Effect of peer health workers and a mobile phone support intervention on AIDS care in Rakai, Uganda: a cluster-randomized trial*. Geneva: International AIDS Society; 2010 (abstract WEPED158 2009 11/23/2010). Available from: http://www.iasociety.org/Default.aspx?pageId=11&abstractId=200722818 [accessed 24 January 2013].
62. Chasombat S, Kantipong P, Pathipvanich P, Luakamlung N, Malai S, Kohreanudom S et al. *Thailand national surveillance system to determine the development of HIV drug resistance among ARV treated patients*. Geneva: International AIDS Society; 2010. (abstract THPE0427 2010 11/23/2010). Available from: http://www.iasociety.org/Default.aspx?pageId=11&abstractId=200739558 [accessed 24 January 2013].
63. Crabtree-Ramírez B, Caro-Vega Y, Sierra-Madero J. *Late diagnosis of HIV infection results in a higher mortality but not in virological failure after starting HAART*. Geneva: International AIDS Society; 2010 (abstract THPE0122 2010 11/23/2010). Available from: http://www.iasociety.org/Default.aspx?pageId=11&abstractId=200740133 [accessed 24 January 2013].
64. Lockman S, Smeaton L, Ogwu A, Shapiro R, Leidner J, Powis K et al. Long-term maternal and pediatric virologic outcomes on nevirapine-based HAART following receipt of peripartum single-dose nevirapine or placebo, Botswana. In: *Proceedings of the 16th Conference on Retroviruses and Opportunistic Infections, 8–11 February 2009, Montréal, Canada*. Alexandria: CROI; 2009. Available from: http://www.retroconference.org/2009/Abstracts/36058.htm [accessed 24 January 2013].
65. Messou E, Chaix M-L, Gabillard D, Minga A, Losina E, N'Dri-Yoman T et al. Strong association between medication possession ratio and early virological outcomes in adults on ART in Côte d'Ivoire. In: *Proceedings of the 17th Conference on Retroviruses and Opportunistic Infections, 16–19 February 2010, San Francisco, United States of America*. Alexandria: CROI; 2010. Available from: http://www.retroconference.org/2010/Abstracts/38493.htm [accessed 24 January 2013].
66. Ratsela A, Polis M. Phidisa II: A randomized 2x2 factorial trial comparing initial therapy of efavirenz with lopinavir/ritonavir and zidovudine + didanosine with stavudine + lamivudine in treatment-naive HIV-infected persons with < 200 CD4+ cells/mm³ or a prior AIDS diagnosis. In: *Proceedings of the 16th Conference on Retroviruses and Opportunistic Infections, 8–11 February 2009, Montréal, Canada*. Alexandria: CROI; 2009. Available from: http://www.retroconference.org/2009/Abstracts/34300.htm [accessed 24 January 2013].
67. Reynolds S, Sendagire H, Newell K, Castelnuovo B, Kiragga A, Namuggala I et al. Routine VLM reduces the rate of accumulated genotypic resistance to commonly used ART in Uganda. In: *Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections, 27 February to 2 March 2011, Boston, United States of America*. Alexandria: CROI; 2011. Available from: http://www.retroconference.org/2011/Abstracts/41522.htm [accessed 24 January 2013].
68. Scarsi K, Darin K, Rawizza H, Meloni S, Chang C, Olaitan R et al. *TDF-3TC-NVP is inferior to AZT-3TC-NVP in a large ART program in Nigeria*. Geneva: International AIDS Society; 2010 (abstract THPE0115 2010 11/23/2010). Available from: http://www.iasociety.org/Default.aspx?pageId=11&abstractId=200738740 [accessed 24 January 2013].
69. Stafford K, Hossain M, Mesubi R, Etienne M, Oshi R, Bositis A et al. *Viral suppression outcomes of patients using nevirapine in combination with tenofovir and a cytosine analog (3TC or FTC) as a first line regimen in resource limited settings*. Geneva: International AIDS Society; 2010 (abstract CDB080 2009 11/23/2010). Available from: http://www.iasociety.org/Default.aspx?pageId=11&abstractId=200721588 [accessed 24 January 2013].
70. van Leeuwen R, Katlama C, Murphy RL, Squires K, Gatell J, Horban A et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003;17:987–99. doi:10.1097/00002030-200305020-00007 PMID:12700448
71. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 1999;341:1865–73. doi:10.1056/NEJM199912163412501 PMID:10601505
72. Bartlett JA, Fath MJ, Demasi R, Hermes A, Quinn J, Mondou E et al. An updated systematic overview of triple combination therapy in antiretroviral-naive HIV-infected adults. *AIDS* 2006;20:2051–64. doi:10.1097/01.aids.0000247578.08449.ff PMID:17053351
73. Bansi L, Sabin C, Gilson R, Gazzard B, Leen C, Anderson J et al.; UK Collaborative HIV Cohort Study. Virological response to initial antiretroviral regimens containing abacavir or tenofovir. *J Infect Dis* 2009;200:710–4. doi:10.1086/605024 PMID:19635022
74. Uy J, Armon C, Buchacz K, Wood K, Brooks JT; HOPS Investigators. Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr* 2009;51:450–3. doi:10.1097/QAI.0b013e3181acb630 PMID:19474757
75. Moore DM, Mermin J, Awor A, Yip B, Hogg RS, Montaner JS. Performance of immunologic responses in predicting viral load suppression: implications for monitoring patients in resource-limited settings. *J Acquir Immune Defic Syndr* 2006;43:436–9. doi:10.1097/01.qai.0000243105.80393.42 PMID:17019367
76. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach – 2006 revision*. Geneva: World Health Organization; 2006.
77. Hoffmann CJ, Charalambous S, Sim J, Ledwaba J, Schwikkard G, Chaisson RE et al. Viremia, resuppression, and time to resistance in human immunodeficiency virus (HIV) subtype C during first-line antiretroviral therapy in South Africa. *Clin Infect Dis* 2009;49:1928–35. doi:10.1086/648444 PMID:19911963
78. Wilson D, Kelluhu AK, Kogrum S, Reid T, Seriratana N, Ford N et al. HIV-1 viral load monitoring: an opportunity to reinforce treatment adherence in a resource-limited setting in Thailand. *Trans R Soc Trop Med Hyg* 2009;103:601–6. doi:10.1016/j.trstmh.2008.11.007 PMID:19110288
79. Glaser R. Instructional technology and the measurement of learning outcomes: some questions. In: Notterman JM, editor. *The evolution of psychology: fifty years of the American Psychologist*. Washington: American Psychological Association; 1963. pp. 337–42.
80. *HIV drug resistance early warning indicators: world Health Organization indicators to monitor HIV drug resistance prevention at antiretroviral treatment sites*. June 2010 update. Geneva: World Health Organization; 2010. Available from: www.unaids.org.br/biblioteca/links/OPAS.../OPAS%2014.pdf [accessed 21 February 2013].

Table 1. **Study cohorts included in the systematic review and described in journal articles on viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries**

Study	Country/site	Type of care	Patient paid for ART?	Dates observed	No. of sites	*n*[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Viral suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Bussman et al.[33] (2009)	Botswana (Gaborone)	Public	No	Started 2002–2004, followed to Apr. 2006	5	650	RCT	33; 31; 199; 34% III and 9% IV	NNRTI	12 months	< 400	92 (OT; *n* = 586), 86 (ITT; *n* = 624)	3.4	2.4	NR	NR
Bourgeois et al.[31] (2005)	Cameroon (Yaoundé)	Public, NGO	Partially	Started Jan. 2001-Apr. 2003	1	109	Cohort	36; 34; 150; 54% III and 20% IV	NNRTI	12 months	< 400	97.3 (OT; *n* = 75), 86.9 (ITT; *n* = 84)	NR	NR	NR	NR
Seyler et al.[57] (2003)	Côte d'Ivoire (Abidjan)	Public	Partially	Mar. 1999–Aug. 2002	> 1	101	Cohort	36; 38; 135; 48% III and 39% IV	NNRTI	12 months	< 200	51 (OT; *n* = 29)	NR	NR	NR	NR
Ferradini et al.[37] (2006)	Malawi (Chiradzulu)	Public, NGO	No	Jan.–Apr. 2004	1	398	Cross section	34; 31; 114; 58% III and 24% IV	99% NNRTI, 98% naive	9.5 months (median)	< 1000	87 (OT; *n* = 397)	NR	NR	NR	NR
Laurent et al.[45] (2005)	Senegal	Public	Partially (free in trial)	Started Aug. 1998–Apr. 2001	NR	176	Cohort (*n* = 80 in trial)	38; 48; 144; NR	47% NNRTI, 43% PI, 92% naive	12 months	< 500	77 (OT; *n* = 143), 63 (ITT; *n* = 176)	NR	NR	NR	NR
Gandhi et al.[39] (2009)	South Africa (Msinga)	Public, partner	No	Started Oct. 2003–Jan. 2006	1	119	Cohort	34 (mean); 44; 79; NR	NNRTI	12 months	< 400	94 (OT; *n* = 98), 78 (ITT; *n* = 118)	11	5.9	NR	NR
Wouters et al.[24,25] (2008–09)	South Africa (Free State)	Public	No	NR	> 1	268	Cohort	38 (mean); 33; 109 (mean); NR	NR	12 months (median)	< 400	85 (OT; *n* = 232), 78 (ITT; *n* = 254)	5.6	2.2	NR	5.2

(*continues*. . .)

(. . .*continued*)

Study	Country/site	Type of care	Patient paid for ART?	Dates observed	No. of sites	*n*[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Viral suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Ahoua et al.[21] (2009)	Uganda (Arua)	Public, NGO	No	Started Sept. 2004–Jul. 2005	1	229	Cohort and cross section	37; 34; 100; 18% III/IV	NNRTI, 98% naive	12 months	< 1000	89 (OT; *n* = 229), 69 (ITT; *n* = 297)	5.0	17.0	1.0	5.0
Mujugira et al.[49] (2009)	Botswana (Gaborone)	Public	No	Started Feb–Mar. 2002	1	349	Cohort	35; 41; 22; NR	NNRTI	9 months	< 400	60 (ITT; *n* = 349)	22	13.5	NR	1.1
Fielding et al.[38] (2008)	South Africa	Private (work)	No	Started before 2004, followed to Mar. 2006	39	1760	Cohort	41; 97; 156; 73% III/IV	NNRTI	12 months	< 400	72 (OT; *n* = 953), 51 (ITT; *n* = 1328)	9.9	11.4 (or stopped)	See LTFU	12.1
Keiser et al.[22] (2008)	South Africa (Khayelitsha Gugulethu)	Public	No	Started 2001–2006	13	2348	Cohort	33; 29; 80; 91% III/IV	99.6% NNRTI	10.8 months (median)	< 500	96 (OT; *n* = 1788), 81 (ITT; *n* = 2128)	11[e]	3.5	NR	NR
Bisson et al.[29] (2008)	Sub-Saharan Africa (9 countries)	Private (work)	Insured	Started Dec. 2000–Feb. 2003	> 1	872	Cohort	NR (55% < 35 years old); 37; 165; NR	NNRTI	12 months	< 1000	74 (OT; *n* = 872)	NR	NR	NR	NR
Nachega et al.[52] (2009)	Sub-Saharan Africa (9 countries)	Private (work)	Insured	Started Jan. 1999-Aug. 2006	> 1	7776	Cohort	37; 38; 146; NR	97% NNRTI, 3% PI	12 months	< 400	62 (OT; *n* = 3192)	NR	NR	NR	NR
Garrido et al.[40] (2008)	Angola	NR	NR	NR	1	294	Cross section	36; 28; 144; NR	89% NNRTI, 80% naive	12.6 months (median)	< 1000	74 (OT; *n* = 294)	NR	NR	NR	NR
Vanni et al.[58] (2007)	Brazil (Ribeira Porto)	Public	No	Jan. 2002–Dec. 2003	1	126	Cohort	37; 69; NR; NR	60% NNRTI, 40% PI	12 months	< 400	65 (ITT; *n* = 126)	NR	NR	NR	NR
Ndembi et al.[53] (2010)	Uganda (Kampala, Entebbe)	Public (trial)	No	Started Jan.–Oct. 2004	2	600	RCT	37; 28; 99; 55% III and 18% IV	NNRTI (in one arm)	48 weeks	< 50	77 (ITT; *n* = 300)	4.2	2.0	1.0	NR[f]
As above	–	–	–	–	–	–	–	–	–	48 weeks	< 1000	87 (ITT; *n* = 300)	4.2	2.0	1.0	NR[f]

(*continues. . .*)

(. . .*continued*)

Study	Country/site	Type of care	Patient paid for ART?	Dates observed	No. of sites	*n*[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Viral suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Anonwaronich et al.[26] (2008)	Thailand	Public (trial)	No	Started after 2001	7	272	RCT	34 (mean); 39; NR; NR (28% CDC category B and 2% category C)	PI	48 weeks	< 400	96 (OT; *n* = 164), 79 (ITT; *n* = 129)	NR	6.0	NR	NR
As above	–	–	–	–	–	–	–	–	–	48 weeks	< 50	93 (OT; *n* = 164), 69 (ITT; *n* = 129)	NR	6.0	NR	NR
Bussman et al.[31] (2008)	Botswana (Gaborone)	Public	No	Started Jan.–Aug. 2002	1	633	Cohort	35; 40; 67, 43% III and 38% IV	NNRTI	12 months	< 400	91 (OT; *n* = 467), 67 (ITT; *n* = 633)	17.3	8.9	NR	NR
Kouanfack et al.[43] (2009)	Cameroon (Yaoundé)	Public	Partially	Enrolment Nov. 2006–Oct. 2007	1	249	Cross section	NR (all 35–40 years); 29; NR; NR	99% NNRTI	12 months	< 500	78 (OT; *n* = 249)	NA	NA	NA	NA
As above	–	–	–	–	–	–	–	–	–	12 months	< 1000	84 (OT; *n* = 249)	NA	NA	NA	NA
Djomand et al.[35] (2003)	Côte d'Ivoire (Abidjan)	Public, partners	Partially	Started Aug. 1998–May 2000	6	276	Cohort	35; 50; 182; NR	80% PI, 19% NNRTI	12 months	< 200	50 (ITT; *n* = 276)	NR	NR	NR	NR
Sarna et al.[56] (2008)	Kenya (Mombasa)	Public (2 sites), private	No	Started Sept. 2003–Nov. 2004	3	137	RCT	37; 36; 96–106; NR	NNRTI	12 months	< 400	82 (OT; *n* = 137)	NR	NR	NR	NR

(*continues*. . .)

(. . .*continued*)

Study	Country/site	Type of care	Patient paid for ART?	Dates observed	No. of sites	*n*[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Viral suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Landman et al.[44] (2009)	Senegal (Dakar)	Public, partner	No	Started Jun.–Dec. 2004	1	40	Clinical trial	38 (mean); 40; 111; NR (93% CDC category B/C)	NNRTI	12 months	< 400	94 (OT; *n* = 35), 83 (ITT; *n* = 40)	7.5	5	NR[f]	NR[f]
As above	–	–	–	–	–	–	–	–	–	12 months	< 50	83 (OT; *n* = 35), 73 (ITT; *n* = 40)	7.5	5	NR[f]	NR[f]
Barth et al.[27] (2008)	South Africa (Ndlovu)	NGO	No	Started Sept. 2003–Apr. 2006	1	609	Cohort	35; 29; 67, 62% III and 17% IV	NNRTI	12 months	< 400	83 (OT; *n* = 407), 55 (ITT; *n* = 609)	19	15	NR	NR
As above	–	–	–	–	–	–	–	–	–	–	< 50	70 (OT; *n* = 407), 46 (ITT; *n* = 609)	19	15	NR	NR
Orrell et al.[23] (2003)	South Africa (Cape Town)	Public	No	Started Jan. 1996–May 2001	> 1	289	Clinical trial	33 (mean); 57; 197–268 (mean); < 49% III/IV	42% PI, 33%NNRT, 10% 3NRTI	12 months	< 400	66 (OT; *n* = 242), 58 (ITT; *n* = 278)	See LTFU	16.2 (or died or stopped)	See LTFU	NR
Bedelu et al.[28] (2007)	South Africa (Lusikisiki)	Public, NGO	No	Started Jan. 2005, followed to Jul. 2006	1	430	Cohort	NR	NR	12 months (median)	< 400	78 (OT; *n* = 41)	13.5	19.3	NR	NR
As above	–	Public, NGO	No	Started Jan. 2005, followed to Jul. 2006	12	595	Cohort	NR	NR	12 months (median)	< 400	90 (OT; *n* = 296)	16.8	2.2	NR	NR

(*continues. . .*)

(. . .*continued*)

Study	Country/site	Type of care	Patient paid for ART?	Dates observed	No. of sites	*n*[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Viral suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Nachega et al.[51] (2010)	South Africa (Western Cape)	Public	No	Feb 2005–Jul 2008	1	274	RCT	36; 42; 98; 45% III and 46% IV	NNRTI	13 months	< 400	90 (OT; *n* = 213), 71 (ITT; *n* = 272)	NR	NR	NR	NR
Ramadhani et al.[55] (2007)	United Republic of Tanzania (Kilimanjaro)	Public	Partially	Jun.–Aug. 2008	1	150	Cross section	41; 37; 114; NR	NNRTI	12 months (median)	< 400	68 (OT; *n* = 150)	NA	NA	NA	NA
As above	–	–	–	–	–	–	–	–	–	12 months (median)	< 1000	77 (OT; *n* = 150)	NA	NA	NA	NA
Kamya et al.[42] (2007)	Uganda (Makerere, Ulago)	Public	No	Started Apr. 2004–Jun. 2005	1	526	Cohort	37 (mean); 31; 99; 54% III and 34% IV	NNRTI	12 months	< 400	87 (OT; *n* = 454), 75 (ITT; *n* = 526)	12.5	NR	NR	NR
Charles et al.[34] (2008)	Haiti	NGO	No	Started Mar. 2003–Dec. 2005	1	146	Cohort	NR; 34; 129; 40% II/III and 49% IV	78% NNRTI	12 months	< 50	49 (OT; *n* = 79)	NR	NR	NR	NR
Blacher et al.[30] (2010)	Kenya, Zambia	Public	No	Started May 2005–Jan. 2007	3	661	Clinical trial	32; 100; NR; 49% III and 8% IV	NNRTI, 59% naive	12 months	< 400	87 (OT; *n* = 563), 74 (ITT; *n* = 661)	NR	NR	NR	NR
Fatti et al.[36] (2010)	South Africa (Cape, KZN, Mpumalanga)	Public, NGO	No	Started Dec. 2004–Dec. 2007	59	29 203	Cohort	34; 32; 114; 76% III/IV	NNRTI	12 months	< 400	87 (OT; *n* = 6725)	6.3	NR	NR	NR
Hegazi et al.[41] (2010)	Gambia	Public	No	Started Oct. 2005–Jan. 2007	1	147	Cohort	36; 39; NR; NR	75% NNRTI, 25% PI	12 months	< 100	79 (OT; *n* = 75)	NR	NR	NR	NR

(*continues*. . .)

(. . .*continued*)

Study	Country/site	Type of care	Patient paid for ART?	Dates observed	No. of sites	*n*[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Viral suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Lester et al.[46] (2010)	Kenya (Nairobi, Kajiado)	Public	No	Started May 2007–Oct. 2008	3	538	RCT	37; 35; 161–168; 38% III and 4% IV	NNRTI	12 months	< 400	71 (OT; *n* = 402), 53 (ITT; *n* = 533)	10.2	8.2	NR	0.9
Lyagoba et al.[47] (2010)	Uganda (Kampala, Entebbe)	Public (trial)	No	Started Jan.–Oct. 2004	2	300	RCT	NR; NR; 108; 51% III and 25% IV	3NRTI	12 months	< 200	71 (OT; *n* = 272), 64 (ITT; *n* = 300)	6.3	NR	NR	NR
As above	–	–	–	–	–	–	–	–	–	–	< 1000	77 (OT; *n* = 272), 69 (ITT; *n* = 300)	6.3	NR	NR	NR
Moore et al.[48] (2010)	Malawi (Blantyre)	Public	No	Started 2005	1	300	Cohort	36 (mean); 39; 157 (mean); 29% IV	NNRTI	12 months	< 400	83 (OT; *n* = 212), 62 (ITT; *n* = 284)	14.3	2.7	5.3	5.3
Mutevedzi et al.[50] (2010)	South Africa (KZN)	Public	No	Started Oct. 2004–Sept. 2007	16	3010	Cohort	34–37; 22; 91–128; NR	NNRTI	12 months	< 25	77 (OT; *n* = 758)	10.9	3.7	NR	1.4
Oyomopito et al.[54] (2010)	Asia (TAHOD)	Mixed	NR	Started after 2000	17	784	Cohort	NR; 75; NR; NR	69% NNRTI, 29% PI, 2% 3NRTI	12 months	< 400	79 (OT; *n* = 204)	NR	NR	NR	NR

3NRTI, triple nucleoside reverse transcriptase inhibitors; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HIV RNA, human immunodeficiency virus ribonucleic acid; ITT, intention-to-treat; KZN, Kwa-Zulu Natal; LTFU, lost to follow-up; mo., month; NA, not applicable; NGO, nongovernmental organization; NNRTI, non-nucleoside reverse transcriptase inhibitors; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitors; OT, on-treatment; PI, protease inhibitors; RCT, randomized clinical trial; TAHOD, TREAT Asia HIV Observational Database; TFO, transferred out; WHO, World Health Organization; wk, week.

[a] Number of patients initiating ART.

[b] The values in this column are median age; percentage of males; median CD4+ T-lymphocyte count (cells per ml); and WHO (or, when indicated, CDC) clinical stage.

[c] All patients were ART-naive at baseline unless indicated otherwise.

[d] When outcomes were recorded.

[e] Estimated from a graph in the published article.

[f] Assumed to be 0%, as other outcomes account for all of the individuals who initiated ART.

Table 2. **Study cohorts included in the systematic review and described in conference abstracts dealing with viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries**

Authors and (conference)	Country/site	Type of care	Patients paid for ART?	Dates observed	No. of sites	No. of patients[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Virological suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Chasombat et al.[62] (IAS 2010)	Thailand (4 provinces)	Public	No	Started Feb.–Sept. 2006	6	304	Cohort	38; 54; 56; NR	NNRTI	12 months	< 1000	94.1 (OT; *n* = 269), 83.2 (ITT; *n* = 304)	8.9	NR	NR	NR
Crabtree-Ramirez et al.[63] (IAS 2010)	Mexico	Public	No	2001–2007	1	348	Cohort	33; 72; NR; NR	HAART	12 months	< 50	93.3 (OT; *n* = 348)	NR	NR	NR	NR
Scarsi et al.[64] (IAS 2010)	Nigeria (PEPFAR programmes)	NR	No	Jan. 2006–Dec. 2007	NR	5894	Cohort	34.2; 24.8; NR; NR	NNRTI	24 and 48 weeks	< 1000 (at both 24 and 48 weeks)	89.9 (OT; *n* = 2366)	19.6 (or TFO or LTFU)	See "died"	NR	See "died"
Stafford et al.[89] (IAS 2009)	4 African countries	Public	No	NR	NR	737	Cross-section	NR	NNRTI	9–15 months	< 400	88.1 (OT; *n* = 737)	NR	NR	NR	NR
Chang et al.[61] (IAS 2009)	Uganda (Rakai)	NR	No	May 2006–Jun. 2008	15	1338	RCT	NR	NR	48 weeks	< 400	89.4 (OT; *n* = 606)	NR	NR	NR	NR
Calmy et al.[60] (IAS 2009)	ARTLINC	Mixed	No	NR	NR	3020	Cohort	34; 37; 91; NR	NNRTI	12 months	< 500	89 (OT; *n* = 3020)	NR	NR	NR	NR
Messou et al.[65] (CROI 2010)	Côte d'Ivoire	NR	No	Feb. 2006–May 2007	3	1545	Cohort	NR	NNRTI	12 months	< 300	75.0 (OT; *n* = 928)	39.1	NR	NR	NR
Ratsela et al.[66] (CROI 2009)	South Africa (military)	NR	No	2004–2008	6	1771	RCT	NR; NR; 106; NR	PI or NNRTI	12 months	< 400	66 (ITT; *n* = 1771)	NR	NR	NR	NR
Lockman et al.[84] (CROI 2009)	Botswana	NR	No	NR	1	178	RCT	NR; 0; NR; NR	NNRTI	12 months	< 400	92.1 (ITT; *n* = 178)	NR	NR	NR	NR
Bertagnolio et al.[59] (CROI 2011)	Africa (multiple countries)	Public	NR	2002–2010	6	829	Cohort	NR	NR	12 months	< 1000	90 (OT; *n* = 460)	9.2	12.9	0.8	14.5

(*continues*. . .)

Authors and (conference)	Country/site	Type of care	Patients paid for ART?	Dates observed	No. of sites	No. of patients[a]	Study design	Baseline features[b]	ART regimen[c]	Time on ART[d]	Virological suppression		Percentage of patients			
											Definition (HIV RNA copies/ml)	Percentage meeting definition and type of analysis	Died	LTFU	Stopped ART	TFO
Reynolds et al.[67] (CROI 2011)	Uganda (Kampala)	NR	NR	2004–2008	1	559	Cohort	NR; NR; 86–96; NR	NR	12 months	< 400	88 (OT; *n* = 441) 69 (ITT; *n* = 559)	NR	NR	NR	NR

ART, antiretroviral therapy; ARTLINC, Antiretroviral Therapy in Lower Income Countries Collaboration; CROI, Conference on Retroviruses and Opportunistic Infections; HAART, highly-active antiretroviral therapy; HIV-RNA, human immunodeficiency virus ribonucleic acid; IAS, International AIDS Society; ITT, intention-to-treat; LTFU, lost to follow-up; NNRTI, non-nucleoside reverse transcriptase inhibitors; NR, not reported; OT, on-treatment; PEPFAR, President's Emergency Plan for AIDS Relief; RCT, randomized clinical trial; RNA, ribonucleic acid; TFO, transferred out; WHO, World Health Organization.

[a] Number of patients initiating ART.

[b] The values in this column are median age; percentage of males; median CD4+ T-lymphocyte count (cells per ml); and WHO (or, when indicated, CDC) clinical stage.

[c] All patients were ART-naive at baseline unless indicated otherwise.

[d] When outcomes were recorded.

3.4 Pharmacy based adherence measures to assess treatment and adherence to antiretroviral therapy. Review of the literature and implications for treatment monitoring

3.4.1 Declaration

Declaration for Thesis Chapter 3.4

Declaration by candidate

In the case of Chapter 3.4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript	80

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors
Michael R. Jordan	Helped conceive the idea for the review and an approach to review the literature and development of the manuscript	4
Karen Kelley	Development of the manuscript	2
Silvia Bertagnolio	Development of the manuscript	2
Steven Y. Hong	Development of the manuscript	2
Christine A. Wanke	Development of the manuscript	2
Sharon R. Lewin	Development of the manuscript	2

Julian H. Elliott	Helped conceive the idea for the review and an approach to review the literature and development of the manuscript	6

Candidate's Signature	[redacted]	**Date** **16 APR 2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**Alfred Hospital Infectious Diseases Unit, Melbourne**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	MRJ	[redacted]	**Date** 10/4/2013
Signature 2	KK		16/04/2013
Signature 3	SB		10/4/2013
Signature 4	SYH		8/4/2013

Signature 5	CAW 	14/4/2013
Signature 6	SRL 	16/4/2013
Signature 7	JHE 	16/4/2013

To Whom It May Concern – Professor Stephen Jane is signing as Head of Central Clinical School where attempts to contact co-authors multiple times failed. This was - Karen Kelley (KK)

Signed: 

Date: 15/04/2013

Professor Stephen Jane

Head of Central Clinical School

3.4.2 Paper

INVITED ARTICLE HIV/AIDS
Kenneth H. Mayer, Section Editor

Pharmacy Adherence Measures to Assess Adherence to Antiretroviral Therapy: Review of the Literature and Implications for Treatment Monitoring

James H. McMahon,[1,3] Michael R. Jordan,[2,6] Karen Kelley,[6] Silvia Bertagnolio,[6] Steven Y. Hong,[1] Christine A. Wanke,[1] Sharon R. Lewin,[3,4,5] and Julian H. Elliott[3,4,5]

[1]Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, [2]Tufts University School of Medicine, Boston, Massachusetts, [3]Infectious Diseases Unit, Alfred Hospital, Victoria, [4]Department of Medicine, Monash University, [5]Burnet Institute, Melbourne, Australia, and [6]World Health Organization, Geneva, Switzerland

Prescription or pill-based methods for estimating adherence to antiretroviral therapy (ART), pharmacy adherence measures (PAMs), are objective estimates calculated from routinely collected pharmacy data. We conducted a literature review to evaluate PAMs, including their association with virological and other clinical outcomes, their efficacy compared with other adherence measures, and factors to consider when selecting a PAM to monitor adherence. PAMs were classified into 3 categories: medication possession ratio (MPR), pill count (PC), and pill pick-up (PPU). Data exist to recommend PAMs over self-reported adherence. PAMs consistently predicted patient outcomes, but additional studies are needed to determine the most predictive PAM parameters. Current evidence suggests that shorter duration of adherence assessment (≤6 months) and use of PAMs to predict future outcomes may be less accurate. PAMs which incorporate the number of days for which ART was prescribed without the counting of remnant pills, are reasonable minimum-resource methods to assess adherence to ART.

Since the introduction of combination antiretroviral therapy (ART) in the mid-1990s, human immunodeficiency virus (HIV)–1 infected patients have experienced decreasing levels of morbidity and mortality in both high-income countries (HICs) and low- and middle-income countries (LMICs) [1–3].

Successful HIV treatment largely depends on patient adherence to ART. Suboptimal adherence predicts virological failure [4–7], the development of HIV drug resistance [8–10], and death [11–13]. Standardized, simple, and routine cost-effective monitoring of adherence is necessary to identify patients at risk of poor outcomes who would benefit from targeted adherence support [14]. Two simple methods for assessing adherence are patient self-report or prescription- or pill-based adherence measures, referred to in this review as "pharmacy adherence measures" (PAMs). Unlike patient self-reported adherehence, which can be affected by recall or social desirability bias, PAMs are objective and may be calculated from information routinely available in medical and pharmacy records [14].

The World Health Organization (WHO) recommends the assessment of adherence to ART with every patient contact [15]. Despite these recommendations, there is no consensus regarding the optimal method to estimate individual- and population-level adherence to ART [15, 16]. This review summarizes currently available knowledge on PAMs, identifies their strengths and limitations, proposes factors to consider when selecting

Received 27 September 2010; accepted 19 November 2010.
Correspondence: James McMahon, MD, Div of Geographic Medicine and Infectious Diseases, Tufts Medical Center, 800 Washington St, Boston, MA 02111 [redacted]

Clinical Infectious Diseases 2011;52(4):493–506

1058-4838/2011/524-0001$37.00
DOI: 10.1093/cid/ciq167

a PAM to monitor adherence and predict treatment outcomes, and identifies areas for future research.

DEFINITIONS AND SEARCH STRATEGY

PAMs are prescription- or pill-based adherence estimates calculated using dates of prescription refills and/or pill counts performed during routine clinic visits. Importantly, PAMs do not include self-reported measures, PCs performed outside of routine clinic visits (eg, unannounced PCs), monitoring of antiretroviral drug levels or monitoring with electronic devices (eg, electronic pill bottle [MEMS] caps). For purposes of clarity, we define the period of time over which individual patient adherence is estimated as "the duration of adherence assessment." In addition, we identify 3 broad categories of PAMs: MPR, PC, and PPU. Definitions and formulae used to calculate these adherence estimates are provided in Table 1.

We searched PubMed, the Cochrane Database of Systematic Reviews, and the ISI Scientific Citation Index databases, using the terms "HIV" and "adherence" or "compliance," together with "pharmacy," "prescription," "pill count," "medication possession," or "pick-up," for articles published from inception until April 2010. We also searched reference lists of all included studies. All English-language publications investigating associations between PAMs and the following outcomes of interest were included: virological failure or suppression (ie, viral load greater or less than a defined threshold), change in viral load, immunological failure, HIV drug resistance, or mortality. Studies in which the outcome of interest occurred before the estimation of patient adherence or in which estimates were calculated by combining a PAM with an additional adherence measure were excluded. If different adherence analyses were published using data from a single cohort, we selected the publication that provided the most information. Because of marked study heterogeneity, meta-analyses were not performed.

ASSOCIATION BETWEEN PAMs AND PATIENT OUTCOMES

In total, we identified 36 studies that met our inclusion criteria: 12 from LMICs (Table 2) [4, 13, 17–26] and 24 from HICs (Table 3) [10, 11, 27–48]. All LMIC studies were from sub-Saharan Africa. Eight LMIC studies used MPR [4, 13, 17, 19–23], 3 used PC [18, 25, 26], and 1 used PPU [24]. HIC studies included 18 studies from North America, 5 from Europe, and 1 from Australia. Sixteen studies from HICs estimated adherence using MPR [10, 11, 27, 29–32, 34, 36–39, 41, 45, 47, 48], 5 used PC [28, 33, 35, 40, 43], and 3 used PPU [42, 44, 46].

Association with Virological Outcomes

Twenty-seven (75%) of 36 studies reported virological outcomes; 19 were from HICs [27–37, 39–45, 48], and 8 were from LMICs [4, 17, 18, 22–26]. PAMs predicted virological failure in 14 (88%) of 16 studies, virological suppression in 8 (89%) of 9 studies, and viral load change in 3 (60%) of 5 studies. Studies conducted in LMICs generally assessed ART-naive populations receiving nonnucleoside reverse transcriptase inhibitor (NNRTI)–containing regimens and demonstrated that PAMs were predictive of either virological failure or virological suppression. In contrast, all studies demonstrating no association between PAMs and virological outcome were conducted in HICs and assessed ART-experienced patients using smaller sample sizes (≤115 subjects; range, 40–115 subjects) [30, 31, 43,

Table 1. Pharmacy-Based Adherence Measure (PAM) Categories

PAM category	Definition	Formulae
Medication or drug possession ratio	Measures the amount of time an individual is in possession of ≥1 ARV or prescriptions for the ARVs as a proportion of the time between 2 ARV pick-ups or prescriptions	Number of days ARV prescribed or dispensed/number of days in the interval
Pill count	Measures the quantity of ARV pills an individual has used between 2 ARV pickups as a proportion of the number of pills dispensed or as a proportion of time between pick-ups	1. (Number of ARV pills dispensed – number of ARV pills returned)/number of ARV pills dispensed 2. (Number of days ARV pills dispensed – number of days ARV pills returned)/number of days in the interval
Pill pickup	Measures whether an individual picks up all or a majority of their prescribed ARVs and expresses the adherence estimate in a dichotomous fashion (some measures require that ARVs be picked up on or before the date the previous ARV supply finishes).	1. Where "Adherent" = (ARV refills picked up/ARV refills prescribed) > predefined value 2. Where "Adherent" = (ARV refills picked up prior to previous refill finishing/ARV refills prescribed) > predefined value

Note. ARV, antiretroviral

Table 2. Reported Associations with Pharmacy-Based Adherence Measures (PAMs) in Low- and Middle-Income Countries

Study (year)	Design	Type of care	Region	ART naive	ART regimen (%)[a]	PAM category	PAM definition in study	PAM months[b]	Sample size, no. of persons	Key findings[c]
Nachega et al [13] (2006)	Retrospective cohort	Private	Sub-Saharan Africa (multiple countries)	Yes	NNRTI (82), PI	MPR	Months ART claims submitted (entire regimen)/ months from start to death, withdrawal or censor	Variable; median, 22	6288	1. PAM <80% predicted death and death + LTFU ($P < .01$) 2. compared with PAM adherence of 100%, decreasing PAM strata increasingly predicted death ($P < .01$), except for PAM adherence of 80%–99%
						MPR	Months ART claims submitted (entire regimen)/ Months in the interval	12 (0–12)	3267	PAM <80% in first 12 months predicted death ($P < .01$)
Weidle et al [26] (2006)	Clinical trial	Home based	Uganda	Yes	NNRTI (100)	PC[f]	(Days 3TC delivered - days 3TC returned) /days in the interval	3 (3–6) 3 (9–12)	913 894	1. PAM <95% predicted VF[d] at 6 or 12 months ($P < .01$) 2. self-report predicted VF at 12 ($P < .05$) but not 6 months
						PC	(3TC Pills delivered – 3TC pills returned)/3TC pills delivered	3 (3–6) 3 (9–12)	913 894	PAM <95% predicted VF[d] at 6 or 12 months ($P < .05$)
Nachega et al [4] (2007)	Retrospective cohort	Private	Sub-Saharan Africa (multiple countries)	Yes	NNRTI (100)	MPR	Months ART claims submitted (all ARVs)/months from start to death/leaving/ censor	Variable median, 26	2821	PAM strata >50% increasingly predicted sustained VL suppression ($P < .01$), shorter time to VL suppression ($P < .05$), and increased time to viral rebound [e] ($P < .05$)
Bisson et al [17] (2008)	Retrospective cohort	Private	Sub-Saharan Africa (multiple countries)	Yes	NNRTI (100)	MPR	Months ART claims submitted (all ARVs)/months from start to study endpoint	6 (0–6) 12 (0–12)	958 872	1. PAM <90% predicted VF[c] at 6 and 12 months ($P < .01$) 2.it was better than changes in the CD4 cell count at predicting VF[d] at 6 and 12 months ($P < .01$)
								Variable median, 20	1101	1. PAM <90% predicted viral rebound[e] ($P < .05$) 2.not different than changes in the CD4 cell count from maximum on-treatment value in predicting viral rebound[e]

								3 (0–3) 3 (6–9)	958 872	PAM was no better than changes in the CD4 cell count over first 6 or 12 months in predicting VF[c] at 6 or 12 months
Bisson et al [18] (2008)	Case-control	Public	Botswana	No	NNRTI (100)	PC	Sum of (days ART prescribed – remnant days ART) between last and 3 prior fills/days between last and 3 prior fills	3 (varied)	302	1. Decreasing PAM rates (90%-95%, 80%-90%, and <80% 2. ($P < .05$) and PAM <95% ($P < .01$) in 3 months prior to recruitment predicted VF,[d] compared with PAM >95%
Goldman et al [23] (2008)	Retrospective cohort (all clinical or IF)	Public	Zambia	Yes	NNRTI (100)	MPR	100% - [(days late to pharmacy visits – 3)/days on ART] [g]	Variable median, 24	913	1. Lower PAM (<80%, 80%-94%, and >95%) more likely to predict VF[d] at time of the VL test ($P < .05$) 2. Self-reported adherence did not predict VF[d]
San Lio et al [25] (2008)	Prospective cohort	NGO, free	Mozambique	No	NNRTI (100)	PC	(Days pills prescribed – days pills returned)/ days between appointments	12 (varied)	394	PAM <95% predicted VF[h] after 12 months of follow-up ($P < .05$)
Toure et al [20] (2008)	Retrospective cohort	Public, private and NGO	Cote d'Ivoire	Yes	NNRTI (96), PI, 3NRTI	MPR	Days ART given to patient/days since ART start to last visit, or censor if last visit was after censor date	Variable median, 8	10211	1. PAM <80% predicted increases in the CD4 cell count of <50 cells after 6 months ($P < .01$) 2. PAM <80% predicted LTFU ($P < .01$) but not death over a period of 16 months
Chi et al [19] (2009)	Retrospective cohort	Public	Zambia	Yes	NNRTI (100)	MPR	100% - [(days late to pharmacy visits – 3)[g]/days on ART]	12 (0–12)	27115	1. PAM <80% predicted lower CD4 cell counts after 18–36 months ($P < .01$) 2. decreasing PAM adherence rates (>95%, 80%-94%, and <80%) predicted LTFU after 12-36 months of ART[h] ($P < .01$) PAM <80% predicted death ($P < .01$) at 12–36 months but higher strata (80%-94% and >95%) did not
Danel et al [22] (2009)	Clinical trial (one or both of VF or IF)	Free	Cote d'Ivoire	Yes	NNRTI (87), PI	MPR	Days ART delivered/ days in the interval	6 (0–6)	208	PAM of >90% did not predict CD4 cell counts of >350 cells/μL plus VL suppression at 36 months

								30 (6–36)	208	PAM >90% predicted either or both of the following: a CD4 cell count >350 cells/μL and VL suppression at 36 months ($P < .01$)
Rougemont et al [24] (2009)	Prospective cohort	Private	Cameroon	Yes	NNRTI (99), PI	PPU	"Nonadherent was defined as being >2 weeks late to pick-up medication or as "abandoned ART" on phone tracing	6 (0–6)	194	"Nonadherent" status predicted VF[d] ($P < .01$); no different than CD4 cell count change over 6 months at predicting VF[d]; day 30 Self-reported adherence did not predict 6-month VF[e]
Ross-Degnan et al [21] (2010)	Retrospective cohort	Public, private, and NGO	Sub-Saharan Africa (multiple countries)	Yes	NNRTI, PI (NR)	MPR	Days with ART/days since ART start	Variable median, 6	409	1. PAM <80% (but not 80%-90% or 90%-100%) predicted lower CD4 cell counts (at 4-9 months), compared with PAM 100% ($P < .05$) 2. PAMs were not directly compared with self-reported adherence
						MPR	"Nonadherent" was defined as >30 days without receipt of ART	Variable Median, 6	409	"Nonadherent" status predicted lower CD4 cell counts at 4-9 months ($P < .05$)

NOTE. ART, antiretroviral therapy; ARV, antiretroviral; IF, immunological failure; LTFU, lost to follow-up; MPR, medication possession ratio; NGO, nongovernmental organization; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NR, not reported; PC, pill count; PI, protease inhibitor; 3NRTI, triple nucleoside reverse-transcriptase inhibitor; 3TC, lamivudine; VF, virological failure; PPU, pill pick-up; VL, viral load.

[a] Data are ART regimens for that study. Number in parentheses represents percentage of subjects receiving the predominant regimen.

[b] Duration of adherence assessment, with the months over which assessed in parentheses. If there was a variable duration of adherence assessment, than the median, mean, or range is listed.

[c] Number after PAM is the percentage adherence.

[d] Single viral load above threshold.

[e] Single viral load above threshold after previous VL suppression.

[f] Because remnant pills were counted to determine adherence, this measure comes under the PC category despite being referred to as medication possession ratio in the study.

[g] Subjects not late to pharmacy visit until after 3 days, to account for routine provision of 3 days extra ART.

[h] Statistical significance for association was not reported, so we determined statistical significance using raw data with the χ^2 test.

Table 3. Reported Associations with Pharmacy-Based Adherence Measures (PAMs) in High-Income Countries

Study (year)	Design	Type of care	Region	ART naive (%)	ART regimen (%)[a]	PAM category	PAM descriptionin study	PAM duration, months[b]	Sample size	Key findings[c]
Maher et al [42] (1999)	Retrospective cohort	VA, minor costs	USA	No (26)	PI (100)	PPU	Adherence' occurred if the patient consistently filled 4 prescriptions on time "non-adherent did not do this)	4 (varied)	205	Adherent status predicted VL suppression ($P < .01$) and CD4 cell count increase ($P < .01$), whereas "non-adherent" status predicted VL suppression ($P < .05$) but not CD4 increase over 5–9 months of follow-up
Singh et al [46] (1999)	Prospective cohort	VA, private	USA	No (7)	NR	PPU	Adherence occurred if refills picked-up/refills prescribed was >90%	6 (varied)	123	Adherence predicted greater change in the CD4 cell count ($P < .05$)
Descamps et al [33] (2000)	Case-control study in an RCT	Free	France	Yes	PI, 2NRTI[f]	PC	(Pills prescribed – remnant pills)/pills to cover the interval	6 (0–6)	116	Mean PAM for zidovudine and indinavir predicted VL rebound[e] ($P < .05$)
Low-Beer et al [41] (2000)	Retrospective cohort	Public	Canada	Yes	NNRTI, PI (NR)	MPR	Months ART prescribed/months follow-up in 1st year	12 (0–12)	886	Increasing PAM strata (<70%, 70%-80%, 80%-90%, 90%-95%, and 95%-100%) predicted VL suppression during follow-up (median duration of follow-up, 19 months; $P < .01$)
Liu et al [40] (2001)	Prospective cohort	Private	USA	Yes	NNRTI, PI (NR)	PC	1 – [(actual pills – expected pills)/pills per dose/prescribed doses for the period]	2 (0–2) 6 (0–6)	108	1. Increasing PAM strata predicted VL suppression at 2 and 6 months ($P < .01$) 2. no difference was shown between PC and MEMS at predicting VL at 2 and 6 months, but both were superior to self-reported adherence at 2 months ($P < .01$)
McNabb et al [43] (2001)	Prospective cohort	Private	USA	No	PI (63), NNRTI, 2NRTI	PC	(1) doses taken/doses prescribed, OR if return after 30 days, then(2) doses taken/doses required for interval	3 (varied)	40	PAM and self-report changes were not associated with VL change, whereas increasing MEMS adherence was associated with decreasing VL ($P < .05$) and VL suppression ($P < .01$)

Hogg et al [38] (2002)	Retrospective cohort	Public	Canada	Yes	PI (73), NNRTI	MPR	Months ART prescribed/ months follow-up in first year	12 (0–12)	1282	PAM adherence of <75% predicted mortality, or mortality plus new AIDS diagnosis, over maximum follow-up of 50 months ($P < .01$)
Alcoba et al [30] (2003)	Retrospective cohort	NR	Spain	No	PI (100)	MPR	Patient was "nonadherent" if (days in the interval – days dispensed)/ days in the interval is >10%	3 (varied)	106	"Nonadherent" status, self-report, and ARV plasma levels were not associated with VL
Wood et al [48] (2003)	Retrospective cohort	Public	Canada	Yes	NNRTI, PI (NR)	MPR	Months ART prescribed/ months follow-up in 1st year	12 (0–12)	1422	PAM adherence of >95% predicted time to VL suppression and time to VL rebound[a] over follow-up, which was NR but variable and maximum of 67 months ($P < .01$)
Grossberg et al [37] (2004)	Retrospective cohort	VA, minor costs	USA	No(35)	NNRTI, PI, 3NRTI (NR)	MPR	(Total pills/ daily number of pills)/days between refills	3 (varied)	110	Self-reported adherence and increasing PAM strata predicted VL reductions ($P < .01$), apart from self-report in ART naive
Kitahata et al [39] (2004)	Retrospective cohort	Free ART	USA	Yes	PI (78), NNRTI	MPR	Mean for all ARVs of [(1 – days without ARV)/days in the interval]	6 (0–6)	212	1. Increasing PAM strata (<70%, 70%-90%, and >90%) predicted viral rebound[b] ($P < .01$) and higher CD4 cell counts over 12–24 months ($P < .05$) 2. PAM adherence <70% predicted new AIDS or death, compared with PAM adherence of >70%, over 24 months ($P < .01$) (but PAM adherence of 70%-90%, compared with >90%, did not)
Wood et al [47] (2004)	Retrospective cohort	Public	Canada	Yes	PI (69), NNRTI	MPR	Months ART prescribed/ months follow-up in 1st year	12 (0–12)	1522	PAM adherence <75% predicted a lower increase in the CD4 cell count over 24 months ($P < .01$), whereas PAM strata >75% increasingly predicted increases in the CD4 cell count over 24 months ($P < .01$)

Fairley et al [34] (2005)	Retrospective cohort	Public	Australia	No	NNRTI, PI (NR)	MPR	Days ART prescribed/ days in the interval	Variable range, 12-44	752	Increasing PAM and self-reported adherence predicted VL suppression ($P < .01$)
Fletcher et al [35] (2005)	RCT (Prior VF on PI regimen)	Free ART	USA	No	NNRTI + PI (100)	PC	(doses dispensed – doses returned)/ doses dispensed	1(0–1)	220	PAM did not predict VL changes at 4 months; self-reported adherence ($P < .05$) ($n = 244$) and ARV plasma levels ($P < .05$) ($n = 180$) predicted VL changes at 4 months, wheras MEMS did not ($n = 62$)
Harrigan et al [10] (2005)	Retrospective cohort	Public	Canada	Yes	PI (74), NNRTI	MPR	Months ART prescribed/ months follow-up in 1st year	12 (0–12)	1191	PAM adherence of 80%-90% is the highest predictor of single and multiple category HIVDR over 24 months, compared with PAM adherence of 0%-20% ($P < .01$)
King et al [28] (2005)	RCT	Free ART	Multi- continent	Yes	PI (100)	PC	Pills consumed/pills expected to be consumed	Variable range, 2 – 3	590	Decreasing PAM strata increasingly predicted VF[g] ($P < .01$);the mean PAM adherence rate was lower in persons with detectable HIVDR to PI and/or 3TC ($P < .01$)
Inciardi et al [29] (2005)	Retrospective cohort	Private	USA	No	NNRTI (56), PI	MPR	Sum of (interval days – ARV days) for all ARVs/sum of interval days for all ARVs[i]	Variable[h]	94	Decreasing PAM adherence was associated with VL increase ($P < .01$)
Gross et al [36] (2006)	Retrospective cohort	Public	Canada	No	NNRTI, PI (NR)	MPR	(Days ART [any ARV] dispensed between 3 refills +30)/days between 3 refills	Variable range, 2-6	1634	Decreasing PAM strata (<70%, 70%-95%, and >95%) in a 2-6 observed interval, predicted a higher proportion with VF[d] ($P < .01$)
				Yes	NNRTI, PI (NR)	MPR	(Days ART [any ARV] dispensed +30)/fays between refills	Variable median, 29	1634	PAM adherence <95% (treated as a time-varying variable, with or without a 30-day grace period) predicted viral rebound[e] over the period of observation ($P < .05$)
Braithwaite et al [27] (2007)	Retrospective cohort	VA, minor costs	USA	Yes	PI (58), NNRTI, 3NRTI	MPR	Days ART prescribed/days in interval	12 (0–12)	6394	Increasing PAM strata increasingly predicted VL change, VL suppression, or changes in the CD4 cell count at 12 months

Townsend et al [31] (2007)	Retrospective cohort	VA, minor costs	USA	No	PI(50), NNRTI, NRTI	MPR	Days ART prescribed/days in the interval	6 (varied)	58	PAM was not associated with VL; PAM adherence <70% was associated with changes in the CD4 cell count ($P < .05$), but PAM adherence of 70%-90%, compared with >90%, was not
Saberi et al [45] (2008)	Retrospective cohort	Private	USA	No	NNRTI (100)	MPR	(Pills dispensed/pills prescribed per day)/days between refills	Variable range, 3-18	151	PAM adherence >85% maintained VL suppression in 8 of 10 patients between 2 VL measurements
Lima et al [11] (2009)	Retrospective cohort	Public	Canada	Yes	PI (64), NNRTI	MPR	Days ART prescribed/days of follow-up	Variable maximum, 30	903	PAM adherence <95% predicted mortality over follow-up period (maximum, 55 months) ($P < .05$)
Nellen et al [44] (2009)	Retro- and Prospective cohort	NR	Holland	No	NNRTI (58), PI, 3NRTI	PPU	ART dispensed/ART prescribed	6 (varied)	115	PAM adherence <85% did not predict VF[g] (but did for an ART-naïve subgroup; $P < .01$) over 24 months; self-reported adherence and ARV plasma levels did not predict VF[g] over 24 months
Cambiano et al [32] (2010)	Retrospective cohort	Public	England	No	PI(47), NNRTI, NRTI	MPR	Days with ≥3 ARV prescriptions/ study interval	6 (varied)	1632	PAM strata <95% predicted ($P < .01$) viral rebound, but PAM adherence of 95%-99% did not, [h] over the subsequent 9 months, compared with PAM adherence of 100%

NOTE. ART, antiretroviral therapy; ARV, antiretroviral; HIVDR, HIV drug resistance; MEMS medication event monitoring system; MPR, Medication possession ratio; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NR, not reported; PC, pill count; PI, protease inhibitor; PPU, pill pick-up; RCT, randomized control trial; 3NRTI, triple nucleoside reverse-transcriptase inhibitor; 3TC, lamivudine; 2NRTI, double nucleoside reverse-transcriptase inhibitor; VA, veterans affairs hospital; VF, virological failure; VL, viral load.

[a] Data are ART regimens for that study. The numbers in parentheses represent the percentages of subjects receiving the predominant regimen.

[b] Duration of adherence assessment, with the months over which assessed in parentheses. If there was a variable duration of adherence assessment, than the median, mean, or range is listed.

[c] The number after "PAM" is the percentage adherence.

[d] Two viral loads separated in time above threshold.

[e] Two viral loads above threshold after previous VL suppression.

[f] All patients received triple-drug PI regimens for 3 months and were then randomized to receive double-NRTI (50%) or 1 PI plus 1 NRTI (36%) or to continue the PI regimen (14%).

[g] Single viral load above threshold.

[h] Single viral load above threshold after previous VL suppression.

[i] "Interval days" was the sum of multiple 3-month periods prior to VL tests performed over a 2-year period, and "ARV days" was the sum of ARVs prescribed over these same periods.

44] or estimated adherence over shorter durations of assessment (4 weeks) [35].

Given the importance of PAMs in predicting virological failure or suppression, we considered 2 important sources of study heterogeneity: the duration of adherence assessment and the temporal relationship between the adherence assessment and viral load testing.

The duration of adherence assessment was most commonly the first 6 months [17, 22, 24, 31–33, 39, 40, 44] or 12 months [17, 27, 41, 48] after ART initiation but ranged widely (range, 1–44 months). All studies with a duration of adherence assessment greater than 6 months demonstrated association with virological failure or suppression [4, 17, 22, 23, 25, 27, 34, 36, 41, 48]. However, only 11 (79%) of 14 studies demonstrated an association when the duration of adherence assessment was 2–6 months. Notably, associations were maintained over shorter durations of assessment (2–6 months) when larger sample sizes were used (>115 subjects) [17, 18, 24, 26, 28, 32, 36, 42, 46, 49], suggesting that studies that involved shorter durations of adherence assessment or smaller sample sizes lack power to detect statistically significant associations.

The time at which viral load was assessed varied and occurred either at the end of the period of adherence assessment or at a future time point. Fourteen (88%) of 16 studies demonstrated an association between PAMs and virological failure or suppression at the end of adherence assessment [4, 17, 18, 22–28, 30, 31, 33, 34, 36, 40], whereas in 5 (63%) of 8 studies, PAMs were predictive of future outcomes (range, 1–55 months after adherence assessment) [17, 22, 32, 39, 41, 42, 44, 48]. In 2 studies, PAMs were found to be more predictive of virological outcomes at the end of the period of adherence assessment than at a future time point. However, the duration of adherence assessment used to predict the future outcome was shorter in both studies, making it difficult to draw further conclusions [17, 22].

Association with Nonvirological Outcomes

All studies that assessed the association between PAMs and CD4 cell count response demonstrated that lower levels of adherence were associated with a poorer CD4 cell count responses [19–22, 27, 31, 39, 42, 46, 47]. Of the 6 studies documenting association between PAMs and mortality [11, 13, 19, 20, 38, 39], all but 1 [20] demonstrated increasing mortality with lower levels of adherence. In addition, 2 large studies that assessed African treatment programs showed an association between lower individual adherence and subsequent classification as lost-to-follow-up during the first 12 months after ART initiation [19] or after a median of 7.7 months [20]. Importantly, authors of the study in which PAMs were associated with loss to follow-up and not with mortality acknowledge that many subjects who were lost to follow-up were likely to have died [20].

Data regarding the association between poor adherence to ART, as estimated by PAMs and HIV drug resistance, were limited. However, 2 studies that involved ART-naive patients receiving NNRTI- or protease inhibitor (PI)–based regimens [10, 28] demonstrated an association between adherence and acquired HIV drug resistance.

Studies Assessing Pharmacy and Nonpharmacy Adherence Measures

Ten studies documented PAMs and self-reported adherence and their associations with virological outcomes. Both PAMs and self-report measures were associated with virological outcomes in 3 studies; however, the superiority of one measure over the other could not be inferred [26, 34, 37]. In 4 studies, PAMs predicted virological outcomes, whereas self-reported adherence did not [23, 24, 26, 37]. In 1 study that compared PAMs with self-reported adherence using receiver operating characteristic curves, the PAM was superior to self-reported adherence ($P < .001$) [40]. In contrast, self-reported adherence was superior to a PAM in 1 study [35] in which a 4-week PC assessment failed to predict change in viral load 12 weeks later, whereas improved self-reported adherence measured at the later time point was predictive of a viral load reduction. In 3 additional studies, neither the PAMs nor self-reported adherence predicted virological outcome [30, 43, 44].

Three studies compared PAMs with use of MEMS caps [35, 40, 43]. Better adherence by both measures predicted virological suppression in 1 study [40], neither predicted viral load change in a second study [35], and only use of MEMS cap predicted viral load change in the third [43].

In 3 studies [30, 35, 44] in which PAMs were not predictive of virological outcome, antiretroviral plasma levels were also determined and found to be predictive in only one [35].

Studies Assessing Different PAMs

Only 1 study compared different PAMs by investigating 2 different PC measures—one incorporating time into the denominator and the other without. Lower estimates of adherence by both PC measures predicted virological failure at 6 and 12 months [26]. The ability of the 2 PAMs to predict virological failure was not directly compared; thus, superiority could not be established. Interestingly, the PC measure using time in the denominator classified more individuals as nonadherent and provided greater variability in adherence estimates.

PAM THRESHOLDS AND RELATIONSHIP TO TREATMENT OUTCOMES

To identify patients at risk for suboptimal clinical or virological response using PAMs, an understanding of the relationship between adherence and outcomes, including potential adherence thresholds or cutoffs, is essential. Studies commonly report

adherence estimates dichotomously or across ≥3 strata. All studies that stratified adherence estimates were reviewed to identify potential threshold effects.

PAM Thresholds and Virological Outcomes

Historically, >95% patient adherence to ART has been cited as the threshold to achieve virological suppression. This threshold was based on a single study of ART-experienced patients receiving unboosted-PI regimens [7]. Subsequent studies have suggested that adherence levels of <95% are associated with virological suppression in a considerable proportion of patients receiving NNRTI or boosted-PI regimens [6, 28, 50]. Seven studies using PAMs with stratified adherence estimates [4, 23, 28, 32, 36, 39, 41] failed to detect a threshold effect. Interestingly, in 2 studies, when 100% adherence was used as the highest stratum, no significant difference in the rate of viral rebound was observed, compared with levels of adherence of 95%–99% [32] and 90%–99% [4]; however, both studies reported decreased risk of viral rebound for every 10% increase in adherence across all strata. The ability of some studies to detect a threshold effect may have been limited by the fact that patients received different ART regimens [32, 36, 39, 41]. However, 2 studies that assessed only NNRTI-based regimens [4, 23] reported virological failure rates of 29% at 80%–95% adherence [23] and of ~25% at 80%–99% adherence [4]. These observations are consistent with studies using self-reported adherhence, unannounced PCs, and use of MEMS caps for patients receiving NNRTI regimens in which the majority of individuals had virological suppression in adherence strata below 95% [6, 50].

PAM Thresholds and Mortality

Four studies reported adherence across ≥3 strata and observed a threshold effect for mortality. For individuals receiving predominantly NNRTI [13, 19] or unboosted-PI regimens [38, 39], ≥2 adherence strata above 70% [39], 75% [38], or 80% [13, 19] did not differ in their ability to predict mortality, but lower adherence strata did predict increased mortality. Importantly, investigators attempted to account for "reverse causation" (ie, cessation of ART because of reasons related to poor survival) by using prolonged durations of adherence assessment before observing subjects for survival outcomes. On the basis of these data, a threshold effect predicting increased mortality among patients with a level of adherence of <80% noted by use of PAMs may serve as a potential target for adherence interventions, especially if available resources are limited.

PAM Thresholds and HIV Drug Resistance

Two studies described entirely [28] or predominantly (74% of subjects) [10] ART-naive populations who had received unboosted-PI regimens, with those who had adherence rates of 75%–90% having the highest risk for developing resistance. Because of these limited findings, we were unable to draw conclusions about adherence thresholds for the emergence of HIV drug resistance. Importantly, no studies examined the relationship between PAMs and drug resistant HIV in patients exclusively receiving NNRTI or boosted-PI regimens.

USE OF PAMS TO MONITOR ADHERENCE AND TREATMENT OUTCOMES

PAMs are ideally suited to monitoring adherence because they are objective and can be easily derived from data routinely collected for other purposes, such as clinical care, medication billing, fulfillment of legal requirements, or drug supply management. Importantly, PAMs may overestimate actual pill taking if individuals discard or share pills and, therefore, estimate maximum possible adherence. In addition, PAMs do not provide information on patterns of nonadherence known to be associated with the development of resistance to NNRTIs [51, 52].

Despite their limitations, in settings in which frequent routine viral load monitoring is not available, PAMs can play an important role in monitoring individual and population-level adherence to ART. Although prospective studies of adherence interventions and viral load testing targeted at patients with lower levels of adherence, as determined by PAMs, have not been reported, findings from 2 studies are optimistic [17, 36]. In a study conducted in sub-Saharan Africa, PAMs were superior to CD4 cell count criteria in predicting virological failure, and when PAMs were performed before determinations of viral load and CD4 cell count, PAMs were as accurate as CD4 cell count changes in predicting virological failure. These results support the use of PAMs for potential identification of patients at risk of future virological failure [17]. In a second study, which was from Canada, analysis of repeated measures of adherence, which account for changes in adherence over time, predicted future viral rebound [36], suggesting that routine surveillance of patient adherence with PAMs can be used to alert clinicians to possible future virological failure.

Use of PAMs to monitor adherence requires the following minimum data: ART regimen dispensed, date of dispensing, and number of days of ART dispensed. Selection of a PAM will depend on available resources at a site or in a program, as well as a local assessment of the strengths and limitations of different PAMs. MPR estimates are the most studied and incorporate time in the denominator (Table 1); thus, patients need to return to the dispensary before their medication finishes if taken as prescribed, to be considered 100% adherent. PC and PPU measures that do not incorporate time in the denominator (Table 1) may overestimate adherence, because patients may use all dispensed ART but do so over longer periods than intended. PC measures are limited by the increased resources required to routinely count and record remnant pills at each clinic or pharmacy visit. In

addition, if patients do not bring all remnant pills for counting or share or lose pills, the rate of adherence will be overestimated. Although PC measures may provide a more accurate assessment of adherence by accounting for unused ART, to our knowledge, no data comparing PC to non-PC PAMs are available. PPU measures are the least studied PAM. Unlike MPR and PC measures, PPU estimates are dichotomous and, therefore, do not provide a range of adherence, limiting their ability to identify individuals in need of increased adherence support.

In the absence of data suggesting an advantage of PC over non-PC measures, and considering the extra resources required to count remnant pills, we do not suggest using PC measures. Furthermore, measures incorporating the number of days for which ART was prescribed in their definition, such as MPR and some PPU, measures are likely to be the most informative. Available data suggest that shorter durations of adherence assessment (≤6 months) may be less accurate at predicting virological outcome. Moreover, PAMs are more likely to accurately predict outcomes at the end of a period of adherence assessment than at future time points. Not surprisingly, the balance of studies suggests that PAMs are superior to self-reported adherence in predicting virological outcome. Finally, a threshold effect for mortality is observed at adherence levels of 70%–80%, in contrast to virological outcomes, for which no adherence thresholds were observed.

PAM-based adherence estimates can be used by pharmacists and other health care providers to promote ART adherence. Although the literature on pharmacist-directed interventions is limited, pharmacy-based adherence interventions have successfully combined adherence education [53-55], tailoring regimens to patient lifestyles [54, 56], and the management of adverse drug reactions [55, 56], resulting in improved adherence [53, 54, 56] and improved virological [53, 55] and immunological [55] response. Further investigation of these interventions is warranted in HICs and in LMICs where similar interventions have not been reported.

FUTURE RESEARCH NEEDS

Although many studies have assessed various PAMs and their associations with clinical and virological outcomes, significant gaps in our understanding remain. Research is needed to compare different PAMs in the same population and against other adherence measures and biomarkers, such as antiretroviral levels in hair. In addition, the optimal duration of adherence assessment remains to be clarified for different clinical and virological outcomes. Also, because the relationship between adherence and virological outcomes varies over time [57] and by regimen [6, 50], studies should investigate the predictive value of PAMs in both ART-naive and ART-experienced patients receiving different regimens.

The potential benefit of PAMs includes the identification of individuals at risk for virological failure and undesirable treatment outcomes. Prospective studies incorporating PAMs with interventions designed to improve adherence, clinical outcome, and virological outcome have not been reported but are necessary if PAMs are to be used to optimize clinical care. Researchers attempting to design such studies will face multiple challenges, such as calculating accurate adherence estimates, devising tools for clinicians to easily interpret PAM results, and correctly applying interventions to at-risk patients.

CONCLUSIONS

Pharmacy-based methods for estimating adherence during routine clinical care are heterogeneous, yet they predict virological and other clinical outcomes in the majority of studies. Limited comparative data suggest that PAMs are likely superior to self-reported adherence measures. Nevertheless, additional studies are needed to clarify this finding and to identify which PAM parameters are most predictive of clinical or virological outcomes and which measure is best suited to each treatment setting. Available evidence suggests that PAMs are more accurate in predicting current rather than future outcomes and that PAMs applied over shorter durations of adherence assessment (≤6-months) are likely to be less predictive of outcome than PAMs estimated over longer durations. In conclusion, available data suggest that MPR and PPU estimates, which include the number of days for which ART was prescribed, are appropriate minimum-resource methods to assess patient adherence to ART.

Acknowledgments

Some of the authors are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decision or stated policy of the World Health Organization.

Financial support. National Health and Medical Research Council (Postgraduate Scholarship to J.H.M.), National Institutes of Health (5K23AI074423-04 to M.R.J., 5T32AI007438-18 to S.Y.H.)

Potential conflicts of interest. All authors: no conflicts.

References

1. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 2003; 362:22–9.
2. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006; 367:817–24.
3. Palella FJ Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998; 338:853–60.
4. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase in-

hibitor-based HIV therapy and virologic outcomes. Ann Intern Med 2007; 146:564–73.
5. Martin M, Del Cacho E, Codina C, et al. Relationship between adherence level, type of the antiretroviral regimen, and plasma HIV type 1 RNA viral load: a prospective cohort study. AIDS Res Hum Retroviruses 2008; 24:1263–8.
6. Maggiolo F, Ravasio L, Ripamonti D, et al. Similar adherence rates favor different virologic outcomes for patients treated with nonnucleoside analogues or protease inhibitors. Clin Infect Dis 2005; 40:158–63.
7. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000; 133:21–30.
8. Bangsberg DR, Acosta EP, Gupta R, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS 2006; 20:223–31.
9. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clin Infect Dis 2003; 37:1112–8.
10. Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. J Infect Dis 2005; 191:339–47.
11. Lima VD, Harrigan R, Bangsberg DR, et al. The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. J Acquir Immune Defic Syndr 2009; 50:529–36.
12. Garcia de Olalla P, Knobel H, Carmona A, Guelar A, Lopez-Colomes JL, Cayla JA. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. J Acquir Immune Defic Syndr 2002; 30:105–10.
13. Nachega JB, Hislop M, Dowdy DW, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J Acquir Immune Defic Syndr 2006; 43:78–84.
14. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. J Infect Dis 2008; 197(Suppl. 3):S272–8.
15. WHO. Patient monitoring guidelines for HIV care and antiretroviral therapy (ART). Geneva: WHO, 2006.
16. Chalker J, Wagner A, Tomson G, et al. Urgent need for coordination in adopting standardized antiretroviral adherence performance indicators. J Acquir Immune Defic Syndr 2010; 53:159–61.
17. Bisson GP, Gross R, Bellamy S, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. PLoS Med 2008; 5:e109.
18. Bisson GP, Rowh A, Weinstein R, Gaolathe T, Frank I, Gross R. Antiretroviral failure despite high levels of adherence: discordant adherence-response relationship in Botswana. J Acquir Immune Defic Syndr 2008; 49:107–10.
19. Chi BH, Cantrell RA, Zulu I, et al. Adherence to first-line antiretroviral therapy affects non-virologic outcomes among patients on treatment for more than 12 months in Lusaka, Zambia. Int J Epidemiol 2009; 38:746–56.
20. Toure S, Kouadio B, Seyler C, et al. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Cote d'Ivoire: 2-year outcomes and determinants. AIDS 2008; 22:873–82.
21. Ross-Degnan D, Pierre-Jacques M, Zhang F, et al. Measuring adherence to antiretroviral treatment in resource-poor settings: the clinical validity of key indicators. BMC Health Serv Res 2010; 10:42.
22. Danel C, Gabillard D, Inwoley A, et al. Medium-term probability of success of antiretroviral treatment after early warning signs of treatment failure in West African adults. AIDS Res Hum Retroviruses 2009; 25:783–93.
23. Goldman JD, Cantrell RA, Mulenga LB, et al. Simple adherence assessments to predict virologic failure among HIV-infected adults with discordant immunologic and clinical responses to antiretroviral therapy. AIDS Res Hum Retroviruses 2008; 24:1031–5.
24. Rougemont M, Stoll BE, Elia N, Ngang P. Antiretroviral treatment adherence and its determinants in sub-Saharan Africa: a prospective study at Yaounde Central hospital, Cameroon. AIDS Res Ther 2009; 6:21.
25. San Lio MM, Carbini R, Germano P, et al. Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique. Clin Infect Dis 2008; 46:1609–16.
26. Weidle PJ, Wamai N, Solberg P, et al. Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda. Lancet 2006; 368:1587–94.
27. Braithwaite RS, Kozal MJ, Chang CC, et al. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. AIDS 2007; 21:1579–89.
28. King MS, Brun SC, Kempf DJ. Relationship between adherence and the development of resistance in antiretroviral-naive, HIV-1-infected patients receiving lopinavir/ritonavir or nelfinavir. J Infect Dis 2005; 191:2046–52.
29. Inciardi JE, Leeds AL. Assessing the utility of a community pharmacy refill record as a measure of adherence and viral load response in patients infected with human immunodeficiency virus. Pharmacotherapy 2005; 25:790–6.
30. Alcoba M, Cuevas TJ, Perez-Simon MR, et al. Assessment of adherence to triple antiretroviral treatment including indinavir: role of the determination of plasma levels of indinavir. J Acquir Immune Defic Syndr 2003; 33:253–8.
31. Townsend ML, Jackson GL, Smith R, Wilson KH. Association between pharmacy medication refill-based adherence rates and CD4 count and viral-load responses: a retrospective analysis in treatment-experienced adults with HIV. Clin Ther 2007; 29:711–6.
32. Cambiano V, Lampe FC, Rodger AJ, et al. Use of a prescription-based measure of antiretroviral therapy adherence to predict viral rebound in HIV-infected individuals with viral suppression. HIV Med 2010; 11:216–24.
33. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072 Study Team). JAMA 2000; 283:205–11.
34. Fairley CK, Permana A, Read TR. Long-term utility of measuring adherence by self-report compared with pharmacy record in a routine clinic setting. HIV Med 2005; 6:366–9.
35. Fletcher CV, Testa MA, Brundage RC, et al. Four measures of antiretroviral medication adherence and virologic response in AIDS clinical trials group study 359. J Acquir Immune Defic Syndr 2005; 40:301–6.
36. Gross R, Yip B, Lo Re V, et al. A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. J Infect Dis 2006; 194:1108–4.
37. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. J Clin Epidemiol 2004; 57:1107–10.
38. Hogg RS, Heath K, Bangsberg D, et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. AIDS 2002; 16:1051–8.
39. Kitahata MM, Reed SD, Dillingham PW, et al. Pharmacy-based assessment of adherence to HAART predicts virologic and immunologic treatment response and clinical progression to AIDS and death. Int J STD AIDS 2004; 15:803–10.
40. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001; 134:968–77.
41. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. J Acquir Immune Defic Syndr 2000; 23:360–1.
42. Maher K, Klimas N, Fletcher MA, et al. Disease progression, adherence, and response to protease inhibitor therapy for HIV infection in an

Urban Veterans Affairs Medical Center. J Acquir Immune Defic Syndr 1999; 22:358–63.
43. McNabb J, Ross JW, Abriola K, Turley C, Nightingale CH, Nicolau DP. Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic. Clin Infect Dis 2001; 33:700–5.
44. Nellen JF, Nieuwkerk PT, Burger DM, Wibaut M, Gras LA, Prins JM. Which method of adherence measurement is most suitable for daily use to predict virological failure among immigrant and non-immigrant HIV-1 infected patients? AIDS Care 2009; 21:842–50.
45. Saberi P, Caswell N, Amodio-Groton M, Alpert P. Pharmacy-refill measure of adherence to efavirenz can predict maintenance of HIV viral suppression. AIDS Care 2008; 20:741–5.
46. Singh N, Berman SM, Swindells S, et al. Adherence of human immunodeficiency virus–infected patients to antiretroviral therapy. Clin Infect Dis 1999; 29:824–30.
47. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. The impact of adherence on CD4 cell count responses among HIV-infected patients. J Acquir Immune Defic Syndr 2004; 35:261–8.
48. Wood E, Montaner JS, Yip B, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. CMAJ 2003; 169:656–61.
49. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team). JAMA 2000; 283:205–11.
50. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. Clin Infect Dis 2006; 43:939–41.
51. Parienti JJ, Massari V, Descamps D, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis 2004; 38:1311–6.
52. Oyugi JH, Byakika-Tusiime J, Ragland K, et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. AIDS 2007; 21:965–71.
53. Cantwell-McNelis K, James CW. Role of clinical pharmacists in outpatient HIV clinics. Am J Health Syst Pharm 2002; 59:447–52.
54. Levy RW, Rayner CR, Fairley CK, et al. Multidisciplinary HIV adherence intervention: a randomized study. AIDS Patient Care STDS 2004; 18:728–35.
55. March K, Mak M, Louie SG. Effects of pharmacists' interventions on patient outcomes in an HIV primary care clinic. Am J Health Syst Pharm 2007; 64:2574–8.
56. Hirsch JD, Rosenquist A, Best BM, Miller TA, Gilmer TP. Evaluation of the first year of a pilot program in community pharmacy: HIV/AIDS medication therapy management for Medi-Cal beneficiaries. J Manag Care Pharm 2009; 15:32–41.
57. Rosenblum M, Deeks SG, van der Laan M, Bangsberg DR. The risk of virologic failure decreases with duration of HIV suppression, at greater than 50% adherence to antiretroviral therapy. PLoS One 2009; 4:e7196.

3.5 Summary

Systematic reviews are a method to synthesize biomedical information in a methodologically rigorous fashion to aid healthcare decision making and improve health. This thesis comprises three separate systematic reviews in its review of the literature to address questions of clinical importance to populations living with HIV in diverse clinical settings. The three reviews represent the most recent summary available on the use of pharmacy data to estimate adherence to ART, and clinical outcomes on ART from diverse clinical settings such as rates of virological suppression, retention in care and survival.

Firstly, summary estimates for critical clinical outcomes after a year of ART in LMICs was obtained and stratified according to whether physical tracing was present in the selected studies. We also identified the potential for physical tracing to improve re-engagement in ART care. This is in addition to the finding that tracing leads to a reduction in unknown outcomes as individuals initially classified as LTFU are subsequently re-classified as having died or transferred out. Importantly, these data suggest physically tracing patients who are disengaged from care is an important intervention to improve individual outcomes and programmatic evaluation of HIV infected populations receiving ART. Notably no randomised clinical trials examining the effectiveness of physical tracing interventions are currently available but findings from this work suggest they are needed to definitively establish the ability of this intervention to re-engage patients in ART care.

Secondly, the first summary estimates of virological suppression across LMICs was obtained and stratified by different thresholds of HIV RNA to define virological suppression. These rates of virological suppression compare favourably with outcomes in HICs and represent a significant achievement for programs in LMICs where ART is provided under greater resource constraints. Additionally findings from this review provide ART programme managers and researchers in LMICs with results to inform target setting for rates of virological suppression and support mathematical models of the effects of ART.

Finally, adherence estimates established from routinely available objective pharmacy data were found to consistently predict virological and other clinical outcomes. PAMs were likely more accurate than the most commonly used self-report estimates of adherence, and recommendations were established on how to select PAMs that would be most reliable in predicting clinical outcomes for populations receiving ART. Additional conclusions regarding pharmacy measures that would minimise the resources required to estimate adherence using pharmacy data were also provided.

4 Hunger, Education, and Residential Status Impact Survival in HIV

4.1 Declaration

Declaration for Thesis Chapter 4

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I led the design based on a pre-existing dataset, performed all analyses and wrote the manuscript	75

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors**
Christine A. Wanke	Helped conceive the idea for the analysis and develop the manuscript	7.5
Norma Terrin	Advised on a statistical plan and helped develop the manuscript	5
Sally Skinner	Assisted with accessing data from the pre-existing dataset, formulating statistical code for the analyses and develop the manuscript	5
Tamsin Knox	Helped conceive the idea for the analysis and develop the manuscript	7.5

Candidate's Signature		**Date 16 APR 2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**Tufts University School of Medicine, Department of Public Health and Community Medicine, Boston**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	CAW 	**Date** 14/4/2013
Signature 2	NT 	8/4/2013
Signature 3	SS 	6/4/2013
Signature 4	TK 	8/4/2013

4.2 Introduction

This chapter represents the first of four original research studies that seek to explore how different social and behavioural factors impact clinical outcomes for PLHIV receiving ART. The clinical endpoint selected for this chapter is all-cause mortality. This end point was selected as it is a widely accepted clinical outcome measure (119) and due to the importance of trying to elucidate clinical features that directly impact life expectancy. When considering how different markers of SES may associate with all-cause mortality we adopted an analytic approach that considered the direct effects of SES on mortality but also investigated how these different markers of SES impact survival via other factors know to be potent predictors of survival for individuals receiving ART, namely HIV viral load and CD4 T-cell counts. This "2-step" approach allowed us to consider the potential influence of social factors on survival beyond previous analyses that just looked to associate social factors and all-cause mortality directly (31, 33, 57). This more detailed "2-step" approach allows us to more accurately understand the impact of low SES on mortality compared to single step multivariable analyses that combine markers of SES with other strong predictors of mortality such as CD4 T-cell counts and HIV viral load. An important consideration for populations affected by HIV is the potential for them to be overrepresented by individuals with lower SES as compared to the general population. This is likely related to a higher numbers of individuals from racial minorities, marginalised groups or affected by conditions such as chronic drug or alcohol use being infected with HIV (23, 24). Therefore, a greater understanding of the impact of SES on mortality can improve our understanding of the residual mortality seen in HIV infected populations receiving ART as compared to the non HIV infected population.

Multiple techniques to define SES have been reported and include individual and ecological assessments of either individual or household income, highest level of education attained, type of housing, and food security status (31, 57). In this analysis we were able to examine multiple measures of SES collected prospectively as part of the observational NFHL cohort of HIV infected individuals followed in the North-eastern US in an era of combination ART. These measures included assessment of: personal income, education level attained, homelessness and hunger. Critically, and unlike the following analysis, currently available studies lack individual level

measurements of SES that are repeated over time. These previous cross-sectional studies can draw limited conclusions about causal links as the timing of the outcome in relation to the exposure is often unclear. The use of repeated measures in the following prospective cohort analysis allows for the examination of multiple exposures and to draw greater inference about the possible causal relationships between markers of low SES and survival. Therefore we sought to examine how different individual and repeated assessments of SES in a US cohort of PLHIV impact survival in the setting of ART. Analyses such as this aim to understand the complex relationships between SES, factors related to HIV or ART on clinical endpoints such as survival. Interventional studies can then be accurately targeted at the most likely causes for poor clinical outcomes for populations living with HIV.

4.3 Paper

AIDS Behav
DOI 10.1007/s10461-010-9759-z

ORIGINAL PAPER

Poverty, Hunger, Education, and Residential Status Impact Survival in HIV

James McMahon · Christine Wanke · Norma Terrin · Sally Skinner · Tamsin Knox

Abstract Despite combination antiretroviral therapy (ART), HIV infected people have higher mortality than non-infected. Lower socioeconomic status (SES) predicts higher mortality in many chronic illnesses but data in people with HIV is limited. We evaluated 878 HIV infected individuals followed from 1995 to 2005. Cox proportional hazards for all-cause mortality were estimated for SES measures and other factors. Mixed effects analyses examined how SES impacts factors predicting death. The 200 who died were older, had lower CD4 counts, and higher viral loads (VL). Age, transmission category, education, albumin, CD4 counts, VL, hunger, and poverty predicted death in univariate analyses; age, CD4 counts, albumin, VL, and poverty in the multivariable model. Mixed models showed associations between (1) CD4 counts with education and hunger; (2) albumin with education, homelessness, and poverty; and (3) VL with education and hunger. SES contributes to mortality in HIV infected persons directly and indirectly, and should be a target of health policy in this population.

Supported by the National Institutes of Health grants R01 HL 65947, P30 DA13868, P30 AI42853, and P01 DK45734.

J. McMahon · C. Wanke · T. Knox
Department of Medicine, Tufts Medical Center, Boston, MA 02111, USA

J. McMahon (✉) · C. Wanke · S. Skinner · T. Knox
Nutrition/Infection Unit, Department of Public Health and Community Medicine, Tufts University School of Medicine, Jaharis 276, 150 Harrison Avenue, Boston, MA 02111, USA
e-mail: [redacted]

N. Terrin
Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA

Keywords HIV · Socioeconomic status · Mortality

Introduction

Low socioeconomic status (SES) has been associated with increased mortality across many diseases including cardiovascular disease, cancer, and other smoking related conditions [1–3]. After the introduction of highly active antiretroviral therapy (HAART) to industrialized countries in 1995–1996, there were dramatic reductions in mortality for those infected with HIV [4–6], but data on the association between SES and mortality has been inconsistent over the course of the epidemic.

Prior to the introduction of HAART some studies reported no difference in survival based on SES [7–10] and others reported increased mortality or disease progression associated with low SES [11, 12]. During the HAART era, improved survival has been consistently linked with higher SES [9, 10, 13–17] but these studies are limited by the imprecise assessment of SES. For example, SES for an individual was established by taking neighborhood level [9, 10, 14–16] or county level [13] census derived SES data such as median income [10, 13–16] or a combined "SES index" [9] and applying this to the participant's address at the time they entered the study population. In these studies, the timing of the census-block level SES data relative to the timing of enrollment and follow-up varied considerably. For example, in one of the previous studies [16], a subject who entered in 1998 and died in 2004 would have had SES approximated by median neighborhood income from 2001 census data, using the individual's 1998 address.

As acknowledged by previous authors the ecological assessment of SES has multiple possible limitations [9, 14–16]. It is possible that area SES data may not reflect

Published online: 15 July 2010

individual SES status; that area SES data obtained at the time of census may not accurately reflect area level SES data at the time of enrollment, and that if an individual's residence changes over time the address at enrollment may not accurately reflect SES over time.

The one study in the HAART era that did utilize an individual measure of SES undertook one measurement of SES at baseline and found an association between low SES and mortality [17]. This study was limited by having no biological marker of disease such as viral load data, or repeated measures of CD4 counts. Also, despite being performed in the HAART era, only 22.9% of the subjects were on HAART when the SES measurement was taken.

Therefore, we investigated whether SES predicts mortality in HIV infected persons in the HAART era using prospective and individually collected data while controlling for possible confounding factors. To further understand this relationship we examined whether SES impacted mortality directly or whether its impact was mediated through other known predictors of death.

Methods

Study Population

We examined data from 878 participants enrolled in the Nutrition for Healthy Living (NFHL) Study from 1995 to 2005. This is a prospective cohort study undertaken in the greater Boston and Providence area to investigate the effects of nutritional status on people infected with HIV. Eligible participants were HIV infected adults over 18 years of age. Pregnant women, people with diabetes, thyroid disease or malignancies other than Kaposi sarcoma, and those not fluent in English were excluded from the study. Mortality information was ascertained by quarterly review of the Massachusetts and Rhode Island Registries of Vital Records and Statistics and yearly searches of the National Death Index. These registries were last reviewed in June 2008 to capture all participant deaths occurring through December 31, 2006, the date of censorship for this study.

Clinical and Laboratory Measurements

Participants were interviewed biannually to obtain information on clinical status, use of recreational drugs, sociodemographic information and use of antiretroviral therapy. HAART was defined as receipt of any of the following regimens: two protease inhibitors, one protease inhibitor and two nucleotide reverse-transcriptase inhibitors (NRTI), or one non-nucleotide reverse-transcriptase inhibitor, and two NRTIs. Individuals on triple NRTI regimens were classified as not being on HAART. Blood was collected at each visit for biochemical and immunologic testing; $CD4^+$ cells were counted using flow cytometry, HIV RNA loads were measured by the Amplicor Monitor RT–PCR assay (Roche Molecular Systems) with a lower detection limit of 2.6 $\log_{10}$ copies/ml (400 copies/ml) and albumin was measured by automated colorimetric dye-binding methods (Beckman Coulter) and reported in g/dL. Further details on data collection and subject selection for the NFHL cohort have been previously reported. [18, 19].

Definition of SES and other Clinical Parameters

Poverty was defined as total household income below the federal poverty line, which was adjusted annually per the United States census bureau, or a personal annual income less than $10,000 [20]. Homeless was defined as an individual not having a fixed and regular nighttime residence. This included living in a shelter or welfare hotel, or using public and private places not normally used for sleeping [21] or living in a boarding house. Hunger was defined using questions from the Radimer/Cornell scale that defined individual hunger [22]. The questions used for the current study are also consistent with the validation of the Radimer/Cornell measures performed by Kendall et al. [23]. To meet these criteria a subject had to report going without food due to lack of money plus either; losing weight due to lack of food, or the physical sensation of hunger due to lack of food. If individuals identified themselves as smokers of cigarettes then they were considered active smokers, and if they had used intravenous drugs in the prior 6 months they were identified as active IDU. Average daily alcohol consumption was assessed as part of a 3 days food record. Depression was assessed via an 8-item measure developed by Burnam et al., with scored responses being entered into an algorithm to establish a dichotomous depression variable as per the original study [24].

Statistical Analysis

Individual characteristics were compared based on survival status. Chi-square tests, Student's *t*-tests, and Wilcoxon rank-sum tests were used as appropriate.

Univariate Cox proportional hazards regression for all-cause mortality was used to estimate unadjusted hazard ratios for baseline variables. These were, SES measures (hunger, homelessness, poverty, and education), demographics, mode of HIV transmission, harmful behaviors (intravenous drug use [IDU], smoking, alcohol), viral factors (CD4 counts, HIV viral load), use of HAART, depression, and albumin. Information on demographics,

education, and mode of HIV infection were only collected at baseline, unlike all other variables which were collected at each visit. Unadjusted hazard ratios were then estimated using the Andersen-Gill extension to the Cox hazards regression to account for covariates that may have changed over time. We also tested the relationship between SES and mortality, adjusting for potential confounders with a multivariable Cox regression, with all variables significant to the $P < 0.2$ level in univariate analyses being entered into the model. The time varying form of the variable was used, except for variables where only baseline information was collected. Variable selection was by stepwise elimination, with variables not reaching statistical significance ($P < 0.05$) being deleted from the model. We ran additional analyses to assess whether there were mediating variables between SES and mortality. All variables present in the final multivariable Cox regression, excluding age and any measures of SES itself, were considered to be potential mediators, and were therefore selected as outcome variables for mixed model analyses. These mixed models examined whether baseline SES measures predicted change in the selected outcome. Investigators also confirmed there was a plausible association between SES and the selected outcome variables before proceeding with the mixed models. Also, multivariable Cox regression was performed that did not include outcome variables employed in mixed models, to examine the change in SES parameters between models with and without these potential mediators. For the mixed models, we assumed that missing data were missing at random (that is, unrelated to outcome), based on the typical reasons for missing visits, including difficulty obtaining transport, poor weather, intercurrent illness, forgetting, incarceration, and having to care for dependents. All analysis were conducted using SAS version 9.1 (SAS Institute, Cary, NC) with a 2-tailed P value 0.05 or less indicating a statistically significant association.

Results

Table 1 shows the baseline characteristics of the participants by survival status. There were 200 deaths in the cohort, giving a crude mortality rate of 23%, and median duration of follow up in those that died was 54.8 months (interquartile range 28.9–85.0 months). Mean age of the cohort was 40.2 ± 7.4 years. The participants who died were older (41.5 vs. 39.9 yrs, $P = 0.01$) at their baseline visit. The study population was 56% white and had the following HIV transmission categories: men who have sex with men only (MSM) 47%, only IDU 26%, heterosexual 21%, both MSM and IDU 3%, and transfusion related or undetermined 3%. Interestingly, there was no difference in gender or race by survival status. Gender, ethnicity, and HIV transmission category were all highly reflective of the HIV epidemic in Massachusetts and Rhode Island at the time of the study [25–27]. Individuals who smoked (28% vs. 17%, $P < 0.001$) or used intravenous drugs (40% vs. 21%, $P < 0.001$) had higher mortality rates than those who did not. Individuals who died had lower baseline median CD4 counts (193 vs. 369, $P < 0.001$), and albumin (3.9 vs. 4.1 g/dL, $P < 0.001$); higher HIV $\log_{10}$ viral load (4.5 vs. 3.3, $P < 0.001$).

Unadjusted Cox proportional hazards analyses for baseline and time varying covariates along with the final multivariable analysis are presented in Table 2. There was significant evidence at the $P < 0.001$ level in both baseline and time varying univariate analyses that older age, higher HIV viral load, and lower CD4 counts, and albumin, were associated with increased likelihood of death. An individual's HIV transmission category was a predictor of death in the univariate analysis ($P < 0.001$). When using the category of heterosexual sex only as a referent group there was an increasing likelihood of death with the following categories; MSM only (HR 1.05), history of IDU and MSM (HR 1.26), history of IDU only (1.96) and the highest likelihood with a small group ($n = 20$) with either an undetermined or transfusion related transmission category (HR 3.71). The high hazard ratio for this last category likely reflects patients with conditions such as hemophilia who acquired their infection early in the course of the HIV epidemic and who were possibly co-infected with other blood borne viruses such as Hepatitis C. Consistent with the chi-square analyses in Table 1, active IDU use (HR 2.32, $P < 0.001$) and smoking (HR 1.81, $P < 0.001$) at the baseline visit were predictive of death. The time-varying smoking variable predicted death in the univariate analysis (HR 1.43, $P = 0.01$), unlike active IDU (HR 1.48, $P = 0.23$), but there was not significant evidence in the multivariable model for either of these harmful behavior variables predicting death. In univariate analyses HAART at baseline was not predictive of death (HR 0.89, $P = 0.45$), but as a time-varying variable, HAART did predict a decreased risk of death (HR 0.73, $P = 0.03$). However, being on HAART did not remain in the final multivariable model. In the univariate analyses of baseline measures of SES, there was significant evidence that homelessness, education level and poverty predicted death, while univariate analysis of time-varying SES variables demonstrated significant evidence of poverty and hunger predicting death. The final multivariable model showed that older age (HR 1.06 per year) at baseline and increasing HIV viral load (HR 1.36 per $\log_{10}$ copies), and decreasing CD4 counts (HR 0.997 per count/ml), and albumin (HR 0.36 per g/dL); increased the likelihood of death

Table 1 NFHL cohort characteristics at baseline

	Dead 200 (22.8)	Alive 678 (77.2)	*P*-value[a]
Mean age in years	41.5 ± 7.8	39.9 ± 7.3	0.01
Gender			0.64
Female	60 (23.8)	192 (76.2)	
Male	140 (22.4)	486 (77.6)	
Race			0.58
White	115 (23.5)	375 (76.5)	
Non white	85 (21.9)	303 (78.1)	
HIV transmission category			<0.001
Heterosexual	34 (18.3)	152 (82.7)	
MSM only	85 (20.4)	331 (79.6)	
MSM and IDU	6 (22.2)	21 (77.8)	
IDU only	67 (29.3)	162 (70.7)	
Other[b]	12 (60.0)	8 (40.0)	
Smoker			<0.001
Active	124 (27.4)	329 (72.6)	
Not Active	69 (17.0)	337 (83.0)	
IDU			<0.001
Active	26 (40.0)	39 (60.0)	
Not Active	169 (21.1)	632 (78.9)	
HAART			0.04
On HAART	79 (19.4)	329 (80.6)	
Not on HAART	102 (25.5)	298 (74.5)	
CD4, counts/ml	193 (65–364)	369 (216–560)	<0.001
Log_{10} HIV viral load, copies/ml	4.5 (3.3–5.1)	3.3 (ND[c]–4.3)	<0.001
Serum albumin, g/dL	3.9 ± 0.6	4.1 ± 0.4	<0.001

Note: Sample size varied based on missing data but no more than 3% data missing, except for serum albumin ($n = 754$) and HAART use ($n = 808$). Values represent n (% with that characteristic), median (Q1–Q3) or mean ± SD

[a] *P*-values chi-square (categorical),Student *t*-test (continuous normal distribution)

[b] Transfusion related or indeterminate

[c] *ND* Not Detectable. Lower limit of detection 2.6 log_{10} (400) copies/ml

(all $P < 0.001$). Notably, one of the SES measures, poverty, continued to significantly predict death (HR 1.50, $P = 0.03$) while controlling for age and the three time varying covariates known to predict mortality in HIV infected individuals [5, 6, 28–30].

To explore whether measures of SES had an indirect effect on mortality, CD4 counts, albumin, and HIV viral load, were examined as outcomes in a mixed model to see if the markers of SES predicted the baseline level, or change over time, in these strong predictors of death. Table 3 shows the SES measures at baseline that were significant to the $P \leq 0.05$ level in predicting baseline level and change in CD4 counts, albumin, or viral load in the mixed models, Parameter estimates generated by the mixed models and presented in this table are interpreted as follows. Estimates for the intercept indicate the degree to which presence of the risk factor (e.g., hunger) raises or lowers the baseline value of the outcome (e.g., CD4), and estimates for the slope indicate the degree to which the presence of the risk factor (e.g., college education) raises or lowers the change in the outcome per month (e.g., change in CD4 counts per month). In addition, Fig. 1 is a schematic diagram, using the example of CD4 counts, to visually aid the reader in interpreting the mixed model parameter estimates for intercept and slope.

For the mixed model outcome variable CD4, there was significant evidence that; for those who reported hunger at baseline the trajectory of their CD4 counts would be 89 cells lower at each time point compared to those who did not, and for individuals with a college education their CD4 counts would increase by 1.04 cells per month compared to those without this level of education. In regard to albumin, there was significant evidence for multiple measures of SES to predict change in the parameter estimate for the intercept. More specifically, for participants who met the criteria for homelessness or poverty at baseline, albumin measurements over time were 0.21 and 0.09 g/dL lower, respectively, than in those who did not, and for individuals with a college education, albumin was 0.10 g/dL higher. Furthermore there were no baseline measures of SES that significantly predicted change in g/dL of albumin per month, denoting no significant predictors of the slope for albumin. Lastly, for the outcome variable HIV viral load there was

Table 2 Unadjusted and Multivariable Cox proportional hazards of mortality

	Unadjusted Hazard ratio for baseline data	*P*-value	Unadjusted Hazard ratio for time varying data	*P*-value	Multivariable model Hazard ratio	*P*-value
Age—increase by 1 year	1.03	0.001			1.06	<0.001
HIV transmission category		<0.001			–	
Heterosexual only	1.0					
MSM only	1.05					
IDU and MSM	1.26					
IDU only	1.96					
Other[a]	3.71					
Active IDU	2.32	<0.001	1.48	0.23	–	
Active Smoker	1.81	<0.001	1.43	0.01	–	
CD4 count—increase by 1 cell/μl	0.997	<0.001	0.996	<0.001	0.997[b]	<0.001
HIV Viral Load—increase by 1 $\log_{10}$ copies/ml	1.64	<0.001	1.78	<0.001	1.36[b]	<0.001
Albumin—increase by 1 g/dL	0.38	<0.001	0.26	<0.001	0.36[b]	<0.001
On HAART	.89	0.45	0.73	0.03	–	
Hunger[c]	1.07	0.81	2.13	<0.001	–	
Homeless[d]	1.78	0.004	1.39	0.12	–	
Poverty[e]	1.62	0.001	1.68	<0.001	1.50	0.03
College education	.68	0.02			–	

Note: Gender, race, alcohol, and depression were not significant to the $P < 0.05$ level in unadjusted analyses

[a] Transfusion related or indeterminate

[b] Time-varying

[c] Going without food due to lack of money, plus weight loss and/or hunger pangs due to lack of food

[d] Not having a fixed and regular nighttime residence

[e] Total household income below federal poverty line or personal annual income < $10,000

Table 3 Mixed effects model of CD4, albumin, and viral load over time (months) as predicted by SES

Dependent variable (strong predictor of mortality)	Independent variable (SES measure)	Parameter estimate	*P*-value
CD4 count (cells/μl)			
Intercept	Baseline Hunger[a]	−89.4	0.01
Slope	College educated[b]	1.04	0.01
Albumin (g/dL)			
Intercept	Baseline Homeless[c]	−0.21	<0.001
	Baseline Poverty[d]	−0.09	0.01
	College educated[b]	0.10	0.01
Slope	–		
Viral Load ($\log_{10}$ copies/ml)			
Intercept	Baseline Hunger[a]	0.22	0.05
Slope	College educated[b]	0.005	0.01

[a] Going without food due to lack of money, plus weight loss and/or hunger pangs due to lack of food

[b] Have at least a college education

[c] Not having a fixed and regular nighttime residence

[d] A household below federal poverty line or personal annual income < $10,000

significant evidence that individuals who were hungry at baseline had an HIV viral load with a 0.22 $\log_{10}$ copies/ml higher trajectory, compared to those not hungry, and if college educated there was significant evidence the viral load would decrease at 0.005 $\log_{10}$copies/ml per month compared to those without a college education.

The multivariable Cox regression model that excluded potential mediators (CD4, HIV viral load, albumin)

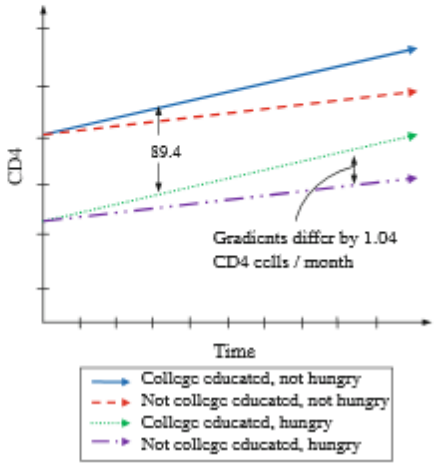


Fig. 1 Schematic representation of differences in trajectory of CD4 over time as predicted by SES measures

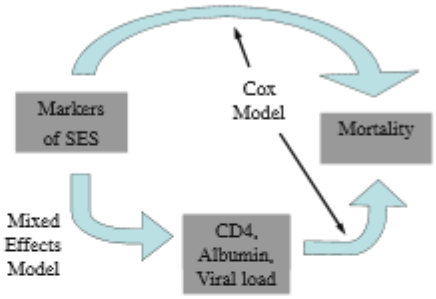


Fig. 2 Model summary—We studied whether SES and other factors directly predicted death via Cox proportional hazards regression. Mixed models were used to see if SES predicted change in the strongest predictors of death from the Cox models (CD4, albumin, and HIV viral load)

selected age (HR 1.05), transmission category (no HR because defined as class variable), poverty (HR 1.6) and hunger (HR 1.7) as predicting mortality, all $P < 0.05$.

A graphical summary of the models used in the analysis is provided in Fig. 2 to illustrate SES directly predicting death, and also having an indirect impact via CD4 counts, albumin, and HIV viral load.

Discussion

This is the first study to examine the relationship between SES and mortality in HIV infected people in the HAART era using individual and repeated measures of SES. We found that SES had a direct impact on mortality in models that accounted for differences in HIV disease parameters and age. Participants who met the US government definition of poverty in the interval before death were found to be 1.5 times as likely to die. As well as this direct effect, markers of SES such as hunger, education, poverty and homelessness have an impact through factors found to be strong predictors of death in this cohort; CD4 counts, albumin, and HIV viral load. Importantly, these three parameters of HIV disease were also reported as predictors of death in other studies of HIV infected subjects [5, 6, 28–30], and are routinely used by clinicians for patient monitoring. The magnitude of the observed effects of SES variables was considerable. CD4 counts were 89 cells lower for individuals with hunger at baseline, and for a subject with a college education at baseline CD4 counts increased by one cell per month or 60 cells in 5 years. Conceivably, individuals with low SES are more likely to incur opportunistic infections or other complications of immunosuppression that accompany lower CD4 counts. We found that poverty and hunger independently predicted mortality in multivariable models without CD4, viral load, and albumin, but hunger dropped out of the model when these HIV parameters were added. Thus, part of the association between SES and mortality is mediated through its relationship with CD4 counts, viral load, and albumin.

Importantly, this is the first study in HIV infected individuals to show that SES is associated with impaired CD4, albumin, and viral load over time. These factors in turn strongly predict death. The findings from this study are consistent with other studies that low SES is associated with increased mortality in HIV infected individuals in the era of HAART [9, 10, 13–17], but differs by applying repeated individual assessments of SES and overcoming acknowledged limitations of ecological assessments [9, 14–16]. This work also extends on data from the pre-HAART era where individual baseline measures of SES predicted clinical outcomes [11, 12], but considers the influence of SES on mortality during an era when clinical outcomes have improved due to HAART [5, 6]. Furthermore, this study is strengthened by having prospectively collected SES measurements allowing us to observe changes in SES over time. This is in comparison to studies using single ecological measures of SES [9, 10, 13–16] such as median personal income derived from neighborhood level census data collected every five [31] or ten [32, 33] years, or single baseline measures of SES [11, 12, 17]. In addition, studies from the HAART era controlled for severity of disease by using single CD4 counts from the time of diagnosis of HIV [13], AIDS [9, 14], when commencing HAART [15, 16] or the lowest known value [17] unlike this study which used multiple CD4 measurements. The other benefit to this method of assessing SES is that clinical and SES measures were obtained repeatedly over time, enabling us to examine whether SES impacted mortality through clinical factors that were found to predict death.

The findings that SES directly predicts mortality while controlling for markers of HIV disease severity, and also

predicts change in CD4 counts, viral load, and albumin over time are plausible. Individuals with low SES can have re-ordered priorities placing less importance on accessing or maintaining medical care, and adequate nutrition in an effort to deal with financial difficulties or unfulfilled food and shelter needs [34]. Their HIV management or nutritional status may subsequently suffer leading to lower CD4 or albumin, or higher viral load measurements, all three of which are known markers of disease progression and mortality in people with HIV infection [6, 29, 30, 35, 36]. Albumin is also considered a marker of chronic illness and nutritional status [37]. Interestingly, markers of low SES such as poverty were found to predict mortality with greater statistical significance than use of HAART in unadjusted and adjusted analyses. This could be explained by individuals with low SES not accessing HIV care, or even if on HAART not being able to regularly maintain therapy, contributing to increased mortality from HIV associated conditions. Additionally, associations between low SES, mental illness and drug use [38] may lead to increased non-HIV related mortality, regardless of HAART use.

Along with the associations reported in this study of HIV positive subjects, seroprevalence studies conducted in North America have shown higher rates of HIV infection in areas of low SES [39–41]. A North American HIV epidemic more focused in areas of low SES is particularly concerning when combined with findings from this and other studies that SES predicts mortality in HIV positive patients. Additionally these findings may go some way to explaining the unexpected mortality still evident in people infected with HIV who are on effective HAART therapy [42, 43]. Thus, interventions aimed at improving SES could have a considerable impact on improving mortality in people infected with HIV. These interventions may take the form of food or transportation vouchers for individuals who fit criteria for markers of low SES such as poverty, employing social workers or case managers to assist patients in obtaining available government subsidies or support to maintain medical and social service appointments. Other strategies to alleviate poor outcomes of low SES include shelter based interventions for those without permanent housing, and harm reduction strategies for individuals taking part in unsafe sex or drug use practices.

A limitation of this study is that it may not be generalizable to all settings due to regional and national differences in the epidemiology of HIV and the way which health care is provided. It should be noted, however, that government funding was available for HIV positive persons in Massachusetts and Rhode Island during the course of the study who did not have medical insurance to receive medical care, ART and other services throughout the duration of the study [44]. Despite this financial support, individuals with low SES may still have difficulty accessing care in this setting or settings of universal health care [45]. Also, we did not use a cause specific mortality measure which may have better explained factors influencing death in different sub-groups. That said, all cause mortality is an accepted outcome measure in a range of clinical fields [46], including HIV clinical research [47], and is not affected by bias associated with incorrect assignment of the cause of death [46, 48]. Another possible limitation is that of recall bias to establish total household income for the poverty covariate in this study, although any misclassification from this self report technique is likely to be considerably less compared with other ecological measures of household income such as neighborhood level census derived income data.

Conclusions

Our data suggest that HIV infected individuals with attributes of low SES are more likely to have increased mortality than those who are not living under these adverse conditions. Our data also indicate that SES factors increase the risk of death through adverse effects on other strong predictors of mortality such as CD4 counts, albumin, and HIV viral load. Despite HAART therapy, HIV infected individuals who are poor, homeless, hungry, or have less education, continue to have a higher risk of death. These findings highlight the importance of being aware of and addressing these issues in our patients as we work to maximize chronic HIV care.

Acknowledgments We wish to thank the participants and investigators of the Nutrition for Healthy Living cohort for their time and enthusiasm.

References

1. Huisman M, Kunst AE, Bopp M, Borgan JK, Borrell C, Costa G, et al. Educational inequalities in cause-specific mortality in middle-aged and older men and women in eight western European populations. Lancet. 2005;365(9458):493–500.
2. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. N Engl J Med. 2002;347(20):1585–92.
3. Pappas G, Queen S, Hadden W, Fisher G. The increasing disparity in mortality between socioeconomic groups in the United States, 1960 and 1986. N Engl J Med. 1993;329(2):103–9.
4. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less AIDS Clinical Trials Group 320 Study Team. N Engl J Med. 1997;337(11):725–33.
5. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality

among patients with advanced human immunodeficiency virus infection HIV outpatient study investigators. N Engl J Med. 1998;338(13):853–60.
6. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003; 362(9377):22–9.
7. Chaisson RE, Keruly JC, Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. N Engl J Med. 1995;333(12):751–6.
8. Katz MH, Hsu L, Lingo M, Woelffer G, Schwarcz SK. Impact of socioeconomic status on survival with AIDS. Am J Epidemiol. 1998;148(3):282–91.
9. Rapiti E, Porta D, Forastiere F, Fusco D, Perucci CA. Socioeconomic status and survival of persons with AIDS before and after the introduction of highly active antiretroviral therapy Lazio AIDS Surveillance Collaborative Group. Epidemiol Cambridge Mass. 2000;11(5):496–501.
10. Fordyce EJ, Singh TP, Nash D, Gallagher B, Forlenza S. Survival rates in NYC in the era of combination ART. J Acquir Immune Defic Syndr. 2002;30(1):111–8. (May 1).
11. Hogg RS, Strathdee SA, Craib KJ, O'Shaughnessy MV, Montaner JS, Schechter MT. Lower socioeconomic status and shorter survival following HIV infection. Lancet. 1994;344(8930): 1120–4.
12. Schechter MT, Hogg RS, Aylward B, Craib KJ, Le TN, Montaner JS. Higher socioeconomic status is associated with slower progression of HIV infection independent of access to health care. J Clin Epidemiol. 1994;47(1):59–67.
13. McDavid Harrison K, Ling Q, Song R, Hall HI. County-level socioeconomic status and survival after HIV diagnosis, United States. Ann Epidemiol. 2008;18(12):919–27.
14. McFarland W, Chen S, Hsu L, Schwarcz S, Katz M. Low socioeconomic status is associated with a higher rate of death in the era of highly active antiretroviral therapy, San Francisco. J Acquir Immune Defic Syndr. 2003;33(1):96–103. (May 1).
15. Wood E, Montaner JS, Chan K, Tyndall MW, Schechter MT, Bangsberg D, et al. Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996. AIDS. 2002;16(15): 2065–72. (Oct 18).
16. Joy R, Druyts EF, Brandson EK, Lima VD, Rustad CA, Zhang W, et al. Impact of neighborhood-level socioeconomic status on HIV disease progression in a universal health care setting. J Acquir Immune Defic Syndr. 2008;47(4):500–5. (Apr 1).
17. Cunningham WE, Hays RD, Duan N, Andersen R, Nakazono TT, Bozzette SA, et al. The effect of socioeconomic status on the survival of people receiving care for HIV infection in the United States. J Health Care Poor Underserved. 2005;16(4):655–76.
18. Forrester JE, Spiegelman D, Woods M, Knox TA, Fauntleroy JM, Gorbach SL. Weight and body composition in a cohort of HIV-positive men and women. Public Health Nutr. 2001;4(3):743–7.
19. Knox TA, Spiegelman D, Skinner SC, Gorbach S. Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. Am J Gastroenterol. 2000;95(12): 3482–9.
20. Poverty Thresholds since 1980. United States Census Bureau; 2009 [June 2 2009]; Available from: http://www.census.gov/hhes/www/poverty/threshld.html.
21. General definition of homeless individual. 42 USC Sec. 11302 Office of the Law Revision Counsel, U.S. House of Representatives; 2007 [June 4 2009]; Available from: http://uscode.house.gov/uscode-cgi/fastweb.exe?getdoc+uscview+t41t42+7022+23++(11302).
22. Radimer KL, Olson CM, Campbell CC. Development of indicators to assess hunger. J Nutr. 1990;120(Suppl 11):1544–8.
23. Kendall A, Olson CM, Frongillo EA Jr. Validation of the Radimer/Cornell measures of hunger and food insecurity. J Nutr. 1995;125(11):2793–801.
24. Burnam MA, Wells KB, Leake B, Landsverk J. Development of a brief screening instrument for detecting depressive disorders. Med Care. 1988;26(8):775–89.
25. Who is currently living with HIV/AIDS?—Detailed data tables and technical notes: Office of HIV/AIDS, Massachussetts Department of Public Health November 2007.
26. Massachusetts HIV/AIDS Data Fact Sheet. Who is most at risk of HIV infection?: Office of HIV/AIDS, Massachussetts Department of Public Health November 2007.
27. 2007 Rhode Island HIV/AIDS Epidemiologic Profile With Surrogate Data: Rhode Island Department of Health. Division of Community Family Health and Equity. Office of HIV/AIDS & Viral Hepatitis August 2008.
28. Anastos K, Kalish LA, Hessol N, Weiser B, Melnick S, Burns D, et al. The relative value of CD4 cell count and quantitative HIV-1 RNA in predicting survival in HIV-1-infected women: results of the women's interagency HIV study. AIDS. 1999;13(13): 1717–26.
29. Feldman JG, Gange SJ, Bacchetti P, Cohen M, Young M, Squires KE, et al. Serum albumin is a powerful predictor of survival among HIV-1-infected women. J Acquir Immune Defic Syndr. 2003;33(1):66–73. (May 1).
30. Lyles RH, Munoz A, Yamashita TE, Bazmi H, Detels R, Rinaldo CR, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men Multicenter AIDS Cohort Study. J Infect Dis. 2000;181(3):872–80.
31. Overview of the Census of Population: A brief history. Statistics Canada; 2009 [June 11 2009]; Available from: http://www12.statcan.ca/english/census06/reference/dictionary/ovpop1b.cfm#dece.
32. What is the Census? : United States Census Bureau; 2009 [June 11 2009]; Available from: http://2010.census.gov/2010census/.
33. Data banks and information systems. Roma: Istat - Istituto nazionale di statistica; 2009 [June 11 2009]; Available from: http://www.istat.it/english/databanks.html.
34. Riley ED, Gandhi M, Hare C, Cohen J, Hwang S. Poverty, unstable housing, and HIV infection among women living in the United States. Current HIV/AIDS reports. 2007;4(4):181–6.
35. Mehta SH, Astemborski J, Sterling TR, Thomas DL, Vlahov D. Serum albumin as a prognostic indicator for HIV disease progression. AIDS Res Hum Retroviruses. 2006;22(1):14–21.
36. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997;126(12):946–54.
37. Mason JB. Nutritional Assessment and Management of the Malnourished Patient,Eighth ed. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. W B Saunders Company; 2006.
38. Klinkenberg WD, Sacks S. Mental disorders and drug abuse in persons living with HIV/AIDS. AIDS care. 2004;16(Suppl 1): S22–42.
39. Diaz T, Chu SY, Buehler JW, Boyd D, Checko PJ, Conti L, et al. Socioeconomic differences among people with AIDS: results from a Multistate Surveillance Project. Am J Prev Med. 1994;10(4): 217–22.
40. Hankins C, Tran T, Hum L, Laberge C, Lapointe N, Lepine D, et al. Socioeconomic geographical links to human immunodeficiency virus seroprevalence among childbearing women in Montreal, 1989–1993. Int J Epidemiol. 1998;27(4):691–7.

41. Zierler S, Krieger N, Tang Y, Coady W, Siegfried E, DeMaria A, et al. Economic deprivation and AIDS incidence in Massachusetts. Am J Public Health. 2000;90(7):1064–73.
42. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4 + count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355(22):2283–96.
43. Emery S, Neuhaus JA, Phillips AN, Babiker A, Cohen CJ, Gatell JM, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. J Infect Dis. 2008;197(8):1133–44.
44. The Ryan White HIV/AIDS Program. U.S. Department of Health and Human Services. Health Resources and Services Administration; 2009 [June 12 2009]; Available from: http://hab.hrsa.gov/about/.
45. Strathdee SA, Palepu A, Cornelisse PG, Yip B, O'Shaughnessy MV, Montaner JS, et al. Barriers to use of free antiretroviral therapy in injection drug users. Jama. 1998;280(6):547–9.
46. Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. J Natl Cancer Inst. 2002;94(3):167–73.
47. Keiser O, Taffe P, Zwahlen M, Battegay M, Bernasconi E, Weber R, et al. All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population. AIDS. 2004;18(13):1835–43.
48. Fox CS, Evans JC, Larson MG, Lloyd-Jones DM, O'Donnell CJ, Sorlie PD, et al. A comparison of death certificate out-of-hospital coronary heart disease death with physician-adjudicated sudden cardiac death. Am J Cardiol. 2005;95(7):856–9.

5 Repeated assessments of food security predict CD4 change in the setting of antiretroviral therapy

5.1 Declaration

Declaration for Thesis Chapter 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I led the design based on a pre-existing dataset, performed all analyses and wrote the manuscript	80

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors**
Christine A. Wanke	Helped conceive the idea for the analysis, prepare an analytic plan and develop the manuscript.	7.5
Julian H. Elliott	Contributed to interpreting the results and develop the manuscript	2.5
Sally Skinner	Assisted with accessing data from the pre-existing dataset, formulating statistical code for the analyses and develop the manuscript	2.5
Alice Tang	Helped conceive the idea for the analysis, prepare an analytic plan and develop the manuscript.	7.5

Candidate's Signature	[redacted]	**Date 16 APR 2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**Tufts University School of Medicine, Department of Public Health and Community Medicine, Boston**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	CAW [redacted]	**Date** 14/4/2013
Signature 2	JHE [redacted]	16/4/2013
Signature 3	SS [redacted]	6/4/2013
Signature 4	AT [redacted]	7/4/2013

5.2 Introduction

The previous chapter reported how different social factors in multivariable models that accounted for the use of ART predicted survival. Specifically assessments of poverty predicted survival directly and there were indirect effects for education, hunger, homelessness and poverty impacting survival via their effects on CD4 T-cell counts, HIV viral load and serum albumin, biomarkers that independently predicted all cause survival (120). This work demonstrates how multiple individual assessments of SES can be independently associated with all-cause mortality; however, all-cause mortality lacks some detail in regard the impact of social and behavioural factors that influence HIV specific clinical outcomes. As a result the next study changed focus to perform a more in-depth analysis of an individual marker of low SES and a HIV specific clinical outcome.

The concept of food insecurity and methods to define it started in the early 1990s out of difficulty in being able to reliably assess hunger. Definitions and measurement of hunger were varied and lacked agreement leading to a situation where hunger was variably defined and considered a rare event (121). This lead to work to define and reliably measure a concept based on the ability to consistently obtain a nutritionally adequate diet in a socially acceptable manner, referred to as food security (121, 122). This concept has been reliably applied to the general population (123) and also specific groups of people such as PLHIV and most commonly assessed using the Radimer/Cornell scale (121, 122). Importantly, assessments of food security for populations living with HIV in North America reveal much higher prevalence of food insecurity than general populations with approximately 10% of the general population being considered food insecure compared to approximately half of PLHIV (61, 62, 64). It is unclear whether additional risk for poor health outcomes for people who are food insecure is conferred by a biological mechanism related to poor diet or whether food security is merely a surrogate for the adverse health outcomes caused by low SES.

One of the primary aims of establishing the NFHL cohort was to study the effects of nutritional status on the outcomes of HIV infection as the era of combination ART began in the mid-1990s. Critical to this undertaking was establishing accurate measures of access to reliable and nutritionally adequate supplies of food, namely

individual food security. Therefore the NFHL cohort had repeated and validated assessments of food security status for enrolled individuals. In addition reliable biomarker data reflecting response to HIV care was also available allowing for an analysis focussing on how repeated assessments of food security predict clinical response for PLHIV in the era of combination ART. In addition analyses involving repeated measures of food security were not available in the published literature for PLHIV and the only assessments studying immunological response were cross-sectional or at ART baseline (62, 63, 65). Therefore we sought to examine how CD4 T-cell counts changed over time in the setting of repeated assessments of food security in the era of combination ART.

The combination of the highly prevalent nature of food insecurity for PLHIV, the potential for it to adversely clinical outcomes and the opportunity to incorporate repeated measures of food security for the first time for PLHIV provided the rationale to undertake this analysis.

5.3 Paper

Repeated Assessments of Food Security Predict CD4 Change in the Setting of Antiretroviral Therapy

James H. McMahon, MBBS, MPH,† Christine A. Wanke, MD,† Julian H. Elliott, MBBS, PhD,*‡§ Sally Skinner, MA,† and Alice M. Tang, PhD†*

Abstract: Food insecurity is highly prevalent in HIV-infected populations, and analyses utilizing multiple assessments of food security to predict CD4 change are lacking. Five hundred Ninety-two patients with ≥ 4 food security assessments were followed prospectively. In the final model, for patients using antiretroviral therapy, increases in CD4 counts were on average 99.5 cells less for individuals with at least 1 episode of food insecurity compared with those consistently food secure ($P < 0.001$). Other sociodemographic factors were not predictive. Repeated assessments of food security are potent predictors of treatment response notwithstanding antiretroviral therapy use. Potential mechanisms for this association are proposed.

Key Words: antiretroviral therapy, food security, immunological response

(*J Acquir Immune Defic Syndr* 2011;58:60–63)

BACKGROUND

In 1990, an expert panel of the American Institute of Nutrition defined food insecurity as "existing whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain."[1] North American surveys of the general population report a 9%–11% prevalence of food insecurity.[2] In contrast, HIV-infected populations consistently report food insecurity at higher rates as follows: Atlanta 52%,[3] San Francisco 49%,[4] and, 48% and 71% in 2 Canadian surveys.[5,6]

Characteristics of HIV-infected patients associated with food insecurity include poverty, other markers of low socioeconomic status (SES), intravenous drug use (IDU), and depression.[4–7] Within the same cohort of HIV-infected subjects as our present study, the Nutrition for Healthy Living (NFHL) cohort, food insecure men were more likely to have a diet characterized by more fast food and less fruits and vegetables.[8] Additionally, food insecurity has been associated with worse outcomes on antiretroviral therapy, including worse adherence, incomplete virological suppression, and lower survival.[3,4,9] Associations with immunological responses have only been reported cross-sectionally, and analyses involving repeated measure of food security are not reported.[3,6,9] We examined the ability of multiple measures of food security to predict CD4 T-cell response in the NFHL cohort.

METHODS

We examined NFHL participants enrolled from 1995 to 2005 who completed 4 or more study visits. This prospective cohort investigated the causes and consequences of nutritional and metabolic abnormalities on HIV-infected adults in the Boston and Providence area. Individuals were excluded if they were pregnant, diabetic, or suffering from thyroid disease or cancer. Biannual study visits obtained information on clinical status, drug use, SES, and highly active antiretroviral therapy (HAART) use. $CD4^+$ T cells were counted using flow cytometry, and HIV RNA was measured by the Amplicor Monitor reverse transcriptase—polymerase chain reaction assay (Roche Molecular Systems) with a lower detection limit of 2.6 $\log_{10}$ copies per milliliter (400 copies/mL). Further details on data collection and subject selection have been previously reported.[10,11]

Food Security was defined using the adult individual food security scale questions originally derived by Radimer et al[12] but later modified by Kendall et al.[13] This scale included 3 questions "I eat less than I think I should because I don't have enough money for food", "I can't afford to eat properly", and "I am often hungry, but I don't eat because I also can't afford enough for food". The fourth question "I eat the same thing for several days in a row because I don't have enough money to buy different things" was adapted by Kendall et al[13] from the qualitative component of the adult household food security scale.[13] Subjects answering "Often true" or "Sometimes true" to any question were food insecure for that visit. For the dichotomous variable in this analysis, subjects who were insecure on 1 or more visits were defined as food insecure and those secure at every visit were defined as food secure. A trichotomous variable was also created for subjects who were

Received for publication March 28, 2011; accepted June 6, 2011.

From the *Department of Infectious Diseases, Alfred Hospital, Melbourne, Australia; †Department of Public Health and Community Medicine, Nutrition/Infection Unit, Tufts University School of Medicine, Boston, MA; ‡Department of Medicine, Monash University; and §Burnet Institute, Melbourne, Australia.

Supported by National Institutes of Health (R01 HL 65947, P30DA13868, P30 AI42853, P01 DK45734), National Health and Medical Research Council (Postgraduate Scholarship to J.H.M).

Presented in part as an abstract at the 18th International AIDS Conference, 2010, Vienna, Austria, as "J. McMahon, et al. Associations between history of food security, body mass index and immunological response". Abstract no. CDC0264.

The authors have no conflicts of interest to disclose.

Correspondence to: James McMahon, MBBS, MPH, Infectious Diseases Unit, Alfred Hospital, Level 2 Burnet Tower, 85 Commercial Road, Melbourne, Australia 3004 (e-mail: [redacted]).

always food insecure, partially food insecure (insecure at ≥1 visit but not all visits), and always food secure. Thus, repeated measures of food security were used to create food security variables for this analysis. Poverty was defined as total household income below the annual federal poverty line or personal annual income below $10,000.[14]

Baseline characteristics were compared by food security status. The χ^2, Student t test, and Wilcoxon rank-sum tests were used as appropriate. Univariate and multivariate linear regression was performed for the dependent variable CD4 T-cell change from baseline to last study visit. Independent variables were as follows: age, gender, race (white or non-white), cumulative years of HAART at final study visit, history of IDU up to final study visit, mean body mass index (BMI) over period observed (<20, 20–25, >25 kg/m^2), poverty at final study visit, and food insecurity (one of the variables as previously defined or baseline food insecurity). Variables with $P < 0.2$ in univariate analyses were entered into the multivariate model. Variables not reaching statistical significance ($P < 0.05$) were deleted from the model. A multivariate model excluding participants who never received HAART was performed as a sensitivity analysis. Interaction terms between BMI categories and food security were examined. All analyses were conducted using SAS v9.2 (SAS Institute, Cary, NC).

RESULTS

Table 1 shows baseline characteristics of participants by food security status. The cohort comprised 592 subjects with a mean age of 40.6 ± 7.5 years of whom 70% were male and 29% had a history of IDU. Two hundred seventeen (37%) were chronically food secure, and 375 (63%) were assessed as food insecure on 1 or more occasions. Of the food insecure, 51 (14%) were insecure at every study visit, 137 (37%) at 50% to <100% of visits, and 187 (50%) were insecure at <50% of visits. Food secure individuals had shorter median duration of follow-up [4.4 years (IQR: 2.9–7.4) versus 6.0 years (IQR: 3.3–7.8), $P < 0.01$] and at baseline were less likely to have a history of IDU (14.8% vs. 47.7%, $P < 0.001$) and had lower BMI (25.0 vs. 26.4, $P = 0.01$). Baseline CD4 T-cell counts were not significantly different between groups (311 vs. 342 cells/μL, $P = 0.08$).

Parameter estimates from regression models are presented in Table 2. Cumulative years of HAART was significantly associated with a positive change in CD4 count (41.3 cell greater change/additional year of HAART), whereas history of IDU, not being white, poverty, and food insecurity predicted negative changes in CD4 over the period observed. In the multivariate model using the dichotomous food insecurity, variable cumulative HAART use remained a potent predictor of CD4 change (40.3 cell greater change/additional year of HAART, $P < 0.001$) with the only additional covariate remaining in the model being food insecurity (99.5 cell less change over the period observed, $P < 0.001$). On the basis of this model, a patient who was food secure and received 5 years of HAART would expect a $[-8.04 + (40.36 \times 5)] = 194$ CD4 cell increase, but if food insecure, only a $[-8.04 + (40.36 \times 5) - 99.52] = 94$ CD4 cell increase. In an alternative multivariate model where food security is trichotomized, those who were partially and always insecure had similar parameter estimates for CD4 change (110.2, $P < 0.001$, and 95.1, $P = 0.03$, cells less change, respectively). Additionally, baseline food security was not predictive of CD4 change in multivariate models. In a sensitivity analysis excluding 67 individuals who did not

TABLE 1. Baseline Characteristics

	Food Secure, 217 (36.7)*	Food Insecure, 375 (63.3)†	Total, 592	P‡
Mean age in years	41.7 ± 8.4	39.9 ± 6.8	40.6 ± 7.5	0.006
Gender				<0.001
Female	40 (18.4)	136 (36.3)	176 (29.7)	
Male	177 (81.6)	239 (63.7)	416 (70.3)	
Race				<0.001
White	169 (77.9)	164 (43.7)	333 (56.3)	
Non white	48 (22.1)	211 (56.3)	259 (43.8)	
IDU				<0.001
Active or past IDU	32 (14.8)	179 (47.7)	211 (35.6)	
Never IDU	185 (85.3)	196 (52.3)	381 (64.4)	
HAART				0.08
On HAART	112 (55.2)	163 (47.7)	275 (50.5)	
Not on HAART	91 (44.8)	179 (52.3)	270 (49.5)	
BMI, kg/m^2	25.0 ± 4.1	26.4 ± 5.5	25.9 ± 5.1	<0.001
CD4, counts/mL	311 (176–484)	342 (189–568)	332 (182–533)	0.08
Log_{10} HIV viral load, copies/mL	3.4 (ND§–4.4)	3.5 (ND§–4.5)	3.4 (ND§–4.5)	0.38

Sample size varied based on missing data but no more than 2% data missing, except for HAART use (n = 545) and viral load (n = 555).
Values represent n (% with that characteristic), median (Q1–Q3), or mean ± SD.
*Food secure at all study visits.
†Food insecure at 1 or more study visits.
‡P values $\chi 2$ (categorical), Student t test (continuous normal distribution), Wilcoxon rank sum test (continuous nonnormal distribution).
§Lower limit of detection 2.6 log_{10} (400) copies per milliliter.
ND, not detectable.

TABLE 2. Single and Multiple Linear Regression for CD4 T Cell Change From Baseline to Final Study Visit

	Univariate Model Parameter Estimate	*P*	Multivariate Model 1 Parameter Estimate*	*P*	Multivariate Model 2 Parameter Estimate†	*P*
Intercept			−8.04		−8.13	
Age—increase by 1 year	2.73	0.09	—	—	—	—
Cumulative years of HAART—increase by 1 year	41.34	<0.001	40.36	<0.001	40.38	<0.001
Active or past IDU	−101.02	<0.001	—	—	—	—
Gender (being female)	−41.98	0.14	—	—	—	—
Race (not being white)	−60.47	0.02	—	—	—	—
Poverty at final visit‡	−90.77	<0.001	—	—	—	—
Mean BMI > 25§	Ref		—	—	—	—
Mean BMI 20–25	11.57	0.65	—	—	—	—
Mean BMI < 20	−82.33	0.16	—	—	—	—
Food insecure‖	−111.84	<0.001	−99.52	<0.001		
Food secure¶	Ref				Ref	
Partially food insecure#	−121.16	<0.001			−100.18	<0.001
Always food insecure**	−110.45	0.01			−95.07	0.03

*Dichotomous definition of food security.
†Alternative model using a trichotomous definition of food security.
‡Total household income below federal poverty line or personal annual income < $10,000.
§Body mass index average over all study visits in kg/m^2.
‖Food insecure at 1 or more study visits.
¶Food secure at all study visits.
#Food insecure at 1 or more, but not all, study visits.
**Food insecure at all study visits.

receive HAART, the multivariate model contained both cumulative HAART (31.5 cell greater change/additional year of HAART, $P < 0.001$), food insecurity (76.4 cell less change over the period observed, $P = 0.004$), and history of IDU (64.8 cell less change over the period observed, $P = 0.02$). There was no evidence of interaction between BMI categories and food security in multivariate models.

DISCUSSION

This is the first study to describe the predictive ability of food insecurity on changes in CD4 counts over time in an HIV-infected population and the first study to document clinical outcomes with repeated measures of food security. These observations persist while controlling for duration of HAART use and SES variables (poverty, race, and IDU) that have been previously studied within this and other observational cohorts.[15–17]

First, this study demonstrates an astonishing rate of food insecurity in this HIV-infected cohort, the composition of which reflects the epidemic as it currently exists. Further, this study reveals multiple baseline characteristics associated with food insecurity, not all of which are consistent with previous reports. HAART, CD4, and HIV viral load at baseline were not significantly associated with food insecurity, in contrast to a history of IDU, being female and non-white, which were all significantly more prevalent in the food insecure. Similar associations between food security status and IDU or gender have been reported in a Canadian cohort[5,6] but not elsewhere for HIV-infected individuals.[3,7] Baseline BMI was higher in this study for food insecure subjects, a finding not replicated in HIV-infected populations but reported in non–HIV-infected subjects.[18,19] The finding of elevated BMI is consistent with prior data from this cohort where food insecure individuals consumed more fast food than the food secure.[8]

Not surprisingly, cumulative years of HAART strongly predicted CD4 response in univariate and multivariate regression models. The parameter estimate of a roughly 40 cell increase in CD4 count per year of HAART is consistent with other large observational cohorts over similar periods of follow-up.[20–22] Importantly, individuals meeting criteria for food insecurity as defined here could have a 100 CD4 T-cell count deficit even in the setting of HAART. Therefore, it is plausible that food insecure individuals are at increased risk for opportunistic infections and other complications of lower CD4. Furthermore, the finding that partially and chronically insecure individuals have a similar negative impact on CD4 response suggests that repeated assessments of food security status to detect even a single assessment of insecurity could be important to identify individuals at risk for poor immunological outcomes. The finding of high levels of food insecurity in this and other HIV-infected cohorts combined with the deleterious impact on immunological outcomes may explain why some individuals experience more HIV-related complications and increased mortality despite HAART.[23] It is also noteworthy that using baseline food security status alone was not predictive of CD4 change, suggesting that regular assessments of food security status are more accurate to detect individuals at risk for poor treatment outcomes. Using the CD4 change outcome not only allows us to examine how food security predicts treatment response over time, but also to account for potential differences in baseline CD4 previously reported in cross-sectional analyses.[3,5–7] In contrast to previous data, baseline CD4 in this cohort did not differ by food security status, with only a trend ($P = 0.08$) toward higher baseline CD4 in the food insecure. Reasons for this trend are unclear but

could reflect a longer duration of infection for individuals infected earlier in the course of the US epidemic, such as men who have sex with men.

The mechanism by which these associations are mediated is unclear, but several possibilities exist. Food insecurity may be a marker of poor access to care, potentially leading to inadequate therapy and subsequent poor immunological response. Food insecurity may also be associated with the presence of sociobehavioral issues such as depression, high risk sexual behavior, drug use, and recent incarceration,[6,7,24] which may manifest as poor adherence[3,4,9] leading to lower CD4. Notably, food insecurity has been linked with poor adherence due to fear of antiretroviral toxicity in the absence of food and the competing demands between food and resources to obtain health care.[3,7] Finally, food insecurity may influence nutritional quality. As previously mentioned, food insecure participants consumed more fast foods and less fruit and vegetables.[8] Micronutrient deficiencies have been associated with lower CD4,[25] whereas multivitamin supplementation has been reported to improve immunological responses.[26] Thus, poor quality diet could conceivably impact CD4 response via micronutrient deficiencies. Last, a combination of both social and nutritional issues may underlie the mechanism of this association.

This study had several strengths and limitations. Food security status was assessed at every study visit, but to be insecure for this analysis, subjects had to complete at least 4 study visits and be insecure on 1 or more occasions. This definition of food security status was a robust predictor of CD4 change implying that chronically food secure individuals are a distinct population for improved treatment response compared with those with one or more episodes of food insecurity over multiple years. In addition, controlling for HAART and factors associated with low SES allows us to draw additional inference about food security as an independent predictor of treatment outcomes. A limitation of this study is that it may not be generalizable to all settings due to regional differences in HIV epidemiology. However, government funding was available for HIV-infected patients to receive medical care and antiretroviral therapy throughout the study.[27]

In summary, food insecurity is a potent predictor of poor immunological response even in the setting of HAART. Regular assessments to identify food insecure individuals and interventions to alleviate food insecurity could prove valuable to improve immunological outcomes for a large number of individuals living with HIV.

ACKNOWLEDGMENTS

We wish to thank the participants and investigators of the NFHL cohort.

REFERENCES

1. Anderson S, ed. Core indicators of nutritional state for difficult-to-sample populations. *J Nutr*. 1990;120(suppl 11):1559–1600.
2. Anema A, Vogenthaler N, Frongillo EA, et al. Food insecurity and HIV/AIDS: current knowledge, gaps, and research priorities. *Curr HIV/AIDS Rep*. 2009;6:224–231.
3. Kalichman SC, Cherry C, Amaral C, et al. Health and treatment implications of food insufficiency among people living with HIV/AIDS, Atlanta, Georgia. *J Urban Health*. 2010;87:631–641.
4. Weiser SD, Frongillo EA, Ragland K, et al. Food insecurity is associated with incomplete HIV RNA suppression among homeless and marginally housed HIV-infected individuals in San Francisco. *J Gen Intern Med*. 2008;24:14–20.
5. Normen L, Chan K, Braitstein P, et al. Food insecurity and hunger are prevalent among HIV-positive individuals in British Columbia, Canada. *J Nutr*. 2005;135:820–825.
6. Anema A, Weiser SD, Fernandes KA, et al. High prevalence of food insecurity among HIV-infected individuals receiving HAART in a resource-rich setting. *AIDS Care*. 2011;23:221–230.
7. Weiser SD, Bangsberg DR, Kegeles S, et al. Food insecurity among homeless and marginally housed individuals living with HIV/AIDS in San Francisco. *AIDS Behav*. 2009;13:841–848.
8. Hendricks KM, Mwamburi DM, Newby PK, et al. Dietary patterns and health and nutrition outcomes in men living with HIV infection. *Am J Clin Nutr*. 2008;88:1584–1592.
9. Weiser SD, Fernandes KA, Brandson EK, et al. The association between food insecurity and mortality among HIV-infected individuals on HAART. *J Acquir Immune Defic Syndr*. 2009;52:342–349.
10. Forrester JE, Spiegelman D, Woods M, et al. Weight and body composition in a cohort of HIV-positive men and women. *Public Health Nutr*. 2001;4:743–747.
11. Knox TA, Spiegelman D, Skinner SC, et al. Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. *Am J Gastroenterol*. 2000;95:3482–3489.
12. Radimer KL, Olson CM, Campbell CC. Development of indicators to assess hunger. *J Nutr*. 1990;120(suppl 11):1544–1548.
13. Kendall A, Olson CM, Frongillo EA Jr. Validation of the Radimer/Cornell measures of hunger and food insecurity. *J Nutr*. 1995;125:2793–2801.
14. United States Census Bureau. How the Census Bureau measures poverty. 2011; Available at: http://www.census.gov/hhes/www/poverty/threshld.html. Accessed February 23, 2011.
15. Joy R, Druyts EF, Brandson EK, et al. Impact of neighborhood-level socioeconomic status on HIV disease progression in a universal health care setting. *J Acquir Immune Defic Syndr*. 2008;47:500–505.
16. McFarland W, Chen S, Hsu L, et al. Low socioeconomic status is associated with a higher rate of death in the era of highly active antiretroviral therapy, San Francisco. *J Acquir Immune Defic Syndr*. 2003;33:96–103.
17. McMahon J, Wanke C, Terrin N, et al. Poverty, hunger, education, and residential status impact survival in HIV. *AIDS Behav*. 2011; [Epub ahead of print. doi:10.1007/s10461-010-9759-z].
18. Adams EJ, Grummer-Strawn L, Chavez G. Food insecurity is associated with increased risk of obesity in California women. *J Nutr*. 2003;133:1070–1074.
19. Larson NI, Story MT. Food insecurity and weight status among U.S. children and families: a review of the literature. *Am J Prev Med*. 2011;40:166–173.
20. Lifson AR, Krantz EM, Eberly LE, et al. Long-term CD4$^+$ lymphocyte response following HAART initiation in a U.S. Military prospective cohort. *AIDS Res Ther*. 2011;8:2.
21. Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4$^+$ T-cell counts during combination antiretroviral therapy for HIV-1 infection. *AIDS*. 2010;24:1867–1876.
22. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22–29.
23. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4$^+$ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355:2283–2296.
24. Shannon K, Kerr T, Zhang R, et al. Hunger and food insufficiency are independently correlated with unprotected sex among HIV+ injection drug users both on and not on HAART. Abstract no. WEPDC101. Presented at: 5th IAS Conference on HIV Pathogenesis and Treatment; July 19–22, 2009; Cape Town, South Africa.
25. Semba RD, Tang AM. Micronutrients and the pathogenesis of human immunodeficiency virus infection. *Br J Nutr*. 1999;81:181–189.
26. Fawzi WW, Msamanga GI, Spiegelman D, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med*. 2004;351:23–32.
27. United States Department of Health and Human Services. The Ryan White HIV/AIDS Program. 2009; Available at: http://hab.hrsa.gov/about/. Accessed February 28, 2011.

6 Targets for intervention to improve virological outcomes for patients receiving free antiretroviral therapy in Tamil Nadu, India.

6.1 Declaration

Declaration for Thesis Chapter 6

Declaration by candidate

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript	70

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors**
Anand Manoharan	Helped design the study, write the study protocol, interpret the results, oversee all study procedures at the study site and develop the manuscript	5
Christine A. Wanke	Helped conceive the analysis, interpret the study results and develop the manuscript.	5
Shoba Mammen	Established procedures for the performance of viral load tests, interpret viral load data and develop the manuscript	2
Hepsibah Jose	Helped recruit and conduct interviews for study participants and develop the manuscript.	2

Thabeetha Malini	Helped recruit and conduct interviews for study participants and develop the manuscript.	2
Tony Kadavanu	Helped recruit and conduct interviews for study participants and develop the manuscript.	2
Michael R. Jordan	Helped design the study, conceive the analysis, interpret the study results and develop the manuscript	3
Julian H. Elliott	Helped design the study, conceive the analysis, interpret the study results and develop the manuscript	2
Sharon R. Lewin	Helped conceive the analysis, interpret the study results and develop the manuscript.	2
Dilip Mathai	Helped design the study, write the study protocol, interpret the results, oversee all study procedures at the study site and develop the manuscript	5

Candidate's Signature	[redacted]	**Date** **16 APR 2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**Christian Medical College Department of Medicine, Vellore**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	AM [redacted]	**Date** 8/4/2013
Signature 2	CAW [redacted]	14/4/2013
Signature 3	SM [redacted]	8/4/2013
Signature 4	H [redacted]	15/04/2013
Signature 5	T [redacted]	15/04/2013
Signature 6	TK [redacted]	15/04/2013
Signature 7	MRJ [redacted]	10/4/2013
Signature 8	JHE [redacted]	16/4/2013
Signature 9	SRL [redacted]	16/4/2013
Signature 10	DM [redacted]	8/4/2013

To Whom It May Concern – Professor Stephen Jane is signing as Head of Central Clinical School where attempts to contact co-authors multiple times failed. These were - Hepsibah Jose (HJ), Thabeetha Malini(TM), Tony Kadavanu (TK)

Signed: [redacted]

Date: 15/04/2013

Professor Stephen Jane

Head of Central Clinical School

6.2 Introduction

After work that examined different markers of SES that predict clinical outcomes for PLHIV in a high-income setting HICs this thesis now turns to LMICs and the public health model of care Tamil Nadu, India. Since the advent of combination ART in HICs in 1996 there has been increasing urgency to provide this life saving therapy in LMICs that endure a disproportionately high burden of the HIV pandemic. The widespread scale-up of ART in LMICs commenced in 2003 under the auspices of the WHO "3 by 5" initiative with an aim to have 3 million people receiving ART in LMICs by the year 2005. By 2005 the availability of ART was becoming a reality with over 1.3 million people in recept of these medications (72). The scale up of ART provision in LMICs continues to this day with over 8 million individuals receiving ART in LMICs as of the end of 2011 (1). In addition to procurement of generic antiretrovirals at reduced cost, ART care in LMICs is typically provided via a public health model of care to maximize the impact of available resources. The public health model of care uses standardized triple drug ART regimens: generally one or two potential first-line regimens with the potential for within class drug substitutions. Furthermore individual patient's success with therapy is assessed following pre-determined national protocols which include monitoring for treatment failure based on clinical findings (change in WHO clinical staging criteria) and CD4 cell counts.

These fundamentally different approaches to the delivery of ART combined with differences in social and clinical settings present in LMICs means that research specific to LMICs is essential to optimise outcomes for PLHIV in these settings. India represents the country with the highest burden of HIV within Asia and is an example of where ART services are provided in the public health model. This free government funded ART has been available via the National AIDS Control Organization since 2004 and rapid scale-up has occurred throughout the country to the point where over 480,000 people are alive and receiving ART (76). HIV is prevalent to a varying extent depending on the region of the country with Tamil Nadu being one of the 6 high prevalence states within India with a prevalence of 0.36% and an epidemic largely characterised by heterosexual transmission. In addition viral load monitoring of ART is not routine as per NACO treatment guidelines and data reporting social and behavioural factors associated with virological suppression are limited (78).

Distinctly different social, cultural and behavioural factors will exist in many LMICs where ART is provided in the public health model and the focus of the following studies is the NACO funded clinic at Christian Medical College in Vellore, Tamil Nadu. The site is one of many public-private clinics in India where non-government organisations collaborate with NACO to provide free ART services according to NACO guidelines. While clinical care is in accordance with NACO guidelines which are also used at purely government sites there is the potential for findings in public-private sites to be less generalizable to government sites. However, due to the consistent use of NACO guidelines and free ART in both public-private and public sites compared to the private clinics where patients pay for individualised ART, study findings in this thesis are likely more generalizable to public sites than the private health care system.. Operational research to identify social and clinical factors present in populations receiving ART that predict validated biomarker outcomes such as HIV viral load are required to identify interventions that are necessary to maximise outcomes in these settings. In addition as HIV viral load is not routinely performed as part of government funded ART care in India the virological endpoint represents an opportunity to identify factors predicting poor outcomes that is not available from the analysis of routinely available clinical data. Furthermore the techniques applied in this work are an example of minimum-resource methods that can be replicated in similar settings to improve ART care. Therefore we sought to examine for different clinical and social elements associated with virological outcomes in the public health model of care in southern India with the aim of identifying factors that can be targeted for interventions to improve outcomes for PLHIV in similar settings throughout India.

6.3 Paper

Targets for intervention to improve virological outcomes for patients receiving free antiretroviral therapy in Tamil Nadu, India

James H McMahon[1,2*], Anand Manoharan[3], Christine Wanke[2], Shoba Mammen[4], Hepsibah Jose[3], Thabeetha Malini[3], Tony Kadavanu[3], Michael R Jordan[2], Julian H Elliott[1,5,6], Sharon R Lewin[1,5,6], Dilip Mathai[3]

[1]Infectious Diseases Unit, Alfred Hospital, Melbourne [2]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston [3]Department of Medicine, and [4]Clinical Virology, Christian Medical College, Vellore [5]Department of Infectious Diseases, Monash University, and [6]Burnet Institute, Melbourne

Running Head: Targets for intervention to improve outcomes on ART, Tamil Nadu, India

Keywords: HIV, intervention targets, antiretroviral therapy, India, virological outcomes, adherence

***Corresponding author:**

James McMahon, Infectious Diseases Unit, Alfred Hospital, Level 2 Burnet Tower, 85 Commercial Road, Melbourne, Australia 3004. Ph: [redacted] Fax: [redacted]; email: [redacted]

Co-authors:

Anand Manoharan, Department of Medicine, Christian Medical College, Ida Scudder Rd, Vellore, India. Phone: [redacted] email: [redacted]

Christine Wanke, Department of Public Health and Community Medicine, Tufts University School of Medicine, 136 Harrison Ave, Boston, MA, USA. Phone: [redacted], email: [redacted]

Targets for intervention to improve outcomes on ART, Tamil Nadu, India

Shoba Mammen, Department of Clinical Virology, Christian Medical College, Ida Scudder Rd, Vellore, India. Phone: [redacted] email: [redacted]

Hepsibah Jose, Department of Medicine, Christian Medical College, Ida Scudder Rd, Vellore, India. Phone: [redacted], email: [redacted]

Thabeetha Malini, Department of Medicine, Christian Medical College, Ida Scudder Rd, Vellore, India. Phone: [redacted], email [redacted]

Tony Kadavanu, Department of Medicine, Christian Medical College, Ida Scudder Rd, Vellore, India. Phone: [redacted] email: [redacted]

Michael R Jordan, Department of Public Health and Community Medicine, Tufts University School of Medicine, 136 Harrison Ave, Boston, MA, USA. Phone: [redacted], email: [redacted]

Julian H Elliott, Infectious Diseases Unit, Alfred Hospital, Level 2 Burnet Tower, 85 Commercial Road, Melbourne, Australia Ph: [redacted] email: [redacted]

Sharon R Lewin, Infectious Diseases Unit, Alfred Hospital, Level 2 Burnet Tower, 85 Commercial Road, Melbourne, Australia Ph: [redacted] email: [redacted]

Dilip Mathai, Department of Medicine, Christian Medical College, Ida Scudder Rd, Vellore, India. Phone: [redacted], email: [redacted]

Targets for intervention to improve outcomes on ART, Tamil Nadu, India

Abstract

Operational research to identify factors predicting poor clinical outcomes are critical to maximize patient care and prolong first-line regimens for those receiving free antiretroviral therapy (ART) in India. We sought to identify social or clinical factors amenable to intervention that predict virological outcomes after 12 months ART. We examined a retrospective cohort of consecutive adults initiating free non-nucleoside reverse transcriptase inhibitor based regimens. Individuals remaining in care 12 months post ART initiation were tested for HIV viral load, and surveyed to identify barriers and facilitators to adherence, and to determine clinic travel times and associated costs. Uni- and multivariate logistic regression identified factors predicting HIV viral load >200 copies/mL after 12 months of ART. Of 230 adults initiating ART 10% of patients died, 8% transferred out, 5% were lost to follow-up and 174/230 (76%) completed 12 months of ART, the questionnaire and viral load testing. HIV viral load was <200 copies/mL in 140/174 (80%) patients. In multivariate models being busy with work or caring for others (OR 2.9, p<.01), having clinic transport times ≥ 3 hours (OR 3.0, p=.02) and alcohol use (OR 4.8, p=.03) predicted viral load >200 copies/mL after 12 months of ART. Clinical outcomes following ART are related to programmatic factors such as prolonged travel time and individual factors such as being busy with family or using alcohol. Simple interventions that alter these factors should be evaluated to improve clinical outcomes for populations receiving free ART in similar settings.

Targets for intervention to improve outcomes on ART, Tamil Nadu, India

Background

The National AIDS Control Organisation (NACO) of India estimates that approximately 2.4 million people in India are living with HIV. Since 2004 NACO has rapidly scaled up access to free antiretroviral therapy (ART) (NACO, 2011) and as of January 2012 over 480,000 people are receiving free ART through NACO funded centers or programs (NACO, 2007, 2012). The identification of factors that predict poor virological outcomes and which are also amenable to intervention represents a critical unmet need for ART programs in India and other low-middle income countries (LMICs) where viral load testing is not routine (NACO, 2007). Identification and increasing support for individuals at risk of poor virological outcomes has the potential to prevent treatment failure and HIV related mortality, and maintain the efficacy of available first line ART (Chi et al., 2009; Nachega et al., 2006; Simoni, Amico, Smith, & Nelson, 2010; Thompson et al., 2012). This is particularly important in countries such as India where switching to second line therapies may be difficult due to increased cost, complexity, and lack of further treatment options (Elliott et al., 2008).

Low adherence to ART predicts poor virological outcomes in a wide range of settings (Bangsberg, 2006; Messou et al., 2011; Nachega et al., 2007; Nieuwkerk & Oort, 2005). In India ART adherence has been assessed by both quantitative and qualitative studies and has identified major barriers to ART adherence including: stigma, ART side effects, depression, co-morbidities and costs of care (Anuradha et al., 2012; Kumarasamy et al., 2005; Sarna et al., 2008; Shah et al., 2007; Shet et al., 2011; Vallabhaneni, Chandy, Heylen, & Ekstrand, 2011; Wanchu, Kaur, Bambery, & Singh, 2007). Important identified facilitators of adherence included the presence of social supports, having reminders to take medications, good mental health and perceived benefits of adherence to overall health and management of HIV disease (Anuradha et al., 2012; Kumarasamy et al., 2005; Shah et al., 2007). Of these studies reporting barriers or facilitators to adherence in India only two cohorts reported virological outcomes but they did not report associations between adherence barriers and viral load. Instead these two cohorts reported associations of viral load with patterns of self reported adherence (Shah et al., 2007; Shet et al., 2011; Vallabhaneni et al., 2011), cost of ART in a setting where patients paid for ART and whether the

patients received three or more antiretrovirals (Shah et al., 2007). Therefore studies reporting associations between HIV viral load and different barriers and facilitators to adherence are not available in India which is important as these factors represent ideal targets for intervention to improve virological outcomes for the large number of people receiving free ART in India

We therefore sought to identify factors that predict virologic outcomes in a clinic providing free ART but where viral load testing is not routinely performed. The objective of this study was to identify individual or programmatic factors predicting virological outcomes that could be targeted for intervention in this setting.

Methods

Population

The study was conducted at the ACC-NACO sponsored ART Clinic at Christian Medical College (ACTFID), Vellore, Tamil Nadu. This site is a public-private clinic where patients receive free clinical care and ART via the government sponsored NACO program. Clinics of this nature started after NACO recognized that many non-governmental and private organizations could continue providing ART services of a high standard and contribute towards NACO's goal of providing free ART to all eligible people living with HIV in India (NACO, 2007). The site is one of 5 providing free government sponsored ART in the Vellore district (population 3.5 million) and one of 36 sites in Tamil Nadu (population 62.4 million) which is considered a high prevalence state (2007 prevalence 0.34%) ("2001 Census - Tamil Nadu," 2001; IIPS, 2007; NACO, 2011). Additionally, the clinic cares for some patients from the nearby higher prevalence (0.97%) state of Andra Pradesh. Within the clinic there is a dedicated pharmacy and pharmacist to dispense ART. Patients attended the clinic monthly for a medical review and to pick-up ART and can nominate one person as a supporter to pick-up ART if they are not able to attend.

Design

The study was a retrospective cohort of consecutive adults initiating ART followed by a survey and HIV viral load measurement performed on patients remaining in care 12 months after ART initiation.

Patients were recruited from October 2009, until October 2010. Patients were eligible for inclusion if they were aged 18 years or older and initiating first line ART at the site per national guidelines (all non-nucleoside reverse transcriptase inhibitor [NNRTI] based regimens) (NACO, 2007). Individuals transferred in from other sites (government or private) with transfer records and patients who had previously stopped ART at the site and who were re-starting were excluded. Individuals not transferring in on ART but with prior antiretroviral exposure (e.g. prevention of mother to child transmission, informal exposure) were eligible for inclusion. The 12 month survey assessed facilitators and barriers to ART adherence based on previously reported literature within India (Kumarasamy et al., 2005; Sarna et al., 2008; Shah et al., 2007; Wanchu et al., 2007) and other LMICs (Mills et al., 2006). These included adherence barriers (e.g., busy with other activities, lowered mood), costs (transport factors, lost wages, income), clinic wait times, physical symptoms, adherence reminders and substance use (alcohol, cigarettes, other drugs). Additional questions assessing social capital were included due to its important relationship to ART adherence outside India (Ware et al., 2009). Core questions assessing 'groups and networks' and 'collective action and cooperation' domains of social capital were included ("The World Bank - Measuring Social Capital," 2009). The survey was originally written in English, translated into Tamil or Telugu and independently back-translated into English to ensure accuracy. To ensure the meaning of the questions was maintained any discrepancies between the original and back translated versions of the survey were clarified by the primary investigator, the translation and back translation teams. All patients completing 12 months ART provided written informed consent and the survey was administered in local languages by trained research nurses experienced in counseling and treatment of HIV. The study was approved by the institutional review boards at the study and collaborating sites.

Procedures

Consecutive individuals who had started ART after August 20, 2008, were identified during a routine clinic visit 11 – 15 months after ART start. This range was used to allow for all consecutive starters to be included but who may not have necessarily attended in person every month to pick-up ART. Patients were defined as lost to follow-up at 12 months if they had not attended the clinic or picked up

ART within 90 days of their last missed appointment. Patients who missed scheduled appointments were traced by phone (3 attempts), and physically if phone tracing failed to ascertain an outcome. Baseline clinical and demographic data were abstracted from clinical records and data on ART dispensing from pharmacy records. HIV viral load testing (Artus HIV-1 RT-PCR [Qiagen]) was performed on blood drawn on the day of the survey and a viral load threshold of 200 copies/mL was used as the outcome, based on data that viral load blips are rarely above this threshold (Nettles et al., 2005).

Analysis

Baseline characteristics were compared by viral load outcome for the individuals assessed 12 months after ART start. The χ^2, Fisher's exact, Student t test, and Wilcoxon rank-sum tests were used as appropriate. Univariate and multivariate logistic regression for a detectable viral load estimated odds ratios for different predictor variables. These were: age, gender, adherence barriers and facilitators as previously described and ART regimen. Variables with $p < 0.2$ in univariate analyses were entered into the multivariate models. Variables not reaching statistical significance ($p < 0.05$) were deleted from the model. Age and gender were considered as potential confounders and retained in final multivariate models. Validation of goodness-of-fit was via the Hosmer-Lemeshow test with a $p > 0.05$ indicating an appropriate fit. All analyses were conducted using SAS v9.2 (SAS Institute, Cary, NC).

Results

Two hundred and thirty consecutive individuals were identified at baseline and at 12 months 77% (177/230) were alive and on ART, 10% died (median 108 days after ART initiation), 8% transferred care to a different site, 5% were lost to follow-up and no patients had switched to second line therapy. Participants were predominantly male (61%) and reported acquisition via heterosexual sex (88%). At baseline, median CD4 T-cell count was146 cells/microL, 56% were classified as WHO Stage III/IV and all individuals were prescribed an appropriate regimen as per recommendations in the national guidelines (Table 1). There were a small proportion of individuals positive for Hepatitis B surface antigen (6%) and consistent with reported transmission categories no patients tested positive for Hepatitis C antibody. For

individuals on treatment at 12 months, 80% (140/174) had HIV viral load < 200 copies/mL. Baseline characteristics were not significantly different when stratified by viral load outcome, although there was a trend (p=0.08) for virological suppression in married individuals Apart from baseline measures in Table 1 other assessments of socioeconomic status (SES) at 12 months revealed median family monthly income of 3000 Rs. (~$60 USD) and 74% of patients were in the lowest 2 (lower and upper lower) of 5 SES categories of the modified Kuppuswamy index (Mishra & Singh, 2003).

Parameter estimates from regression models are presented in Table 2. A detectable viral load at 12 months was associated with being busy doing other things, feeling depressed, transport time, the perception of transport as a barrier to clinic attendance and alcohol use in univariate models (all p<.05). In the multivariate model being busy (OR 2.9, p<.01), alcohol use (OR 4.8, p=.03) and transport time ≥ 3 hours (OR 3.0, p=.02) remained predictive.

Discussion

This study has identified several factors predictive of poor virological outcomes that are amenable to intervention. Patients who reported often being busy with family or work, or had travel times to clinic more than 3 hours had 3 times the odds of a detectable viral load after 12 months of ART. Additionally reporting any history of alcohol use in the previous month resulted in 5 times the odds of a detectable viral load after 12 months of ART.

The finding that individuals with high clinic travel times had higher viral loads represents the first report of transport predicting worse virological outcomes for patients receiving ART. In African settings transport (Mills et al., 2006) and its associated costs (Duff, Kipp, Wild, Rubaale, & Okech-Ojony, 2010; Hardon et al., 2007; Tuller et al., 2010) have been reported as a barrier to adherence, but it has not been known whether this is an important determinate of treatment outcomes in India where transport infrastructure is better than many LMICs. In addition we found that transport time as a perceived barrier to attending clinic significantly predicted virological response in the univariate analysis but was not significant in the multivariate analysis and we found that transport costs did not predict virological

outcomes in either analysis. These results suggest that actual travel time is a more potent predictor of virological outcomes as compared to the patient's perception that travel time is a barrier or the costs of transport. Furthermore, the 3 hour threshold is of interest as 6 or fewer hours of travel plus a clinic visit are likely to be completed in one day as compared to total travel times above 6 hours. Taken together these findings argue for further decentralization as a programmatic level intervention to improve access to ART services. Decentralizing ART services so they are closer to people's homes means care has to be relocated to smaller and more remote ART sites. In addition the responsibility of providing care has to move from doctors to nurses, or other paramedical staff. Maintaining quality of care across a larger number of sites of different size and health care specialization represents a challenge for ART programs but successful outcomes after decentralization of ART services have been reported outside India (Bedelu, Ford, Hilderbrand, & Reuter, 2007; Massaquoi et al., 2009; Mutevedzi et al., 2010). Furthermore, these data suggest that any difficulties encountered by decentralization may be overcome by improvements in virological outcomes associated with decreased travel times.

Individuals who report often being busy with duties such as caring for others or working, and individuals who reported alcohol consumption had worse virological outcomes and demonstrate how these factors interfere with regular pill taking behavior. Interventions for individuals that report being excessively busy caring for others of with work commitments have not been reported but interventions recommended to support adherence and improve virological outcomes in general populations warrant consideration. Examples include ART regimen simplification, increased peer support and individual or group adherence counseling (Thompson et al., 2012). The finding of alcohol intake as a predictor is of particular importance considering other data from India linking alcohol use to poor ART adherence (Venkatesh et al., 2010) and risk taking behaviours amongst men who have sex with men (Mimiaga et al., 2011). A randomized clinical trial in individuals receiving ART with hazardous alcohol consumption in North America of motivational interviewing and cognitive behavioral training led to improved adherence, virological and immunological outcomes and highlights the potential benefits of interventions for individuals receiving ART with increased alcohol intake (Parsons, Golub, Rosof, & Holder, 2007).

Targets for intervention to improve outcomes on ART, Tamil Nadu, India

Increased screening at baseline and while on ART for factors such as alcohol intake or being excessively busy with work or caring for family members can lead to clinician or peer based interventions to improve outcomes for patients receiving first line ART in India.

We also attempted to assess markers of social capital due to qualitative research in Africa describing social capital as critical to adherence (Ware et al., 2009). Using World Bank markers of social capital validated in multiple LMICs ("The World Bank - Measuring Social Capital," 2009), although not specific to the context of HIV, we found no firm link between social capital and virological outcomes. This may be explained by not appropriately exploring domains of social capital as described in the literature (Ware et al., 2009), or not appropriately contextualizing the social capital survey items to the local situation. Alternatively social capital may not truly be as important as the other factors identified in this study if social relationships or obligations that underpin adherence to ART in sub-Saharan Africa are potentially not as strong in India. Considering our findings and the importance of links between social capital and ART adherence (Bangsberg & Deeks, 2010) this relationship warrants further research in settings outside sub-Saharan Africa.

It is unclear how broadly generalizable the findings of this study are to different regions of India and other LMICs. Our finding of 80% virological suppression is consistent with other LMIC cohorts using single viral load results at similar thresholds (100-300 copies/mL) documenting 71-79% virological suppression after 12 months ART (Hegazi, Bailey, Ahadzie, Alabi, & Peterson, 2010; Lyagoba et al., 2010; Messou et al., 2011). In addition we found 12 month mortality (10%) and lost to follow up (LTFU) (5%) figures consistent with some LMIC cohorts (Braitstein et al., 2006; Mutevedzi et al., 2010; Palombi et al., 2009) but LTFU figures that are lower than other sites in India who report 14-32% LTFU after 12 months ART (Hingankar et al., 2012; Sharma et al., 2010; Tassie et al., 2010). The lower LTFU rates seen in our study compared to other Indian sites may reflect the improved classification of individuals with unknown outcomes in our study due to tracing of lost patients by phone or physically to their homes (McMahon, Elliott, Hong, & Jordan, 2012).

Conclusions

This study identified multiple factors predicting a detectable viral load after 12 months of ART. Important factors such as prolonged travel times, individuals reporting busy schedules, or use of alcohol serve as programmatic or individual level targets for interventions such as decentralization of ART services or increased screening and support for patients reporting alcohol use. Studies to evaluate these interventions are critical to improve clinical outcomes for people receiving ART in the public health model of care in India.

Acknowledgements

We thanks the study participants and all staff within the ACC-NACO sponsored ART Clinic at Christian Medical College (ACTFID)

The study was supported via a Lifespan/Tufts/Brown Center for AIDS Research grant from the National Institutes of Health (1P30 A142853-12)

James McMahon was supported by a fellowship from the Tufts Medical Center Department of Geographic Medicine and Infectious Diseases, and an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship. Michael Jordan was supported by a grant from the National Institutes of Health (5K23AI074423-04). SRL is an NHMRC Practitioner Fellow

Conflicts of Interest

Sharon Lewin's institution receives grant funding from Merck and Gilead, payment for lectures from Viiv Healthcare and Janssen, and payment for educational presentations from Janssen

All other authors, no conflicts

References

2001 Census - Tamil Nadu. (2001). Retrieved April 10 2009, from http://www.census.tn.nic.in/framers.asp?id=16&dcode=vel

Anuradha, S., Joshi, A., Negi, M., Nischal, N., Rajeshwari, K., & Dewan, R. (2012). Factors Influencing Adherence to ART: New Insights from a Center Providing Free ART under the National Program in Delhi, India. *J Int Assoc Physicians AIDS Care (Chic)*. doi: 1545109711431344 [pii], 10.1177/1545109711431344

Bangsberg, D. R. (2006). Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis, 43*(7), 939-941. doi: CID38663 [pii], 10.1086/507526

Bangsberg, D. R., & Deeks, S. G. (2010). Spending more to save more: interventions to promote adherence. *Ann Intern Med, 152*(1), 54-56; W-13. doi: 152/1/54 [pii], 10.1059/0003-4819-152-1-201001050-00012

Bedelu, M., Ford, N., Hilderbrand, K., & Reuter, H. (2007). Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. [Review]. *J Infect Dis, 196 Suppl 3*, S464-468. doi: 10.1086/521114

Braitstein, P., Brinkhof, M. W., Dabis, F., Schechter, M., Boulle, A., Miotti, P., . . . Egger, M. (2006). Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet, 367*(9513), 817-824. doi: S0140-6736(06)68337-2 [pii], 10.1016/S0140-6736(06)68337-2

Chi, B. H., Cantrell, R. A., Zulu, I., Mulenga, L. B., Levy, J. W., Tambatamba, B. C., . . . Stringer, Jeffrey S. A. (2009). Adherence to first-line antiretroviral therapy affects non-virologic outcomes among patients on treatment for more than 12 months in Lusaka, Zambia. [Multicenter Study, Research Support, N.I.H., Extramural, Research Support, Non-U.S. Gov't, Research Support, U.S. Gov't, P.H.S.]. *International Journal of Epidemiology, 38*(3), 746-756.

Duff, P., Kipp, W., Wild, T. C., Rubaale, T., & Okech-Ojony, J. (2010). Barriers to accessing highly active antiretroviral therapy by HIV-positive women attending an antenatal clinic in a regional hospital in western Uganda. [Research Support, Non-U.S. Gov't]. *J Int AIDS Soc, 13*, 37. doi: 10.1186/1758-2652-13-37

Elliott, J. H., Lynen, L., Calmy, A., De Luca, A., Shafer, R. W., Zolfo, M., . . . Schapiro, J. M. (2008). Rational use of antiretroviral therapy in low-income and middle-income countries: optimizing regimen sequencing and switching. *Aids, 22*(16), 2053-2067.

Hardon, A. P., Akurut, D., Comoro, C., Ekezie, C., Irunde, H. F., Gerrits, T., . . . Laing, R. (2007). Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa. *AIDS Care, 19*(5), 658-665. doi: 778664177 [pii], 10.1080/09540120701244943

Hegazi, A., Bailey, R. L., Ahadzie, B., Alabi, A., & Peterson, K. (2010). Literacy, education and adherence to antiretroviral therapy in The Gambia. *AIDS Care, 22*(11), 1340-1345.

Hingankar, N. K., Thorat, S. R., Deshpande, A., Rajasekaran, S., Chandrasekar, C., Kumar, S., . . . Paranjape, R. S. (2012). Initial virologic response and HIV drug resistance among HIV-infected individuals initiating first-line antiretroviral therapy at 2 clinics in Chennai and Mumbai, India. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Clin Infect Dis, 54 Suppl 4*, S348-354. doi: 10.1093/cid/cis005

IIPS. (2007). 2005-06 National Family Health Survey, India. Retrieved 6 February 2012, from http://www.nfhsindia.org/nfhs3_national_report.html

Kumarasamy, N., Safren, S. A., Raminani, S. R., Pickard, R., James, R., Krishnan, A. K., . . . Mayer, K. H. (2005). Barriers and facilitators to antiretroviral medication adherence among patients with HIV in Chennai, India: a qualitative study. *AIDS Patient Care STDS, 19*(8), 526-537.

Lyagoba, Fred, Dunn, David T., Pillay, Deenan, Kityo, Cissy, Robertson, Val, Tugume, Stephano, . . . Trial, Team. (2010). Evolution of drug resistance during 48 weeks of zidovudine/lamivudine/tenofovir in the absence of real-time viral load monitoring. [Research

Support, Non-U.S. Gov't]. *Journal of Acquired Immune Deficiency Syndromes: JAIDS, 55*(2), 277-283.

Massaquoi, M., Zachariah, R., Manzi, M., Pasulani, O., Misindi, D., Mwagomba, B., . . . Harries, A. D. (2009). Patient retention and attrition on antiretroviral treatment at district level in rural Malawi. [Multicenter Study Research Support, Non-U.S. Gov't]. *Trans R Soc Trop Med Hyg, 103*(6), 594-600. doi: 10.1016/j.trstmh.2009.02.012

McMahon, JH, Elliott, JH , Hong, SY, & Jordan, MR. (2012). *Effects of patient tracing on estimates of lost to follow-up, mortality and retention in antiretroviral therapy programs in low-middle income countries: a systematic review. Abstract MOAC0302*. Paper presented at the 19th International AIDS Conference, Washington DC, USA.

Messou, E., Chaix, M. L., Gabillard, D., Minga, A., Losina, E., Yapo, V., . . . Anglaret, X. (2011). Association between medication possession ratio, virologic failure and drug resistance in HIV-1-infected adults on antiretroviral therapy in Cote d'Ivoire. *J Acquir Immune Defic Syndr, 56*(4), 356-364. doi: 10.1097/QAI.0b013e3182084b5a

Mills, E. J., Nachega, J. B., Bangsberg, D. R., Singh, S., Rachlis, B., Wu, P., . . . Cooper, C. (2006). Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med, 3*(11), e438. doi: 05-PLME-RA-0713R3 [pii], 10.1371/journal.pmed.0030438

Mimiaga, M. J., Thomas, B., Mayer, K. H., Reisner, S. L., Menon, S., Swaminathan, S., . . . Safren, S. A. (2011). Alcohol use and HIV sexual risk among MSM in Chennai, India. *Int J STD AIDS, 22*(3), 121-125. doi: 22/3/121 [pii], 10.1258/ijsa.2009.009059

Mishra, D., & Singh, H. P. (2003). Kuppuswamy's socioeconomic status scale--a revision. *Indian J Pediatr, 70*(3), 273-274.

Mutevedzi, P. C., Lessells, R. J., Heller, T., Barnighausen, T., Cooke, G. S., & Newell, M. L. (2010). Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? [Research Support, Non-U.S. Gov't, Research Support, U.S. Gov't, Non-P.H.S.]. *Bull World Health Organ, 88*(8), 593-600. doi: 10.2471/BLT.09.069419

Nachega, J. B., Hislop, M., Dowdy, D. W., Chaisson, R. E., Regensberg, L., & Maartens, G. (2007). Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Ann Intern Med, 146*(8), 564-573.

Nachega, J. B., Hislop, M., Dowdy, D. W., Lo, M., Omer, S. B., Regensberg, L., . . . Maartens, G. (2006). Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *J Acquir Immune Defic Syndr, 43*(1), 78-84.

NACO. (2007). Antiretroviral Therapy Guidelines for HIV-Infected Adults and Adolescents Including Post-exposure Prophylaxis: National AIDS and Control Organisation, Ministry of Health & Family Welfare, Government of India.

NACO. (2011). Department of AIDS Control Ministry of Health & Family Welfare Annual Report 2010-11 Retrieved 8 July 2012, from http://www.nacoonline.org/upload/REPORTS/NACO%20Annual%20Report%202010-11.pdf

NACO. (2012). National Aids Control Organisation, India HIV data Retrieved July 12 2012, from http://www.nacoonline.org/Quick_Links/HIV_Data/

Nettles, R. E., Kieffer, T. L., Kwon, P., Monie, D., Han, Y., Parsons, T., . . . Siliciano, R. F. (2005). Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA, 293*(7), 817-829. doi: 293/7/817 [pii], 10.1001/jama.293.7.817

Nieuwkerk, P. T., & Oort, F. J. (2005). Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis. *J Acquir Immune Defic Syndr, 38*(4), 445-448.

Palombi, L., Marazzi, M. C., Guidotti, G., Germano, P., Buonomo, E., Scarcella, P., . . . De Luca, Andrea. (2009). Incidence and predictors of death, retention, and switch to second-line regimens in

antiretroviral- treated patients in sub-Saharan African Sites with comprehensive monitoring availability. [Research Support, Non-U.S. Gov't]. *Clinical Infectious Diseases, 48*(1), 115-122.

Parsons, J. T., Golub, S. A., Rosof, E., & Holder, C. (2007). Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. [Multicenter Study, Randomized Controlled Trial, Research Support, N.I.H., Extramural]. *J Acquir Immune Defic Syndr, 46*(4), 443-450.

Sarna, A., Pujari, S., Sengar, A. K., Garg, R., Gupta, I., & Dam, J. (2008). Adherence to antiretroviral therapy & its determinants amongst HIV patients in India. *Indian J Med Res, 127*(1), 28-36.

Shah, B., Walshe, L., Saple, D. G., Mehta, S. H., Ramnani, J. P., Kharkar, R. D., . . . Gupta, A. (2007). Adherence to antiretroviral therapy and virologic suppression among HIV-infected persons receiving care in private clinics in Mumbai, India. *Clin Infect Dis, 44*(9), 1235-1244.

Sharma, Surendra K., Dhooria, Sahajal, Prasad, K. T., George, Ninoo, Ranjan, Sanjay, Gupta, Deepak, . . . Vajpayee, Madhu. (2010). Outcomes of antiretroviral therapy in a northern Indian urban clinic. [Research Support, Non-U.S. Gov't]. *Bulletin of the World Health Organization, 88*(3), 222-226.

Shet, A., DeCosta, A., Heylen, E., Shastri, S., Chandy, S., & Ekstrand, M. (2011). High rates of adherence and treatment success in a public and public-private HIV clinic in India: potential benefits of standardized national care delivery systems. *BMC Health Serv Res, 11*, 277. doi: 1472-6963-11-277 [pii], 10.1186/1472-6963-11-277

Simoni, J. M., Amico, K. R., Smith, L., & Nelson, K. (2010). Antiretroviral adherence interventions: translating research findings to the real world clinic. [Review]. *Curr HIV/AIDS Rep, 7*(1), 44-51. doi: 10.1007/s11904-009-0037-5

Tassie, Jean-Michel, Malateste, Karen, Pujades-Rodriguez, Mar, Poulet, Elisabeth, Bennett, Diane, Harries, Anthony, . . . Collaborations, M. S. F. (2010). Evaluation of three sampling methods to monitor outcomes of antiretroviral treatment programmes in low- and middle-income countries. [Research Support, Non-U.S. Gov't]. *PLoS ONE [Electronic Resource], 5*(11), e13899.

Thompson, M. A., Mugavero, M. J., Amico, K. R., Cargill, V. A., Chang, L. W., Gross, R., . . . Nachega, J. B. (2012). Guidelines for Improving Entry Into and Retention in Care and Antiretroviral Adherence for Persons With HIV: Evidence-Based Recommendations From an International Association of Physicians in AIDS Care Panel. *Ann Intern Med, 156*(11), 817-833. doi: 10.1059/0003-4819-156-11-201206050-00419

Tuller, D. M., Bangsberg, D. R., Senkungu, J., Ware, N. C., Emenyonu, N., & Weiser, S. D. (2010). Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: a qualitative study. *AIDS Behav, 14*(4), 778-784. doi: 10.1007/s10461-009-9533-2

Vallabhaneni, S., Chandy, S., Heylen, E., & Ekstrand, M. (2011). Reasons for and correlates of antiretroviral treatment interruptions in a cohort of patients from public and private clinics in southern India. *AIDS Care*. doi: 10.1080/09540121.2011.630370

Venkatesh, K. K., Srikrishnan, A. K., Mayer, K. H., Kumarasamy, N., Raminani, S., Thamburaj, E., . . . Safren, S. A. (2010). Predictors of nonadherence to highly active antiretroviral therapy among HIV-infected South Indians in clinical care: implications for developing adherence interventions in resource-limited settings. *AIDS Patient Care STDS, 24*(12), 795-803. doi: 10.1089/apc.2010.0153

Wanchu, A., Kaur, R., Bambery, P., & Singh, S. (2007). Adherence to generic reverse transcriptase inhibitor-based antiretroviral medication at a Tertiary Center in North India. *AIDS Behav, 11*(1), 99-102.

Ware, N. C., Idoko, J., Kaaya, S., Biraro, I. A., Wyatt, M. A., Agbaji, O., . . . Bangsberg, D. R. (2009). Explaining adherence success in sub-Saharan Africa: an ethnographic study. *PLoS Med, 6*(1), e11. doi: 08-PLME-RA-1572 [pii], 10.1371/journal.pmed.1000011

The World Bank - Measuring Social Capital. (2009). Retrieved 21 December 2009, from http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/EXTSOCIALDEVELOPMENT/EXT

Targets for intervention to improve outcomes on ART, Tamil Nadu, India

TSOCIALCAPITAL/0,,contentMDK:20193059~menuPK:418220~pagePK:148956~piPK:216618~theSitePK:401015,00.html

Table 1. Baseline characteristic stratified by detectable viral load

Baseline characteristic		Total (n=174)	Viral load < 200 copies/mL (n=140)	Viral load > 200 copies/mL (n=34)	p-value
Age		38.3 ± 8.7	38.5 ± 8.7	37.3 ± 9.3	0.5
Gender	Male	105 (60.7)	84 (60.4)	21 (61.8)	0.9
	Female	68 (39.3)	55 (39.6)	13 (38.2)	
Transmission Risk Factor	Heterosexual	136 (87.7)	108 (87.1)	28 (90.3)	0.5
	MSM	2 (1.3)	2 (1.6)	0	
	Other	13 (8.4)	10 (8.0)	3 (9.7)	
Education level	Non-literate	31 (19.4)	25 (19.5)	6 (18.8)	0.8
	Primary School	43 (26.9)	34 (26.6)	9 (28.1)	
	Secondary School	68 (42.5)	56 (43.8)	12 (37.5)	
	College	18 (11.3)	13 (10.2)	5 (15.6)	
Employed	No	53 (33.3)	45 (44.4)	9 (29.0)	0.5
	Yes	106 (66.7)	84 (65.6)	22 (71.0)	
Marital Status	Single / Separated / Partner Died	50 (29.0)	36 (25.9)	14 (41.2)	0.08
	Married	123 (71.1)	103 (74.1)	20 (58.8)	
Previous ARV exposure	None	160 (97.0)	130 (97.7)	30 (93.4)	0.13
	PMTCT	2 (1.2)	2 (1.5)	0	
	ART	3 (1.8)	1 (0.8)	2 (6.3)	
Baseline WHO clinical stage	I/II	74 (42.5)	58 (41.4)	16 (47.1)	0.7
	III	38 (21.8)	30 (21.4)	8 (23.5)	
	IV	62 (35.6)	52 (37.1)	10 (29.4)	
Weight (kg)		54.0 ± 11.9	53.8 ± 10.8	54.6 ± 11.3	0.7
Anti-tuberculous treatment	No	131 (76.6)	104 (75.4)	27 (81.8)	0.4
	Yes	40 (23.4)	34 (24.6)	6 (18.2)	
Opportunistic infections excluding tuberculosis	No	144 (82.8)	114 (81.4)	30 (88.2)	0.3
	Yes	30 (17.2)	26 (18.6)	4 (11.8)	
ART regimen	D4T/3TC/NVP	78 (44.8)	59 (42.1)	19 (55.9)	0.5
	AZT/3TC/NVP	58 (33.3)	49 (35.0)	9 (26.5)	
	D4T/3TC + EFV	27 (15.5)	22 (15.7)	5 (14.7)	
	AZT/3TC + EFV	11 (6.3)	10 (7.1)	1 (2.9)	
CD4 (cells/microL)		146 (77-202)	142 (73-201)	159 (81-219)	0.5
HepBsAg positive		9 (6.0)	6 (5.0)	3 (10.0)	0.4

NOTE: MSM, men who have sex with men; ARV, antiretroviral; PMTCT, prevention of mother to child transmission; ART, antiretroviral therapy; WHO, World Health Organization; D4T, stavudine; 3TC, lamivudine; NVP, nevirapine; AZT, zidovudine; EFV, efavirenz

Table 2. Uni- and Multivariate logistic regression predicting detectable viral load (n=174)

Factor of interest	Predicting viral load > 200 copies/mL			
	Univariate Model OR	p-value	Multivariate Model[a] OR	p-value
Barriers				
Busy doing other things as a barrier[b] (Often vs < Often)	2.9	<0.01	2.9	0.01
Illness as a barrier over last 30 days (> Never vs Never)	0.5	0.5		
Nausea and vomiting last 30 days (Yes vs No)	1.4	0.6		
Diarrhea last 30 days (Yes vs No)	2.5	0.2		
Bothered by feeling down and depressed last 30 days (A lot vs < a lot)	3.3	0.03	-	
Facilitators				
Discuss HIV with friends (Yes vs No)	1.3	0.6		
Support from family and friends (Satisfied vs dissatisfied)	2.0	0.4		
Family and friends help to remind you to take ART (A lot vs < a lot)	1.8	0.2		
Assisted people around you in last 12 months (Yes vs No)	1.8	0.13	-	
Transport and costs				
Transport time one way (≥ 3 versus < 3 hours)	2.6	0.03	3.0	0.02
Transport time is a barrier to attendance (Yes vs No)	8.9	0.01	-	
Transport cost – two way (For every one Rs increase)	1.0	0.7		
Lost wages (For every one Rs increase)	1.001	0.4		
Other clinical factors				
Alcohol intake last 30 days (Any intake vs None)	4.5	0.02	4.8	0.03
Nevirapine versus Efavirenz based regimen	1.2	0.8		

Age, gender, disclosure of diagnosis, peripheral neuropathy symptoms, clinic wait time, family monthly income, socioeconomic status (modified Kuppuswamy) index, being a member of a group, would co-operate to solve a problem of water scarcity, cigarette use and drug use were not predictive to the P < 0.2 level in univariate analyses

[a] Multivariate models also include age and gender (p >0.2 for both variables in both multivariate models)

[b]Examples provided to subjects were: caring for others, or working

NOTE: OR, Odds Ratio; ART, Antiretroviral Therapy; Rs, Indian rupee

7 Pharmacy and self-report adherence measures to predict virological outcomes for patients on free antiretroviral therapy in Tamil Nadu, India

7.1 Declaration

Declaration for Thesis Chapter 7

Declaration by candidate

In the case of Chapter 7, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
I led the design, wrote the protocol, established and supervised the studies, analysed the results and wrote the manuscript	70

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors**
Anand Manoharan	Helped design the study, write the study protocol, interpret the results, oversee all study procedures at the study site and develop the manuscript	5
Christine A. Wanke	Helped conceive the analysis, interpret the study results and develop the manuscript.	5
Shoba Mammen	Established procedures for the performance of viral load tests, interpret viral load data and develop the manuscript	2
Hepsibah Jose	Helped recruit and conduct interviews for study participants and develop the manuscript.	2

Thabeetha Malini	Helped recruit and conduct interviews for study participants and develop the manuscript.	2
Tony Kadavanu	Helped recruit and conduct interviews for study participants and develop the manuscript.	2
Michael R. Jordan	Helped design the study, conceive the analysis, interpret the study results and develop the manuscript	3
Julian H. Elliott	Helped design the study, conceive the analysis, interpret the study results and develop the manuscript	2
Sharon R. Lewin	Helped conceive the analysis, interpret the study results and develop the manuscript.	2
Dilip Mathai	Helped design the study, write the study protocol, interpret the results, oversee all study procedures at the study site and develop the manuscript	5

Candidate's Signature	[redacted]	**Date** **16 APR 2013**

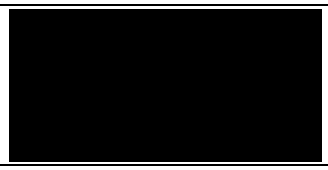
Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	**Christian Medical College Department of Medicine, Vellore**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	AM 	**Date** 8/4/2013
Signature 2	CAW 	14/4/2013
Signature 3	SM 	8/4/2013
Signature 4	HJ 	15/04/2013
Signature 5	TM 	15/04/2013
Signature 6	TK 	15/04/2013
Signature 7	MRJ 	10/4/2013
Signature 8	JHE 	16/4/2013
Signature 9	SRL 	16/4/2013
Signature 10	DM 	8/4/2013

To Whom It May Concern – Professor Stephen Jane is signing as Head of Central Clinical School where attempts to contact co-authors multiple times failed. These were - Hepsibah Jose (HJ), Thabeetha Malini(TM), Tony Kadavanu (TK)

Signed: 

Date: 15/04/2013

Professor Stephen Jane

Head of Central Clinical School

7.2 Introduction

Analyses in the previous chapter identified multiple attributes of PLHIV attending the ART clinic at Christian Medical College Vellore that were associated with virological outcomes after 12-months of ART. These factors identified in multivariate analysis were; reporting consumption of alcohol, having transport times to clinic over 3 hours and reporting being busy attending to care needs of other family members or with work. Importantly these factors were all considered as potential predictors of worse virological outcomes as they were considered potential barriers to ART adherence.

In addition to understanding barriers optimal ART outcomes another critical element to identify people at risk of poor virological outcomes is to assess methods to estimate ART adherence that are low-cost and can be carried out during routine clinical care. The most commonly used method of estimating adherence is patient self-report. While self-report is amenable to use during routine clinical care it has many limitations including being subject to social desirability bias and inter-observer variability. Additionally there are resource implications in LMICs for clinicians to accurately and regularly ask appropriate questions and record this data at every patient visit. Furthermore recommended questions about self-report adherence have been validated in HIC settings (124) and cultural and language differences may render them less accurate.

Objectively estimating adherence using pre-existing pharmacy data of the dates and volume of ART picked-up has the potential to more accurately identify individuals with poor adherence and at risk of virological failure. Pharmacy measures are objective estimates of adherence, cost efficient as they rely on routinely collected pharmacy data and therefore feasible in routine clinical practice. In addition they have the potential to be used in real time to identify periods of suboptimal adherence prior to an episode of virological failure (41, 125). Data of self-report adherence and its association with virological outcomes for populations exclusively receiving free ART in India is not available and there is also no data available from India reporting adherence estimates using pharmacy data. Therefore we sought to obtain estimates of adherence to free ART using self-report and pharmacy data and assess for their associations with virological outcomes in the public health model of ART care in India.

The previous chapter reported on work to identify specific elements that could be targeted for intervention to improve virological outcomes from a range of different social factors. The following study in this chapter aims to identify individuals at increased need of adherence support which is complimentary to the analysis in the previous chapter as they both seek to optimise clinical ART care for populations living with HIV in a LMIC setting.

7.3 Paper

AIDS Behav
DOI 10.1007/s10461-013-0436-x

BRIEF REPORT

Pharmacy and Self-Report Adherence Measures to Predict Virological Outcomes for Patients on Free Antiretroviral Therapy in Tamil Nadu, India

James H. McMahon · Anand Manoharan · Christine A. Wanke · Shoba Mammen · Hepsibah Jose · Thabeetha Malini · Tony Kadavanu · Michael R. Jordan · Julian H. Elliott · Sharon R. Lewin · Dilip Mathai

Abstract Over 480,000 individuals receive free antiretroviral therapy (ART) in India yet data associating ART adherence with HIV viral load for populations exclusively receiving free ART are not available. Additionally estimates of adherence using pharmacy data on ART pick-up are not available for any population in India. After 12-months ART we found self-reported estimates of adherence were not associated with HIV viral load. Individuals with <100 % adherence using pharmacy data predicted HIV viral load, and estimates combining pharmacy data and self-report were also predictive. Pharmacy adherence measures proved a feasible method to estimate adherence in India and appear more predictive of virological outcomes than self-report. Predictive adherence measures identified in this study warrant further investigation in populations receiving free ART in India to allow for identification of individuals at risk of virological failure and in need of adherence support.

Keywords HIV · Adherence · Antiretroviral therapy · India · Virological outcomes

J. H. McMahon (✉) · J. H. Elliott · S. R. Lewin
Infectious Diseases Unit, Alfred Hospital, Level 2 Burnet Tower, 85 Commercial Road, Melbourne 3004, Australia
e-mail: [redacted]

J. H. McMahon · C. A. Wanke · M. R. Jordan
Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

A. Manoharan · H. Jose · T. Malini · T. Kadavanu · D. Mathai
Department of Medicine and Infectious Diseases, Christian Medical College, Vellore, Tamil Nadu, India

S. Mammen
Department of Clinical Virology, Christian Medical College, Vellore, Tamil Nadu, India

J. H. Elliott · S. R. Lewin
Department of Medicine, Monash University, Melbourne, VIC, Australia

J. H. Elliott · S. R. Lewin
Burnet Institute, Melbourne, VIC, Australia

Background

It is estimated that 2.4 million people are living with HIV in India with over 480,000 people receiving free National AIDS Control Organization (NACO) funded antiretroviral therapy (ART) [1] However, ART coverage remains a challenge with somewhere between 23 and 55 % of eligible patients receiving ART during 2009 [2]. Furthermore a smaller group of individuals estimated to be somewhere between 6 and 25 % of the population receiving ART [3] pay for these medications in the private system. Rapid scale-up of free government funded ART has occurred since 2004 yet it is recognized that nearly 20 % of patients are presenting at a very late stage (CD4 count < 50) with an increased risk of mortality. NACO has responded by decentralizing ART services to the district and sub-district level in an attempt to close gaps in public health infrastructure between HIV testing and treatment programs, and non-HIV related health services [4].

Achieving optimal adherence to ART is critical to prevent treatment failure, HIV related mortality, emergence of HIV drug resistance, and preserve the efficacy of available ART [5–8]. High levels of adherence have been reported in meta-analyses of studies performed in sub-Saharan Africa and understanding this success has become a focus of investigation [9, 10]. Maintaining maximal adherence is particularly important in countries such as India where switching to second line ART is more costly, complex, and

Published online: 24 February 2013

restricts future treatment options [11]. In addition patients in India suspected of treatment failure on first-line ART are only recommended to commence second-line ART once good adherence has been ensured [12].

Multiple methods to estimate adherence to ART are available and they include: self report, pharmacy adherence measures (PAMs), electronic pill container caps (MEMS caps), measuring antiretroviral drug concentrations and web-enabled pill boxes [13] MEMS caps are considered the gold standard for estimating adherence by many authors but their use is largely confined to research settings in a similar manner to measuring drug levels or web based systems that record the opening of pill boxes [13, 14]. PAMs estimate ART adherence using pill pick-up data that is routinely recorded at pharmacies dispensing ART according to the prescription of a medical practitioner. This contrasts with the most widely utilized "over the counter" practice for delivering medication in India where pick-up data is often not available. PAMs predict virological and other clinical outcomes in high and low-middle income countries [15] (LMICs) and have been adopted by the World Health Organisation (WHO) as a standard for estimating population level adherence [16, 17]. Interestingly most LMIC data originates from sub-Saharan Africa [15], with many prominent studies performed in the private health sector [7, 18, 19]. Until now, no studies from India have reported PAMs and their association with virological outcomes which is notable considering the potential advantages of PAMs over self-report adherence measures [13, 15]. Furthermore, only two cohorts in India have documented adherence to ART in association with virological outcomes with both cohorts assessing adherence by self-report. Importantly neither cohort reported on populations exclusively receiving free ART [20–23]. Shah reports on patients in the private system who paid out-of-pocket for ART [21], while a Bangalore cohort document self-reported adherence predicting virological outcomes for individuals receiving free ART, or paying for ART in the private system [20, 22–24]. The Bangalore cohort also documented more treatment interruptions [23] and virological failures [22] in patients paying for ART but did not document associations between adherence and virological outcomes for individuals only receiving free ART. This is an important distinction as at least 75 % of individuals now receive free NACO funded ART [1, 3, 25] and ART cost has been repeatedly reported as a barrier to ART adherence in India [22, 23, 26, 27]. Therefore relationships between adherence and viral load may be different from what is currently reported for most individuals receiving ART in India. In addition to ART cost other barriers to adherence have also been reported in India including: stigma, ART side effects, depression and co-morbid medical conditions [21–23, 26–29].

Therefore, our objective was to determine associations between ART adherence and HIV viral load for individuals receiving free ART within the public sector in India using both self-reported and pharmacy measures of adherence.

Methods

Population

The study was conducted at a NACO sponsored ART Clinic at Christian Medical College (ACTFID), Vellore, Tamil Nadu and is one of five sites providing free government sponsored ART in the Vellore district (population 3.5 million) The clinic is one of many public–private partnership sites in India where non-governmental and private organizations collaborate with NACO to provide free clinical care and ART services via the NACO program [12]. Patients attended monthly for medical review and picked-up ART from a pharmacy staffed by a dedicated pharmacist within the clinic. Patients did not require specific appointment times to attend the clinic which was open 6 days a week and all routine pathology including testing for CD4 T cell counts was performed at a laboratory approximately 10 min walk from the clinic. At the time of the study 500 people were receiving ART and the clinic was staffed by two doctors, a social worker, pharmacist and clerical staff. The clinic was also able to manage some other medical conditions such as intercurrent respiratory or skin infections. Patients requiring hospital admission or other specialist medical care were referred to inpatient services or other outpatient clinics within Christian Medical College.

Design

The study was a retrospective cohort of consecutive adults initiating ART and followed for 12-months. Patients were recruited from October 26, 2009, until October 10, 2010 and eligible for inclusion if initiating first line ART [12]. Patients transferred in from other sites or re-initiating ART after a treatment interruption were excluded. Self-reported adherence [30, 31] and HIV viral load were determined for patients remaining in care 12-months after ART start.

Procedures

Two hundred and thirty consecutive initiators of ART were identified during a routine clinic visit after 11–15 months of ART. Patients were considered lost to follow-up (LTFU) at 12-months if they had not attended or picked up ART within 90 days of their last missed appointment. All baseline clinical and demographic data was abstracted from

clinical records and ART dispensing data from pharmacy records.

Standardized self-report adherence measures asked about adherence since; initiating ART, or the preceding 30-days [30]. An additional 30-day self-report measure was the visual analog scale (VAS) where patients indicated on a line marked from 0 to 100 % the point that best corresponded to the percentage of pills taken [31]. Adherence questions were originally written in English, translated into Tamil or Telugu and independently back-translated. Questionnaires were administered in local languages by trained staff experienced in HIV counseling and treatment. ART adherence was also estimated using the medication possession ratio (MPR). This was calculated by dividing the days of ART dispensed by the period of time from ART start to the day of recruitment. All patients completing 12-months ART provided written informed consent and the study was approved by the institutional review boards of Christian Medical College, Tufts University Health Sciences and Monash University.

Laboratory Testing

The HIV viral load test was performed at the same time as the routine assessment of CD4 T cell counts (FACSCount) after 12-months of ART. HIV viral load was assessed by the Artus HIV-1 RT-PCR (Qiagen) with a detectable viral load defined as greater than 200 copies/mL based on viral load blips rarely being above 200 copies/mL [32].

Analysis

Baseline characteristics and dichotomous adherence estimates after 12-months ART were compared to 12-month viral load using χ^2, Fisher's exact, Student's t test, and Wilcoxon rank-sum tests as appropriate. Odds ratios of a detectable viral load after 12-months ART were also calculated for the estimates of adherence. The 30-day self-report question was dichotomized around excellent (highest adherence category) versus less than excellent adherence, the self-report question for the entire period receiving ART was dichotomized around those reporting never having missed versus ever having missed ART and the VAS was dichotomized around 95 % adherence. Dichotomous MPR estimates were created with different thresholds to define low adherence (<95, <100 %). To establish if MPR accuracy could be improved we combined the most predictive MPR measure with the 30-day and 12-month self-report questions. Individuals with low pharmacy adherence and less than excellent adherence in last 30-days, or ever reported missing ART were considered to have low adherence for this variable. Overall accuracy of adherence estimates was also assessed by calculating the area under receiver operating characteristic curves (AUROCs) and 95 % confidence intervals (CIs) for continuous (MPR) or ordinal variables (self-report). 95 % CIs of the AUROC that did not cross 0.5 indicated a statistically significant association. All analyses were conducted using SAS v9.2 (SAS Institute, Cary, NC, USA).

Results

Baseline Demographics

Baseline characteristics of 230 patients included: 65 % male, 41 % WHO clinical stage IV, active tuberculosis in 27 %, and median CD4 141 T cells/μL (Table 1). After 12-months: 77 % ($n = 177$) were on ART of which 98 % ($n = 174$) undertook HIV viral load testing, 10 % died, 8 % transferred out, 5 % were LTFU and no patients switched to second line therapy. Median CD4 T-cell count after 6 months was 309 cells/μL and after 12 months was 410 cells/μL which were both significant increases from baseline ($p < 0.001$) and 80 % ($n = 140$) of patients on treatment at 12-months had HIV viral load <200 copies/mL. There were no significant differences in baseline characteristics when stratified by viral load although a trend ($p = 0.08$) for virological suppression was present in married individuals (Table 1).

Adherence Measures

Table 2 demonstrates associations between adherence estimates after 12-months ART and HIV viral load. All estimates of adherence solely using self-report were not associated with the virological outcome ($p > 0.4$). Furthermore AUROCs for self-report estimates demonstrated no association including: 30-day self-report 0.52 (95 % CI: 0.42–0.61), last time missed ART 0.55 (95 % CI: 0.45–0.65) and 30-day VAS 0.54 (95 % CI: 0.44–0.63). The 12-month MPR with a 95 % threshold was not associated with the virological outcome (OR 1.7, $p = 0.2$) but there was a significant association with the 100 % threshold (OR 2.6, $p = 0.01$), although a greater number of individuals were considered to have low adherence with the 100 % threshold (48.9 %) compared to the 95 % adherence threshold (16.7 %). The MPR AUROC was 0.61 (95 % CI: 0.50–0.72) demonstrating a statistical association albeit on the borderline of significance The variable that combined the 12-month MPR of 100 % threshold with the 2 self-report questions was associated with HIV viral load (OR 2.1, $p = 0.05$) and less patients were considered to have low adherence (35.6 %) compared to the MPR with 100 % threshold not combined with self-report.

Table 1 Baseline characteristic stratified by detectable viral load

Baseline characteristic		Total (n = 174)	Viral load <200 copies/mL (n = 140)	Viral load >200 copies/mL (n = 34)	p Value
Age		38.3 ± 8.7	38.5 ± 8.7	37.3 ± 9.3	0.5
Gender	Male	105 (60.7)	84 (60.4)	21 (61.8)	0.9
Transmission risk factor	Heterosexual	136 (87.7)	108 (87.1)	28 (90.3)	0.5
	MSM	2 (1.3)	2 (1.6)	0	
	Other	13 (8.4)	10 (8.0)	3 (9.7)	
Education level	Non-literate	31 (19.4)	25 (19.5)	6 (18.8)	0.8
	Primary school	43 (26.9)	34 (26.6)	9 (28.1)	
	Secondary school	68 (42.5)	56 (43.8)	12 (37.5)	
	College	18 (11.3)	13 (10.2)	5 (15.6)	
Employed		106 (66.7)	84 (65.6)	22 (71.0)	0.5
Marital status	Single/separated/partner died	50 (29.0)	36 (25.9)	14 (41.2)	0.08
	Married	123 (71.1)	103 (74.1)	20 (58.8)	
Previous ARV exposure		5 (3.0)	3 (2.3)	2 (6.3)	0.2
Baseline WHO clinical stage	I/II	74 (42.5)	58 (41.4)	16 (47.1)	0.7
	III	38 (21.8)	30 (21.4)	8 (23.5)	
	IV	62 (35.6)	52 (37.1)	10 (29.4)	
Receiving TB treatment		40 (23.4)	34 (24.6)	6 (18.2)	0.4
ART regimen	D4T/3TC/NVP	78 (44.8)	59 (42.1)	19 (55.9)	0.5
	AZT/3TC/NVP	58 (33.3)	49 (35.0)	9 (26.5)	
	D4T/3TC + EFV	27 (15.5)	22 (15.7)	5 (14.7)	
	AZT/3TC + EFV	11 (6.3)	10 (7.1)	1 (2.9)	
CD4 (cells/μL)		146 (77–202)	142 (73–201)	159 (81–219)	0.5
HepBsAg positive		9 (6.0)	6 (5.0)	3 (10.0)	0.4

MSM men who have sex with men, *ARV* antiretroviral, *PMTCT* prevention of mother to child transmission, *ART* antiretroviral therapy, *WHO* World Health Organization, *TB* tuberculosis, *D4T* stavudine, *3TC* lamivudine, *NVP* nevirapine, *AZT* zidovudine, *EFV* efavirenz

Discussion

This is the first report from India describing PAMs for individuals receiving ART and the first report from India documenting associations between any measure of adherence and HIV viral load for a population that has exclusively received free ART.

Importantly, and different from studies including patients who paid for ART [20, 21], we did not observe self-reported adherence predicting virological outcomes. A potential explanation is the increased likelihood of a social desirability bias [33, 34] leading to underreporting of missed doses in programs where patients receive free care compared to patients who pay for ART. Inaccurate and more socially desirable responses by individuals receiving free care may fail to detect associations between ART adherence and virological outcomes. Furthermore, objective assessments of adherence using pharmacy data were more closely associated with virological outcomes, with the 100 % threshold variable significantly associated with viral load. This is notable as the 100 % threshold establishes if individuals were in possession of ART for the entire 12-month period since initiation. By definition individuals with less than 100 % pharmacy adherence did not have enough ART to take medication as prescribed for these first 12-months.

The 95 % threshold of adherence is the most widely cited threshold to maximise virological suppression based on data from Paterson in treatment experienced patients receiving unboosted protease inhibitor based ART [35]. Furthermore, attaining individual adherence above 95 % is cited by NACO as one of the key goals of the national ART program [12]. Subsequent studies have reported higher and lower thresholds predicting virological outcomes for populations receiving non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens in high-income and LMICs [19, 36]. Therefore alternative thresholds to identify groups at risk for poor virological outcomes warrant consideration. Findings in this study suggest an MPR threshold of 100 % may be more useful for defining individuals at risk of poor virological outcomes in this population. However, this threshold classifies approximately

Table 2 Adherence measures and CD4 change after 12-months ART predicting viral load ($n = 174$)

Adherence measure or CD4 criteria		Total	Viral load >200 copies	Viral load <200 copies	Odds ratio	*p* Value
30 day self-report (5 point Likert item)	<Excellent	130 (76.5)	25 (73.5)	105 (77.2)	0.8	0.7
	Excellent	40 (23.5)	9 (26.5)	31 (22.8)		
Self-report—last time missed	>Never	57 (33.5)	13 (38.2)	44 (32.3)	1.3	0.5
	Never	113 (66.5)	21 (61.8)	92 (67.7)		
30 day visual analog scale	≤95 %	50 (29.4)	12 (35.3)	38 (27.9)	1.4	0.4
	>95 %	120 (70.6)	22 (64.7)	98 (72.1)		
12 month MPR (days ART/whole time receiving ART)	<95 %	29 (16.7)	8 (23.5)	21 (15.0)	1.7	0.2
	≥95 %	145 (83.3)	26 (76.5)	119 (85.0)		
	<100 %	85 (48.9)	23 (67.7)	62 (44.3)	2.6	0.01
	≥100 %	89 (51.1)	11 (32.3)	78 (55.7)		
Combined self-report and MPR (12 month MPR < 100 % + suboptimal adherence on either of 2two self-report measures)[a]	Low adherence	62 (35.6)	17 (50.0)	45 (32.1)	2.1	0.05
	High adherence	112 (64.4)	17 (50.0)	95 (67.9)		
NACO immunological criteria for treatment failure[b]	Positive	18 (10.9)	3 (8.8)	15 (11.5)	0.7	1.0
	Negative	147 (89.1)	31 (91.2)	116 (88.5)		

Values represent *n* (% with that characteristic)

Characteristics compared by χ^2 test or Fisher's exact test if expected cell frequencies ≤5

ART antiretroviral therapy, *MPR* medication possession ratio, *NACO* India national AIDS control organization

[a] <Excellent adherence in last 30 days, or ever reported missing ART

[b] Minimum requirement baseline and 6 month CD4. Positive criteria; 6 or 12 month CD4 < 100, or 12 month CD4 50 % lower than 6 month CD4, or 6 or 12 month CD4 < baseline CD4

half the study population as having low adherence. The ability to target this patient group for viral load testing or adherence intervention may depend on available resources. Therefore selection of optimal adherence measures for different settings may be influenced by costs of subsequent interventions for patients with low adherence.

Combining a PAM with questions measuring self-reported adherence to more accurately identify a subpopulation at risk of a detectable viral load, in this study was above 200 copies/mL, is an innovative technique. This resulted in approximately one third of individuals defined as having low adherence yet this group was still significantly associated with the virological outcome. This finding suggests that combining different adherence measures should be further examined in populations receiving free ART in India. Replicating this technique in different settings may reinforce findings from this study and potentially identify alternate methods to accurately identify sub-populations at risk for virological failure or that require adherence support. In addition further research is necessary to identify risk factors for low adherence and virological failure for people receiving free ART in India. Barriers such as the stigma of HIV, medication side effects and depression have already been identified in studies where patients paid for ART and cost was the most commonly reported barrier [21–23, 26–29]. Identifying barriers to adherence and targeting interventions to these factors is an essential step to improve virological outcomes for individuals receiving free ART in India, in addition to identifying the best methods to estimate adherence.

Finally, immunological criteria recommended to define treatment failure in India performed poorly for predicting viral load greater than 200 copies/mL with only 9 % of subjects with detectable viral load satisfying CD4 change criteria. This is consistent with other LMIC data concerning the limited ability of CD4 criteria to detect virological failure [18, 37, 38] and supports efforts to identify non-virological factors that accurately identify individuals with virological failure, including assessments of ART adherence. Failure to correctly identify individuals failing virologically that continue NNRTI containing regimens, leads to accumulation of HIV drug resistance mutations, decreased efficacy of the current regimen, potential reduction in the activity of future regimens, immunological progression and increased risk of clinical deterioration. Furthermore, individuals who satisfy CD4 change criteria but remain virologically suppressed results in unnecessary switching to expensive second line ART. Despite the limited availability of testing for HIV drug resistance in India, surveys performed on patients initiating ART in 2007 and 2008 reported 8–9 % of individuals initiating ART had drug resistance detected after 12-months ART

[39]. These data highlight the need for accurate measures to identify individuals at risk of failing ART that can limit the development of HIV drug resistance.

Pharmacy adherence measures were established using routinely collected data in the pharmacy register. This register is an essential element to establish the volume of ART stock by documenting the amount of ART dispensed, hence there is an emphasis on accurate recording of data to ensure continuous antiretroviral supply. In practical terms estimating the MPR requires a clinic staff member to tally up the days of ART dispensed and divide that by the number of days since the patient initiated ART. This adherence estimate can be easily updated at subsequent ART pick-ups and integrated into the work flow of the clinic. Furthermore, if dispensing data is recorded electronically there is the potential for pharmacy databases to automatically generate the MPR based on the dates of ART pick-up and amount of ART dispensed.

Limitations of this study include the generalisability to other people in India receiving free antiretrovirals in different settings. However, considering the paucity of data examining adherence measures and virological outcomes for those on free ART in India the findings of this study still merit consideration in alternate settings. In addition MPR estimates in this study did not account for remnant pills which may have lead to estimates of adherence with different characteristics for predicting viral load. However a recent systematic review did not find evidence that adherence estimates that included counting remaining pills were superior to MPR for predicting virological outcomes [15]. Finally the findings of this study were limited by a relatively low sample size to detect significant association between the measures of adherence and virological outcomes.

Conclusions

Pharmacy adherence measures such as the MPR are a feasible method to assess adherence within the public health model of care in India and appear more predictive of virological outcomes that commonly employed self-reported assessments of adherence. Combining the MPR with self-reported adherence is an innovative technique to further define at risk populations in this setting and warrants further investigation. As viral load testing is not currently required for monitoring ART in India and immunological criteria performed poorly for predicting HIV viral load, adherence measures such as the ones identified in this study should be further investigated to identify individuals at risk of virological failure and in need of increased adherence support.

Acknowledgments We thank the study participants and all staff within the NACO sponsored ART Clinic at Christian Medical College (ACTFID).

Conflict of interest SRL receives payment for lectures (Viiv Healthcare and Janssen), payment for educational presentations (Janssen) and SRL's institution receives grant funding (Merck and Gilead). All other authors, no conflicts.

Funding sources JM was supported by a fellowship from Tufts Medical Center Department of Geographic Medicine and Infectious Diseases, and an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship. The study was supported by a Lifespan/Tufts/Brown Center for AIDS Research NIH Grant (1P30A142853-12). AM was supported by a Fogarty International Center training Grant (5D43TW000237-15). MRJ was supported by an NIH Career Development Award (5K23AI074423-04). SRL is an NHMRC Practitioner Fellow.

References

1. NACO. National Aids Control Organisation, India HIV data. New Delhi: National Aids Control Organisation, India. 2012. http://www.nacoonline.org/Quick_Links/HIV_Data/. Accessed 12 July 2012.
2. WHO. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2010. Geneva, World Health Organization. 2010.
3. USAID. Private Sector Utilization of HIV/AIDS Services & Health Expenditures by People Living with HIV/AIDS in India: findings from five high-prevalence states. 2009.
4. NACO. Annual Report 2011–12. India: Department of AIDS Control. Ministry of Health & Family Welfare. Government of India. 2012.
5. Nieuwkerk PT, Oort FJ. Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis. J Acquir Immune Defic Syndr. 2005;38(4):445–8.
6. Harrigan PR, Hogg RS, Dong WW, Yip B, Wynhoven B, Woodward J, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. J Infect Dis. 2005;191(3):339–47.
7. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J Acquir Immune Defic Syndr. 2006; 43(1):78–84.
8. Chi BH, Cantrell RA, Zulu I, Mulenga LB, Levy JW, Tambatamba BC, et al. Adherence to first-line antiretroviral therapy affects non-virologic outcomes among patients on treatment for more than 12 months in Lusaka Zambia. Int J Epidemiol. 2009;38(3):746–56.
9. Ware NC, Idoko J, Kaaya S, Biraro IA, Wyatt MA, Agbaji O, et al. Explaining adherence success in sub-Saharan Africa: an ethnographic study. PLoS Med. 2009;6(1):e11.
10. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006;296(6): 679–90.
11. Elliott JH, Lynen L, Calmy A, De Luca A, Shafer RW, Zolfo M, et al. Rational use of antiretroviral therapy in low-income and middle-income countries: optimizing regimen sequencing and switching. AIDS. 2008;22(16):2053–67.

12. NACO. Antiretroviral therapy guidelines for HIV-infected adults and adolescents including post-exposure prophylaxis. National AIDS and Control Organisation, Ministry of Health & Family Welfare, Government of India. 2007.
13. Nachega JB, Mills EJ, Schechter M. Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of knowledge and research priorities. Curr Opin HIV AIDS. 2010;5(1):70–7.
14. van den Boogaard J, Lyimo RA, Boeree MJ, Kibiki GS, Aarnoutse RE. Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study. Bull World Health Organ. 2011;89(9):632–9.
15. McMahon J, Jordan M, Kelley K, Bertagnolio S, Hong S, Wanke C, et al. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. Clin Infect Dis. 2011;52(4):493–506.
16. Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. Antivir Ther. 2008;13(Suppl 2):1–13.
17. WHO. Meeting report on assessment of World Health Organization HIV drug resistance early warning indicators: report of the Early Advisory Indicator Panel meeting, 11–12 August 2011, Geneva, Switzerland. 2012. http://apps.who.int/iris/bitstream/10665/75186/1/9789241503945_eng.pdf. Accessed 22 Aug 2012.
18. Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, Regensberg L, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. PLoS Med. 2008;5(5):e109.
19. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. Ann Intern Med. 2007;146(8):564–73.
20. Ekstrand ML, Chandy S, Heylen E, Steward W, Singh G. Developing useful highly active antiretroviral therapy adherence measures for India: the Prerana study. J Acquir Immune Defic Syndr. 2010;53(3):415–6.
21. Shah B, Walshe L, Saple DG, Mehta SH, Ramnani JP, Kharkar RD, et al. Adherence to antiretroviral therapy and virologic suppression among HIV-infected persons receiving care in private clinics in Mumbai, India. Clin Infect Dis. 2007;44(9):1235–44.
22. Shet A, DeCosta A, Heylen E, Shastri S, Chandy S, Ekstrand M. High rates of adherence and treatment success in a public and public-private HIV clinic in India: potential benefits of standardized national care delivery systems. BMC Health Serv Res. 2011;11:277.
23. Vallabhaneni S, Chandy S, Heylen E, Ekstrand M. Reasons for and correlates of antiretroviral treatment interruptions in a cohort of patients from public and private clinics in southern India. AIDS Care. 2011;24(6):687–94.
24. Ekstrand ML, Shet A, Chandy S, Singh G, Shamsundar R, Madhavan V, et al. Suboptimal adherence associated with virological failure and resistance mutations to first-line highly active antiretroviral therapy (HAART) in Bangalore, India. Int Health. 2011;3(1):27–34.
25. Private Healthcare in Developing Countries. 2012. http://ps4h.org/hiv_aids.html. Accessed 31 July 2012.
26. Kumarasamy N, Safren SA, Raminani SR, Pickard R, James R, Krishnan AK, et al. Barriers and facilitators to antiretroviral medication adherence among patients with HIV in Chennai, India: a qualitative study. AIDS Patient Care STDs. 2005;19(8):526–37.
27. Wanchu A, Kaur R, Bambery P, Singh S. Adherence to generic reverse transcriptase inhibitor-based antiretroviral medication at a Tertiary Center in North India. AIDS Behav. 2007;11(1):99–102.
28. Sarna A, Pujari S, Sengar AK, Garg R, Gupta I, Dam J. Adherence to antiretroviral therapy & its determinants amongst HIV patients in India. Indian J Med Res. 2008;127(1):28–36.
29. Anuradha S, Joshi A, Negi M, Nischal N, Rajeshwari K, Dewan R. Factors influencing adherence to ART: new insights from a center providing free art under the national program in Delhi, India. J Int Assoc Physicians AIDS Care (Chic). 2012. Epub 2012/01/17.
30. Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care. 2000;12(3):255–66.
31. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. HIV Clin Trials. 2004;5(2):74–9.
32. Nettles RE, Kieffer TL, Kwon P, Monie D, Han Y, Parsons T, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. JAMA. 2005;293(7):817–29.
33. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. J Infect Dis. 2008;197(Suppl 3):S272–8.
34. Nieuwkerk PT, de Boer-van KIM, Prins JM, Locadia M, Sprangers MA. Self-reported adherence is more predictive of virological treatment response among patients with a lower tendency towards socially desirable responding. Antivir Ther. 2010;15(6):913–6.
35. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133(1):21–30.
36. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. Clin Infect Dis. 2006;43(7):939–41.
37. Mee P, Fielding KL, Charalambous S, Churchyard GJ, Grant AD. Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa. AIDS. 2008;22(15):1971–7.
38. Chaiwarith R, Wachirakaphan C, Kotarathititum W, Praparatanaphan J, Sirisanthana T, Supparatpinyo K. Sensitivity and specificity of using CD4+ measurement and clinical evaluation to determine antiretroviral treatment failure in Thailand. Int J Infect Dis. 2007;11(5):413–6.
39. Hingankar NK, Thorat SR, Deshpande A, Rajasekaran S, Chandrasekar C, Kumar S, et al. Initial virologic response and HIV drug resistance among HIV-infected individuals initiating first-line antiretroviral therapy at 2 clinics in Chennai and Mumbai, India. Clin Infect Dis. 2012;54(Suppl 4):S348–54.

8 General Discussion

This thesis combines six published and one submitted manuscript comprising three systematic reviews and four original research papers. All of these studies are focused on clinical outcomes for individuals living with HIV and receiving ART and address the overarching goal of this thesis. The goal was to identify patient specific factors associated with worse clinical outcomes and the identification of methods to better assess adherence to ART in diverse clinical settings. This work will allow for the identification of factors that can be targeted for intervention to improve treatment outcomes for populations living with HIV in diverse clinical settings. Importantly studies for this thesis were performed in different settings of United States and India which are countries that reflect the widespread impact of the HIV epidemic in both higher and lower income countries.

This body of work is a significant contribution as it identifies multiple novel factors that predict clinical outcomes for PLHIV in diverse clinical settings. All three systematic reviews represent the most recent data in their respective fields and present evidence to support physically tracing patients lost to ART care, provide a benchmark for virological outcomes for people receiving ART in LMICs and provide a framework for the use of pharmacy data to estimate adherence to ART.

The studies performed in the United States investigated the contribution of socio-economic factors to important patient outcomes. This included the first study in PLHIV to show that individual assessments of SES is associated with impaired CD4 counts and HIV viral load over time by virtue of the mixed model regression analysis that was used. In addition this work details how SES can impact survival directly but also indirectly via effects on CD4 T-cell counts and HIV viral load. The second study from the NFHL cohort is significant as it is the first to report on multiple assessments of food security status and the association with a clinical outcome. Furthermore it demonstrated how even a single episode of documented food insecurity is a risk for poor immunological response, similar to individuals documented to be chronically food insecure.

Studies from India were significant as they are one of the first studies to document virological outcomes for populations exclusively receiving free ART in the public

health model of care. The research techniques applied to identify social factors that predict virological outcomes are significant as they represent minimum-resource methods to identify targets for intervention to improve outcomes at the site and also potentially in similar settings in the region. The second study in India demonstrated how pre-existing pharmacy records can be utilized to estimate ART adherence and the advantages of this approach over the commonly used self-report estimates.

Multiple clinical recommendations can be made based on this thesis relevant to populations in higher and lower income countries receiving ART:

1. Interventions to physically trace individuals in ART care with unknown outcome should be considered to improve programmatic evaluation of HIV infected populations receiving ART and individual outcomes by:
    a. Potentially improving re-engagement and retention in ART care.
    b. Reducing unknown outcomes as patients are re-classified as having died or transferred care out.
2. Understanding summary estimates of virological outcomes in LMICs is necessary to allow ART program managers to define desirable levels of clinic and program performance and set targets of virological suppression
3. Pharmacy based methods are reliable minimum-resource methods to estimate adherence to ART.
4. PAMs such as the Medication Possession Ratio that include the number of days for which ART is prescribed and that are of longer duration ($\geq$ 6 months) are likely to be more predictive of virological outcomes for PLHIV receiving ART.
5. Assessments of socioeconomic status in HICs with questions about personal income, highest level of education, housing and access to a nutritionally adequate diet are suggested to identify individuals at risk of decreased survival despite receiving ART.
6. Interventional studies aimed at alleviating factors that classify PLHIV in HICs as having low SES are necessary to improve clinical outcomes for this population despite the advances achieved with ART.
7. Repeated assessments of food security status of PLHIV are an additional tool to identify individuals at risk of poor immunological response even in the setting of ART.

8. Interventions that provide access to safe and reliable sources of food may improve clinical outcomes of PLHIV in HICs on ART
9. Incorporating operational research methods into busy clinics providing ART in a public health model of care is a mechanism to establish factors that predict poor virological outcomes for people receiving ART in this setting.
10. People who are enrolled in ART care in public programs similar to that of southern India and have busy schedules due to work or caring for others, consume alcohol or have long transport times to clinic may benefit from interventions to improve virological outcomes. These interventions may also prolong the availability of first line ART in this setting.
11. Potential interventions include: clinician or peer based interventions to provide extra support for people with busy schedules (126), motivational interviewing and cognitive behavioral training for individuals with increased alcohol use (127), and decentralisation of ART services as a program level intervention to reduce transport times (128-130).
12. Pharmacy adherence measures such as the Medication Possession Ratio are a feasible method to assess ART adherence in Tamil Nadu India and are potentially more predictive of virological outcomes than the nationally recommended self-reported assessments of adherence.

This thesis has a number of limitations. Considering the diversity of social, cultural, behavioural and clinical context in which people receive ART, there are limits to the generalizability of the associations documented here. Furthermore different outcomes for the different studies have been considered, including; survival immunological response and virological response. Different outcomes were used for studies reported here as it was not feasible to study the three outcomes in both settings. Ultimately implementation of interventions targeted against identified factors that predicted worse clinical outcomes will require interventional studies to understand efficacy and effectiveness, including cost effectiveness, of the interventions.

Findings from this thesis provide the platform for multiple future avenues of research. The systematic review of PAMs highlights the need for research to confirm whether PAMs are superior to self-reported adherence assessments and to accurately identify

PAM parameters most predictive of virological outcomes. Findings from the review of physical tracing revealed a critical need for randomised controlled trials to investigate the effectiveness of patient tracing to improve re-engagement of patients on ART and assess the cost-effectiveness of tracing interventions. In addition the systematic review of virological outcomes provides a benchmark for these outcomes in LMIC settings. There will be a need to update these findings in future years as viral load testing increases in LMICs as test costs fall or programs seek to prioritise this method of monitoring.

Studies performed in the NFHL cohort highlight the need to examine structured interventions that alleviate poverty and other identified factors contributing to low SES. In addition, further work is required to assess if multiple assessments of food security predict clinical outcomes other than changes in CD4 count. Further research to try and elucidate the mechanism by which food security impacts poor immunological response is also required, including exploring whether a biological mechanism exists whereby food insecure individuals have a poor quality diet deficient in nutrients that effects response to ART. Also important is determining whether food security is a surrogate for poor access to ART care, poor adherence to ART or depression.

The findings from the studies in India lead us to enquire if interventions directed against those factors that predicted poor virological outcomes would increase the proportion of individuals virologically suppressed in settings such as the one studied. Further study is needed to confirm the utility of PAMs in India, as the published study was the first to report such a finding and establish the parameters of PAMs that best predict virological failure. Monitoring of ART adherence using pharmacy data has implications not only for the centre where this research was performed but is a potential mechanism for ART programs within India and other LMICs to effectively monitor adherence at an individual or site level. Results of these monitoring efforts can identify patients or sites that may require increased adherence support. Use of pharmacy based monitoring tools is recommended by the WHO as population based method to assess adherence to prevent the emergence of HIV drug resistance (131). The optimal PAM characteristics including the duration of adherence assessment and

thresholds to define low or high adherence are not known and warrants further research to identify PAMs with optimal characteristics for treatment monitoring in LMICs. In addition to research to identify PAMs with optimal characteristics trials that examine the effect of adherence interventions for individuals identified as having low pharmacy adherence also represent a future need.

In conclusion this thesis has collated a body of work that aims to contribute to improved clinical outcomes for the millions of individuals receiving ART in diverse settings around the world. As the global response to HIV continues with numerous successes, including the provision of this therapy to over 8 million people around the world, many challenges remain. World leaders and agencies such as the WHO and UNAIDS have adopted the goal of 15 million individuals receiving ART by the year 2015 and the vision of an AIDS free generation (132). Despite these achievements and goals 1.5 – 1.8 million AIDS related deaths still occurred in 2010 and 2.5 million new HIV infection occurred in 2011 highlighting the need for a sustained global effort (16, 133). Maintaining this global response will require increased levels of funding, improved synergies and integration of HIV and non-HIV related healthcare systems and improved methods to engage with populations living with and at risk of HIV (17). As all stakeholders strive to improve care for PLHIV and indeed aim for an AIDS free generation all avenues to improve clinical outcomes for PLHIV need to be investigated and understood. Social and behavioural aspects remain a critical component to the lives of PLHIV that can influence the response to life saving ART. These factors should remain a constant focus of clinical enquiry and ongoing research efforts as clinicians and investigators strive to improve chronic HIV care for populations living with HIV in diverse clinical settings.

9 References

1. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2012. Joint United Nations Programme on HIV/AIDS (UNAIDS), 2012.

2. Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. The New England journal of medicine. 1998 Mar 26;338(13):853-60. PubMed PMID: 9516219. eng.

3. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. 2006 Mar 11;367(9513):817-24. PubMed PMID: 16530575. Epub 2006/03/15. eng.

4. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. The New England journal of medicine. 1987 Jul 23;317(4):185-91. PubMed PMID: 3299089. Epub 1987/07/23. eng.

5. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature. 1995 Jan 12;373(6510):123-6. PubMed PMID: 7816094. Epub 1995/01/12. eng.

6. Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. Science. 1989 Mar 31;243(4899):1731-4. PubMed PMID: 2467383. Epub 1989/03/31. eng.

7. Hammer SM, Katzenstein DA, Hughes MD, Gundacker H, Schooley RT, Haubrich RH, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. The New England journal of medicine. 1996 Oct 10;335(15):1081-90. PubMed PMID: 8813038. Epub 1996/10/10. eng.

8. D'Aquila RT, Hughes MD, Johnson VA, Fischl MA, Sommadossi JP, Liou SH, et al. Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection. A randomized, double-blind, placebo-controlled trial. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group Protocol 241 Investigators. Annals of internal medicine. 1996 Jun 15;124(12):1019-30. PubMed PMID: 8633815. Epub 1996/06/15. eng.

9. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. The New England journal of medicine. 1997 Sep 11;337(11):725-33. PubMed PMID: 9287227. Epub 1997/09/11. eng.

10. Montaner JS, Reiss P, Cooper D, Vella S, Harris M, Conway B, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. JAMA. 1998 Mar 25;279(12):930-7. PubMed PMID: 9544767. Epub 1998/04/17. eng.

11. Djomand G, Roels T, Ellerbrock T, Hanson D, Diomande F, Monga B, et al. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire. AIDS. 2003 Jul;17 Suppl 3:S5-15. PubMed PMID: 14565604. Epub 2003/10/21. eng.

12. Torres RA, Barr M. Impact of combination therapy for HIV infection on inpatient census. The New England journal of medicine. 1997 May 22;336(21):1531-2. PubMed PMID: 9157292.

13. Centers for Disease C, Prevention. Update: trends in AIDS incidence, deaths, and prevalence--United States, 1996. MMWR Morbidity and mortality weekly report. 1997 Feb 28;46(8):165-73. PubMed PMID: 9072676.

14. Gupta A, Nadkarni G, Yang WT, Chandrasekhar A, Gupte N, Bisson GP, et al. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis. PloS one. 2011;6(12):e28691. PubMed PMID: 22220193. Pubmed Central PMCID: 3248405.

15. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. AIDS. 2008 Oct 1;22(15):1897-908. PubMed PMID: 18784453.

16. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2095-128. PubMed PMID: 23245604. Epub 2012/12/19. eng.

17. Sidibe M, Piot P, Dybul M. AIDS is not over. Lancet. 2012 Dec 15;380(9859):2058-60. PubMed PMID: 23245599. Epub 2012/12/19. eng.

18. Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA. 2010 Jul 21;304(3):321-33. PubMed PMID: 20639566. Epub 2010/07/20. eng.

19. DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services 2012 [May 12 2012]. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

20. Asboe D, Aitken C, Boffito M, Booth C, Cane P, Fakoya A, et al. British HIV Association guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011. HIV Med. 2012 Jan;13(1):1-44. PubMed PMID: 22171742. Epub 2011/12/17. eng.

21. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sorensen HT, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Annals of internal medicine. 2007 Jan 16;146(2):87-95. PubMed PMID: 17227932. Epub 2007/01/18. eng.

22. Losina E, Schackman BR, Sadownik SN, Gebo KA, Walensky RP, Chiosi JJ, et al. Racial and sex disparities in life expectancy losses among HIV-infected persons in the united states: impact of risk behavior, late initiation, and early discontinuation of antiretroviral therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009 Nov 15;49(10):1570-8. PubMed PMID: 19845472. Pubmed Central PMCID: 2783631. Epub 2009/10/23. eng.

23. Wada N, Jacobson LP, Cohen M, French A, Phair J, Munoz A. Cause-Specific Life Expectancies After 35 Years of Age for Human Immunodeficiency Syndrome-Infected and Human Immunodeficiency Syndrome-Negative Individuals Followed Simultaneously in Long-term Cohort Studies, 1984-2008. American journal of epidemiology. 2013 Jan 15;177(2):116-25. PubMed PMID: 23287403. Epub 2013/01/05. eng.

24. Reekie J, Kowalska JD, Karpov I, Rockstroh J, Karlsson A, Rakhmanova A, et al. Regional differences in AIDS and non-AIDS related mortality in HIV-positive individuals across Europe and Argentina: the EuroSIDA study. PloS one.

2012;7(7):e41673. PubMed PMID: 22911841. Pubmed Central PMCID: 3402435. Epub 2012/08/23. eng.

25. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of clinical endocrinology and metabolism. 2007 Jul;92(7):2506-12. PubMed PMID: 17456578. Pubmed Central PMCID: 2763385.

26. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. The New England journal of medicine. 2002 Nov 14;347(20):1585-92. PubMed PMID: 12432046. eng.

27. Huisman M, Kunst AE, Bopp M, Borgan JK, Borrell C, Costa G, et al. Educational inequalities in cause-specific mortality in middle-aged and older men and women in eight western European populations. Lancet. 2005 Feb 5-11;365(9458):493-500. PubMed PMID: 15705459. eng.

28. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979 May 11;241(19):2035-8. PubMed PMID: 430798. Epub 1979/05/11. eng.

29. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA. 1996 May 22-29;275(20):1571-6. PubMed PMID: 8622248. Epub 1996/05/22. eng.

30. Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, et al. Class of antiretroviral drugs and the risk of myocardial infarction. The New England journal of medicine. 2007 Apr 26;356(17):1723-35. PubMed PMID: 17460226. Epub 2007/04/27. eng.

31. Joy R, Druyts EF, Brandson EK, Lima VD, Rustad CA, Zhang W, et al. Impact of neighborhood-level socioeconomic status on HIV disease progression in a universal health care setting. Journal of acquired immune deficiency syndromes (1999). 2008 Apr 1;47(4):500-5. PubMed PMID: 18197117. eng.

32. McDavid Harrison K, Ling Q, Song R, Hall HI. County-level socioeconomic status and survival after HIV diagnosis, United States. Annals of epidemiology. 2008 Dec;18(12):919-27. PubMed PMID: 19041591. eng.

33. Wood E, Montaner JS, Chan K, Tyndall MW, Schechter MT, Bangsberg D, et al. Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996. Aids. 2002 Oct 18;16(15):2065-72. PubMed PMID: 12370506. eng.

34. Fordyce EJ, Singh TP, Nash D, Gallagher B, Forlenza S. Survival rates in NYC in the era of combination ART. Journal of acquired immune deficiency syndromes (1999). 2002 May 1;30(1):111-8. PubMed PMID: 12048371. eng.

35. Weiser SD, Bangsberg DR, Kegeles S, Ragland K, Kushel MB, Frongillo EA. Food insecurity among homeless and marginally housed individuals living with HIV/AIDS in San Francisco. AIDS Behav. 2009 Oct;13(5):841-8. PubMed PMID: 19644748. Pubmed Central PMCID: PMC2758196. Epub 2009/08/01. eng.

36. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Annals of internal medicine. 2000 Jul 4;133(1):21-30. PubMed PMID: 10877736. Epub 2000/07/06. eng.

37. Lima VD, Harrigan R, Bangsberg DR, Hogg RS, Gross R, Yip B, et al. The Combined Effect of Modern Highly Active Antiretroviral Therapy Regimens and Adherence on Mortality Over Time. Journal of acquired immune deficiency syndromes (1999). 2009 Apr;50(5):529-36. PubMed PMID: 19223785. Eng.

38. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. Journal of acquired immune deficiency syndromes (1999). 2006 Sep;43(1):78-84. PubMed PMID: 16878045. eng.

39. Nachega JB, Hislop M, Dowdy DW, Chaisson RE, Regensberg L, Maartens G. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. Annals of internal medicine. 2007 Apr 17;146(8):564-73. PubMed PMID: 17438315. eng.

40. Bangsberg DR, Acosta EP, Gupta R, Guzman D, Riley ED, Harrigan PR, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS. 2006 Jan 9;20(2):223-31. PubMed PMID: 16511415. Epub 2006/03/03. eng.

41. Nachega JB, Mills EJ, Schechter M. Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of

knowledge and research priorities. Curr Opin HIV AIDS. 2010 Jan;5(1):70-7. PubMed PMID: 20046150. Epub 2010/01/05. eng.

42. Nieuwkerk PT, Oort FJ. Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis. Journal of acquired immune deficiency syndromes (1999). 2005 Apr 1;38(4):445-8. PubMed PMID: 15764962.

43. Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, Regensberg L, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. PLoS medicine. 2008 May 20;5(5):e109. PubMed PMID: 18494555. Pubmed Central PMCID: 2386831.

44. Deering KN, Shannon K, Sinclair H, Parsad D, Gilbert E, Tyndall MW. Piloting a peer-driven intervention model to increase access and adherence to antiretroviral therapy and HIV care among street-entrenched HIV-positive women in Vancouver. AIDS patient care and STDs. 2009 Aug;23(8):603-9. PubMed PMID: 19591602.

45. Koenig LJ, Pals SL, Bush T, Pratt Palmore M, Stratford D, Ellerbrock TV. Randomized controlled trial of an intervention to prevent adherence failure among HIV-infected patients initiating antiretroviral therapy. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2008 Mar;27(2):159-69. PubMed PMID: 18377134.

46. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010 Nov 27;376(9755):1838-45. PubMed PMID: 21071074.

47. March K, Mak M, Louie SG. Effects of pharmacists' interventions on patient outcomes in an HIV primary care clinic. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2007 Dec 15;64(24):2574-8. PubMed PMID: 18056946.

48. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS medicine. 2006 Nov;3(11):e438. PubMed PMID: 17121449. Pubmed Central PMCID: 1637123. Epub 2006/11/24. eng.

49. Reid DD, Brett GZ, Hamilton PJ, Jarrett RJ, Keen H, Rose G. Cardiorespiratory disease and diabetes among middle-aged male Civil Servants. A study of screening

and intervention. Lancet. 1974 Mar 23;1(7856):469-73. PubMed PMID: 4131881. Epub 1974/03/23. eng.

50. Marmot MG, Smith GD, Stansfeld S, Patel C, North F, Head J, et al. Health inequalities among British civil servants: the Whitehall II study. Lancet. 1991 Jun 8;337(8754):1387-93. PubMed PMID: 1674771. Epub 1991/06/08. eng.

51. Sugisawa H, Liang J, Liu X. Social networks, social support, and mortality among older people in Japan. Journal of gerontology. 1994 Jan;49(1):S3-13. PubMed PMID: 8282987. Epub 1994/01/01. eng.

52. Stringhini S, Berkman L, Dugravot A, Ferrie JE, Marmot M, Kivimaki M, et al. Socioeconomic status, structural and functional measures of social support, and mortality: The British Whitehall II Cohort Study, 1985-2009. American journal of epidemiology. 2012 Jun 15;175(12):1275-83. PubMed PMID: 22534202. Pubmed Central PMCID: 3372313. Epub 2012/04/27. eng.

53. Polednak AP. Poverty, comorbidity, and survival of colorectal cancer patients diagnosed in Connecticut. Journal of health care for the poor and underserved. 2001 Aug;12(3):302-10. PubMed PMID: 11475548. Epub 2001/07/31. eng.

54. Schootman M, Jeffe DB, Lian M, Gillanders WE, Aft R. The role of poverty rate and racial distribution in the geographic clustering of breast cancer survival among older women: a geographic and multilevel analysis. American journal of epidemiology. 2009 Mar 1;169(5):554-61. PubMed PMID: 19103608. Pubmed Central PMCID: 2727182. Epub 2008/12/24. eng.

55. Ponnambalam L, Samavedham L, Lee HR, Ho CS. Understanding the socioeconomic heterogeneity in healthcare in US counties: the effect of population density, education and poverty on H1N1 pandemic mortality. Epidemiology and infection. 2012 May;140(5):803-13. PubMed PMID: 21835071. Epub 2011/08/13. eng.

56. Kaler SG. Diseases of poverty with high mortality in infants and children: malaria, measles, lower respiratory infections, and diarrheal illnesses. Annals of the New York Academy of Sciences. 2008;1136:28-31. PubMed PMID: 18579873. Epub 2008/06/27. eng.

57. McFarland W, Chen S, Hsu L, Schwarcz S, Katz M. Low socioeconomic status is associated with a higher rate of death in the era of highly active antiretroviral

therapy, San Francisco. Journal of acquired immune deficiency syndromes (1999). 2003 May 1;33(1):96-103. PubMed PMID: 12792361. eng.

58. Katz MH, Hsu L, Lingo M, Woelffer G, Schwarcz SK. Impact of socioeconomic status on survival with AIDS. American journal of epidemiology. 1998 Aug 1;148(3):282-91. PubMed PMID: 9690366. eng.

59. Chaisson RE, Keruly JC, Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. The New England journal of medicine. 1995 Sep 21;333(12):751-6. PubMed PMID: 7643881. eng.

60. Knox TA, Spiegelman D, Skinner SC, Gorbach S. Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. The American journal of gastroenterology. 2000 Dec;95(12):3482-9. PubMed PMID: 11151881. eng.

61. Weiser SD, Frongillo EA, Ragland K, Hogg RS, Riley ED, Bangsberg DR. Food insecurity is associated with incomplete HIV RNA suppression among homeless and marginally housed HIV-infected individuals in San Francisco. J Gen Intern Med. 2008 Jan;24(1):14-20. PubMed PMID: 18953617. Pubmed Central PMCID: PMC2607506. Epub 2008/10/28. eng.

62. Kalichman SC, Cherry C, Amaral C, White D, Kalichman MO, Pope H, et al. Health and treatment implications of food insufficiency among people living with HIV/AIDS, Atlanta, Georgia. J Urban Health. 2010 Jul;87(4):631-41. PubMed PMID: 20419478. Pubmed Central PMCID: 2900577. Epub 2010/04/27. eng.

63. Anema A, Weiser SD, Fernandes KA, Ding E, Brandson EK, Palmer A, et al. High prevalence of food insecurity among HIV-infected individuals receiving HAART in a resource-rich setting. AIDS Care. 2011 Feb;23(2):221-30. PubMed PMID: 21259135. Epub 2011/01/25. eng.

64. Anema A, Vogenthaler N, Frongillo EA, Kadiyala S, Weiser SD. Food insecurity and HIV/AIDS: current knowledge, gaps, and research priorities. Curr HIV/AIDS Rep. 2009 Nov;6(4):224-31. PubMed PMID: 19849966. Epub 2009/10/24. eng.

65. Weiser SD, Fernandes KA, Brandson EK, Lima VD, Anema A, Bangsberg DR, et al. The association between food insecurity and mortality among HIV-infected individuals on HAART. Journal of acquired immune deficiency syndromes (1999). 2009 Nov 1;52(3):342-9. PubMed PMID: 19675463. Epub 2009/08/14. eng.

66. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003 Jul 5;362(9377):22-9. PubMed PMID: 12853195. eng.

67. Marin B, Thiebaut R, Bucher HC, Rondeau V, Costagliola D, Dorrucci M, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. AIDS. 2009 Aug 24;23(13):1743-53. PubMed PMID: 19571723. Pubmed Central PMCID: 3305466.

68. Cohen OJ, Fauci AS. HIV/AIDS in 1998--gaining the upper hand? JAMA. 1998 Jul 1;280(1):87-8. PubMed PMID: 9660369. Epub 1998/07/11. eng.

69. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. The New England journal of medicine. 1997 Sep 11;337(11):734-9. PubMed PMID: 9287228. Epub 1997/09/11. eng.

70. UNAIDS. Access to drugs: UNAIDS Technical Update. 1998 October 1998. Report No.

71. UNGASS. Declaration of Commitment on HIV/AIDS. United Nations General Assembly Special Session on HIV/AIDS, 2001.

72. WHO/UNAIDS. Progress on global access to HIV antiretroviral therapy: a report on “3 by 5” and beyond. 2006.

73. WHO. Towards universal access : scaling up priority HIV/AIDS interventions in the health sector : progress report 2011. Geneva: World Health Organization, 2011.

74. IIPS. National Family Health Survey (NFHS-3), 2005-06. Mumbai: International Institute for Population Sciences (IIPS) and Macro International, 2007.

75. Steinbrook R. HIV in India--a downsized epidemic. The New England journal of medicine. 2008 Jan 10;358(2):107-9. PubMed PMID: 18184956. eng.

76. NACO. National Aids Control Organisation, India HIV data New Delhi: National Aids Control Organisation, India; 2012 [January 25 2013]. Available from: http://www.nacoonline.org/Quick_Links/HIV_Data/.

77. WHO. Towards universal access : scaling up priority HIV/AIDS interventions in the health sector : progress report 2010. Geneva: World Health Organization, 2010.

78. NACO. Antiretroviral Therapy Guidelines for HIV-Infected Adults and Adolescents Including Post-exposure Prophylaxis. National AIDS and Control Organisation, Ministry of Health & Family Welfare, Government of India., 2007.

79. Neogi U, Heylen E, Shet A, Chandy S, Shamsunder R, Sonnerborg A, et al. Long-term efficacy of first line antiretroviral therapy in Indian HIV-1 infected patients: a longitudinal cohort study. PloS one. 2013;8(1):e55421. PubMed PMID: 23383185. Pubmed Central PMCID: 3559582.

80. Kumarasamy N, Madhavan V, Venkatesh KK, Saravanan S, Kantor R, Balakrishnan P, et al. High frequency of clinically significant mutations after first-line generic highly active antiretroviral therapy failure: implications for second-line options in resource-limited settings. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009 Jul 15;49(2):306-9. PubMed PMID: 19522657.

81. Ekstrand ML, Shet A, Chandy S, Singh G, Shamsundar R, Madhavan V, et al. Suboptimal adherence associated with virological failure and resistance mutations to first-line highly active antiretroviral therapy (HAART) in Bangalore, India. International health. 2011 Mar 1;3(1):27-34. PubMed PMID: 21516199. Pubmed Central PMCID: 3079268. Epub 2011/04/26. Eng.

82. Hingankar NK, Thorat SR, Deshpande A, Rajasekaran S, Chandrasekar C, Kumar S, et al. Initial virologic response and HIV drug resistance among HIV-infected individuals initiating first-line antiretroviral therapy at 2 clinics in Chennai and Mumbai, India. Clin Infect Dis. 2012 May;54 Suppl 4:S348-54. PubMed PMID: 22544202. Pubmed Central PMCID: 3338312. Epub 2012/05/11. eng.

83. Elliott JH, Lynen L, Calmy A, De Luca A, Shafer RW, Zolfo M, et al. Rational use of antiretroviral therapy in low-income and middle-income countries: optimizing regimen sequencing and switching. AIDS (London, England). 2008 Oct 18;22(16):2053-67. PubMed PMID: 18753937. eng.

84. Emenyonu NI, Muyindike W, Habyarimana J, Pops-Eleches C, Thirumurthy H, Ragland K, et al. Cash Transfers to Cover Clinic Transportation Costs Improve Adherence and Retention in Care in a HIV Treatment Program in Rural Uganda. Clinical Retroviruses and Opportunistic Infections; San Francisco, USA2010.

85. Munoz M, Bayona J, Sanchez E, Arevalo J, Sebastian JL, Arteaga F, et al. Matching social support to individual needs: a community-based intervention to

improve HIV treatment adherence in a resource-poor setting. AIDS Behav. 2011 Oct;15(7):1454-64. PubMed PMID: 20383572.

86. Gross R, Bellamy SL, Chapman J, Han X, O'Duor J, Palmer SC, et al. Managed problem solving for antiretroviral therapy adherence: a randomized trial. JAMA internal medicine. 2013 Feb 25;173(4):300-6. PubMed PMID: 23358784.

87. Nachega JB, Chaisson RE, Goliath R, Efron A, Chaudhary MA, Ram M, et al. Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy. AIDS. 2010 Jun 1;24(9):1273-80. PubMed PMID: 20453627. Pubmed Central PMCID: 2888722.

88. Chang LW, Kagaayi J, Nakigozi G, Ssempijja V, Packer AH, Serwadda D, et al. Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial. PloS one. 2010;5(6):e10923. PubMed PMID: 20532194. Pubmed Central PMCID: 2880005.

89. Nieuwkerk PT, de Boer-van der Kolk IM, Prins JM, Locadia M, Sprangers MA. Self-reported adherence is more predictive of virological treatment response among patients with a lower tendency towards socially desirable responding. Antiviral therapy. 2010;15(6):913-6. PubMed PMID: 20834104. Epub 2010/09/14. eng.

90. Arnsten JH, Demas PA, Farzadegan H, Grant RW, Gourevitch MN, Chang CJ, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2001 Oct 15;33(8):1417-23. PubMed PMID: 11550118. Pubmed Central PMCID: 2692641.

91. WHO. Priority interventions: HIV/AIDS prevention, treatment and care in the health sector, September 2008. World Health Organization, 2008.

92. Munoz M, Finnegan K, Zeladita J, Caldas A, Sanchez E, Callacna M, et al. Community-based DOT-HAART accompaniment in an urban resource-poor setting. AIDS Behav. 2010 Jun;14(3):721-30. PubMed PMID: 19370409.

93. Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. Journal of acquired immune deficiency syndromes (1999). 2006 Dec 1;43 Suppl 1:S23-35. PubMed PMID: 17133201.

94. Kumarasamy N, Safren SA, Raminani SR, Pickard R, James R, Krishnan AK, et al. Barriers and facilitators to antiretroviral medication adherence among patients with HIV in Chennai, India: a qualitative study. AIDS patient care and STDs. 2005 Aug;19(8):526-37. PubMed PMID: 16124847. eng.

95. Sarna A, Pujari S, Sengar AK, Garg R, Gupta I, Dam J. Adherence to antiretroviral therapy & its determinants amongst HIV patients in India. The Indian journal of medical research. 2008 Jan;127(1):28-36. PubMed PMID: 18316850. eng.

96. Shah B, Walshe L, Saple DG, Mehta SH, Ramnani JP, Kharkar RD, et al. Adherence to antiretroviral therapy and virologic suppression among HIV-infected persons receiving care in private clinics in Mumbai, India. Clin Infect Dis. 2007 May 1;44(9):1235-44. PubMed PMID: 17407045. eng.

97. Wanchu A, Kaur R, Bambery P, Singh S. Adherence to generic reverse transcriptase inhibitor-based antiretroviral medication at a Tertiary Center in North India. AIDS and behavior. 2007 Jan;11(1):99-102. PubMed PMID: 16607479. eng.

98. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Tropical Medicine & International Health. 2010 Jun;15 Suppl 1:1-15. PubMed PMID: 20586956. Pubmed Central PMCID: Source: NLM. NIHMS237422
Source: NLM. PMC2948795.

99. Wools-Kaloustian K, Kimaiyo S, Diero L, Siika A, Sidle J, Yiannoutsos CT, et al. Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya. AIDS. 2006 Jan 2;20(1):41-8. PubMed PMID: 16327318.

100. Ugbena R, Aberle-Grasse J, Diallo K, Bassey O, Jelpe T, Rottinghaus E, et al. Virological response and HIV-1 drug resistance 12 months after antiretroviral therapy initiation at two clinics in Nigeria Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(S4):S375-79.

101. Laurent C, Meilo H, Guiard-Schmid JB, Mapoure Y, Noel JM, M'Bangue M, et al. Antiretroviral therapy in public and private routine health care clinics in Cameroon: lessons from the Douala antiretroviral (DARVIR) initiative. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005 Jul 1;41(1):108-11. PubMed PMID: 15937770. Epub 2005/06/07. eng.

102. Hingankar N, Thorat S, Deshpande A, Rajasekaran S, Chandrasekar C, Kumar S, et al. Initial virologic response and HIV drug resistance among HIV-1 infected individuals initiating first-line antiretroviral therapy at two clinics in Chennai and Mumbai India. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(S4):S348-54.

103. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. PLoS medicine. 2011;8(1):e1000390. PubMed PMID: 21267057. Pubmed Central PMCID: 3022522.

104. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. JAMA. 2008 Aug 6;300(5):506-7. PubMed PMID: 18677022.

105. Zachariah R, Teck R, Buhendwa L, Fitzerland M, Labana S, Chinji C, et al. Community support is associated with better antiretroviral treatment outcomes in a resource-limited rural district in Malawi. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007 Jan;101(1):79-84. PubMed PMID: 16962622. Epub 2006/09/12. eng.

106. Vella V, Govender T, Dlamini S, Taylor M, Moodley I, David V, et al. Retrospective study on the critical factors for retaining patients on antiretroviral therapy in KwaZulu-Natal, South Africa. Journal of Acquired Immune Deficiency Syndromes: JAIDS. 2010 Sep 1;55(1):109-16. PubMed PMID: 20595904.

107. Palombi L, Marazzi MC, Guidotti G, Germano P, Buonomo E, Scarcella P, et al. Incidence and predictors of death, retention, and switch to second-line regimens in antiretroviral- treated patients in sub-Saharan African Sites with comprehensive monitoring availability. Clinical Infectious Diseases. 2009 Jan 1;48(1):115-22. PubMed PMID: 20380075.

108. WHO. Patient monitoring guidelines for HIV care and antiretroviral therapy. Integrated management of adolescent and adult illness / Integrated management of childhood illness. Geneva: World Health Organization, 2006.

109. UNAIDS. Monitoring the Declaration of Commitment on HIV/AIDS : guidelines on construction of core indicators : 2010 reporting. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2009.

110. PEPFAR. Next Generation Indicator Reference Guide. Version 1.1. The President's Emergency Plan for AIDS Relief. Department of Health and Human Services. United States Government, 2009.

111. Tassie J-M, Malateste K, Pujades-Rodriguez M, Poulet E, Bennett D, Harries A, et al. Evaluation of three sampling methods to monitor outcomes of antiretroviral treatment programmes in low- and middle-income countries. PLoS ONE [Electronic Resource]. 2010;5(11):e13899. PubMed PMID: 21085709. Pubmed Central PMCID: Source: NLM. PMC2978082.

112. Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, Yiannoutsos CT, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. Journal of Acquired Immune Deficiency Syndromes: JAIDS. 2010 Mar 1;53(3):405-11. PubMed PMID: 19745753.

113. Cornell M, Grimsrud A, Fairall L, Fox MP, van Cutsem G, Giddy J, et al. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002-2007. AIDS. 2010 Sep 10;24(14):2263-70. PubMed PMID: 20683318. Pubmed Central PMCID: Source: NLM. NIHMS221830 [Available on 09/01/11]
Source: NLM. PMC2948209 [Available on 09/01/11].

114. DeSilva MB, Merry SP, Fischer PR, Rohrer JE, Isichei CO, Cha SS, et al. Youth, unemployment, and male gender predict mortality in AIDS patients started on HAART in Nigeria. AIDS Care. 2009 Jan;21(1):70-7. PubMed PMID: 19085222.

115. Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2010 Mar;10(3):155-66. PubMed PMID: 20185094. Epub 2010/02/27. eng.

116. Gupta RK, Hill A, Sawyer AW, Cozzi-Lepri A, von Wyl V, Yerly S, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. Lancet Infect Dis. 2009 Jul;9(7):409-17. PubMed PMID: 19555900. Epub 2009/06/27. eng.

117. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006 Aug 9;296(6):679-90. PubMed PMID: 16896111. Epub 2006/08/10. eng.
118. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. AIDS Behav. 2006 May;10(3):227-45. PubMed PMID: 16783535. Epub 2006/06/20. eng.
119. Black WC, Haggstrom DA, Welch HG. All-cause mortality in randomized trials of cancer screening. Journal of the National Cancer Institute. 2002 Feb 6;94(3):167-73. PubMed PMID: 11830606. eng.
120. McMahon J, Wanke C, Terrin N, Skinner S, Knox T. Poverty, hunger, education, and residential status impact survival in HIV. AIDS Behav. 2011 Oct;15(7):1503-11. PubMed PMID: 20632079. Pubmed Central PMCID: 3010417. Epub 2010/07/16. eng.
121. Radimer KL, Olson CM, Campbell CC. Development of indicators to assess hunger. The Journal of nutrition. 1990 Nov;120 Suppl 11:1544-8. PubMed PMID: 2243303. eng.
122. Kendall A, Olson CM, Frongillo EA, Jr. Validation of the Radimer/Cornell measures of hunger and food insecurity. The Journal of nutrition. 1995 Nov;125(11):2793-801. PubMed PMID: 7472659. eng.
123. Frongillo EA, Jr. Validation of measures of food insecurity and hunger. The Journal of nutrition. 1999 Feb;129(2S Suppl):506S-9S. PubMed PMID: 10064319.
124. Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care. 2000 Jun;12(3):255-66. PubMed PMID: 10928201. Epub 2000/08/06. eng.
125. Bangsberg DR. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. J Infect Dis. 2008 May 15;197 Suppl 3:S272-8. PubMed PMID: 18447613. Epub 2008/06/14. eng.
126. Thompson MA, Mugavero MJ, Amico KR, Cargill VA, Chang LW, Gross R, et al. Guidelines for Improving Entry Into and Retention in Care and Antiretroviral Adherence for Persons With HIV: Evidence-Based Recommendations From an

International Association of Physicians in AIDS Care Panel. Annals of internal medicine. 2012 Jun 5;156(11):817-33. PubMed PMID: 22393036. Epub 2012/03/07. Eng.

127. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. Journal of acquired immune deficiency syndromes (1999). 2007 Dec 1;46(4):443-50. PubMed PMID: 18077833. Pubmed Central PMCID: 2666542. Epub 2007/12/14. eng.

128. Mutevedzi PC, Lessells RJ, Heller T, Barnighausen T, Cooke GS, Newell ML. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? Bulletin of the World Health Organization. 2010 Aug 1;88(8):593-600. PubMed PMID: 20680124. Pubmed Central PMCID: 2908968. Epub 2010/08/04. eng.

129. Massaquoi M, Zachariah R, Manzi M, Pasulani O, Misindi D, Mwagomba B, et al. Patient retention and attrition on antiretroviral treatment at district level in rural Malawi. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009 Jun;103(6):594-600. PubMed PMID: 19298993. Epub 2009/03/21. eng.

130. Bedelu M, Ford N, Hilderbrand K, Reuter H. Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. J Infect Dis. 2007 Dec 1;196 Suppl 3:S464-8. PubMed PMID: 18181695. Epub 2008/01/10. eng.

131. WHO. Assessment of Word Health Organization HIV Drug Resistance Early Warning Indicators. Report of the Early Warning Indicator Advisory Panel Meeting. Geneva: World Health Organization. Department of HIV/AIDS, 2012.

132. UNAIDS. Together we will end AIDS. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2012.

133. UNAIDS. Global report 2012: UNAIDS report on the global AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2012.