

Outcomes and cost-effectiveness of different models of delivery of antiretroviral therapy

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Signed by candidate

Rory Leisegang

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Abstract

Background: HIV remains a major contributor to the burden of disease in the Eastern and Southern African region, where around half of those with HIV/AIDS reside, according to the 2016 UNAIDS estimates. Data on the direct costs and outcomes of providing health care are important due to competing health needs and limited budgets in resource-limited settings, especially if we are to reach the UNAIDS 90-90-90 goals. This thesis presents a series of studies, which together represent the typical journey followed within an economic evaluation, starting with the establishment of a cohort, then onto cost and outcome analyses and, finally, the development of a Markov model for the purpose of establishing the cost-effectiveness of a particular intervention.

Methods: Data for this thesis come from several cohorts within South Africa, with patients commencing ART between 1998 and 2014, and with care provided within a number of different models: private (Aid for AIDS), public-private partnerships or PPP (BroadReach), and public sector (Khayelitsha). The study design for all were retrospective cohort analyses. These cohorts had important strengths in their data: adherence measures (private, PPP); initiating ART at CD4 counts > 200 cells/ μL (private); detailed cost data (private); long duration of follow-up with a larger proportion on second-line ART (private); ability to assess health care utilization pre-ART and in patient loss to ART follow-up (private); and availability of national identity numbers, allowing us to confirm mortality from national death register data (private, PPP).

Results: The results sections of this thesis are presented in the form of published papers and chapters. In the first analysis (Chapter 4), we present a cohort profile for Aid for AIDS, where we describe the history of the programme and contrast it with the public sector programme in South Africa. In the second analysis (Chapter 5), we present a paper highlighting the profile and determinants of costs on ART over time in the private cohort. We draw attention to the impact of baseline stage and adherence to ART on early and late costs respectively. In the third analysis (Chapter 6), we explore different models of HIV care: GP versus clinic for public sector patients and courier versus collect pharmacy for private sector patients. In the third analysis (Chapter 7), we present a paper which reviews cost-effectiveness studies in LMICs and explores the relative impact of various factors on costs and mortality in preparation for the final analysis (Chapter 8), which required the development of a novel HIV Markov model.

Conclusion: Interventions, such as public-private partnerships with GPs or home-refill by courier, which we have found to be associated with lower costs and improved outcomes respectively, should be considered for implementation in South Africa, especially in light of the proposed National Health Insurance. The focus of this thesis on models of ART delivery and the inclusion of under-represented or novel models are significant strengths.

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Preface

This thesis includes published papers, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy in Clinical Pharmacology (Ph.D.) (University of Cape Town), and with the approval of the University Doctoral Degrees Board. Three papers are included as part of the thesis and are presented as self-contained chapters. I confirm that no part of this thesis has been submitted in the past, or is being, or is to be submitted for a degree at any other university. I hereby grant the University of Cape Town free licence to reproduce this thesis in whole or in part for research or teaching. This thesis is presented for examination in fulfillment of the requirements for the degree of Doctor of Philosophy in Clinical Pharmacology.

Three of the manuscripts included in this thesis have been published in international peer-reviewed journals, as detailed below. The contents of each remain unchanged from that which has been published or submitted for publication. The papers are listed below, with a description of the contribution of each author. The contribution of the candidate is outlined in the acknowledgments section of each paper. The candidate was the lead author for each paper and prepared all the data for the analyses, conceptualized and conducted all analyses and drafted all versions of the manuscripts during the period of the doctoral degree registration. All co-authors critically reviewed and approved the submitted manuscripts, and the candidate reviewed co-author comments and suggestions and integrated them into the manuscript where appropriate. All supervisors have separately confirmed to the University of Cape Town Doctoral Degrees Board that the included papers overwhelmingly reflect the candidate's independent and original thinking and his scientific work.

Chapter 5:

Leisegang R, Cleary S, Hislop M, Davidse A, Regensberg L, Little F, Maartens G. (2009). "Early and late direct costs in a Southern African antiretroviral treatment programme: a retrospective cohort analysis." *PLoS Med*: 6(12).

Rory Leisegang was the lead investigator on this analysis and drafted the first version manuscript, with Gary Maartens as the overall supervisor. Susan Cleary and Gary Maartens contributed to the overall study design and methodology. Michael Hislop both collected and provided source data and, together with Leon Regensberg, provided input on working with the source data; Rory Leisegang analyzed the data. Input on statistical analyses was provided by Alistair Davidse, Gary Maartens, and Susan Cleary; additional statistical consultation in the revision of this paper was

provided by Francesca Little. All authors contributed to the writing of the paper and agreed with the results and conclusions.

Chapter 7:

Leisegang R, Maartens G, Hislop M, Regensberg L, Cleary S. (2009). "*Improving the evidence base of Markov models used to estimate the costs of scaling up antiretroviral programmes in resource-limited settings.*" *BMC Health Serv Res*: 10 (Suppl 1: S3).

Rory Leisegang was the lead investigator on this analysis and drafted the first version manuscript, with Susan Cleary as the overall supervisor. Susan Cleary and Gary Maartens contributed to the overall study design and methodology. Michael Hislop both collected and provided source data and, together with Leon Regensberg, provided input on working with the source data; Rory Leisegang analyzed the data. Input on statistical analyses was provided by Gary Maartens and Susan Cleary. All authors contributed to the writing of the paper and agreed with the results and conclusions.

Chapter 8:

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Rory Leisegang was the lead investigator on this analysis and drafted the first version of the manuscript, with Susan Cleary as the overall supervisor. Susan Cleary and Gary Maartens contributed to the overall study design and methodology. Andrew Boule and Michael Hislop collected and provided source data and input on working with the source data; Rory Leisegang analyzed the data. John Sargent and Ernst Darkoh provided insight into the BroadReach programme. Gary Maartens and Susan Cleary provided input on the statistical analyses. All authors contributed to the writing of the paper and agreed with the results and conclusions.

Two chapters in this thesis are presented as papers for publication in international peer-reviewed journals, as detailed below. The intended papers are listed below, with a description of the contribution of each author. The candidate was the lead author for each paper and prepared all data for the analyses, conceptualized and conducted all analyses and drafted all versions of the manuscripts during the period of the doctoral degree registration. All co-authors critically reviewed and approved the submitted manuscripts, and the candidate reviewed co-author comments and suggestions and integrated them into the manuscript where appropriate.

Chapter 4:

Leisegang R, Sarkin L, Ball J, Cleary S, Hislop M, Karamchund S, Naidoo P, Barnabus S, Cotton M, Maartens G & Nachega J. "*Cohort profile: adults within Aid for AIDS (AfA) antiretroviral programme, South Africa.*"

Rory Leisegang was the lead investigator on this analysis and drafted the first version of the manuscript, with Jean Nachega and Gary Maartens as the overall supervisors. Michael Hislop collected and provided both source data and, together with Jane Ball, provided input on the cohort; Rory Leisegang analyzed the data together with Lee Sarkin. All authors contributed to the writing of the paper and agreed with the results and conclusions.

Chapter 6:

Leisegang R, Maartens G, Kalkins K &, Ball J, Hislop M, Karamchund S, Naidoo P, , Cotton M & Cleary S, Dowdy D & Nachega J. "*The impact of antiretroviral therapy home-refill by courier compared to self-refill on patient clinical, immunological, and virologic outcomes: a cohort analysis in HIV-infected adults.*"

Rory Leisegang was the lead investigator on this analysis and drafted the first version of the manuscript, with Jean Nachega and David Dowdy as the overall supervisors. Michael Hislop collected and provided both source data and, together with Jane Ball, provided input on the cohort; Rory Leisegang analyzed the data together with Keri Kalkins, All authors contributed to the writing of the paper and agreed with the results and conclusions.

Glossary

Designated service provider (DSP) is a healthcare provider/s that has been "selected by the scheme to provide its member's diagnosis, treatment, and care in respect of one or more of the PMB conditions" (Medical Schemes Act 133 of 1998).

Emergency medical condition (EMC) is a medical condition which is of "sudden and unexpected onset" and requires immediate medical or surgical treatment. Should treatment for this condition be withheld, then "impairment of bodily functions, serious dysfunction of a bodily organ or part of" would "place the person's life in serious jeopardy" (Medical Schemes Act 133 of 1998).

Prescribed minimum benefits (PMBs) are legislated minimum benefits that medical scheme members are entitled to. "Subject to the provisions of this regulation, any benefit option that is offered by a medical scheme must pay in full, without co-payment or the use of deductibles, the diagnosis, treatment, and care costs of the prescribed minimum benefit conditions" (Medical Schemes Act 131 of 1998). Broadly speaking this refers to (a) any emergency medical condition and (b) a range of conditions as specified in Annexure A of the Act. Included in this list of conditions are the following: Addison's disease; asthma; bi-polar mood disorder; bronchiectasis; cardiac failure; cardiomyopathy disease; chronic renal disease; coronary artery disease; Crohn's disease; chronic obstructive pulmonary disorder (COPD); diabetes insipidus; diabetes mellitus type 1 and 2; dysrhythmias; epilepsy; glaucoma; haemophilia; HIV/AIDS; hyperlipidaemia; hypertension; hypothyroidism; multiple sclerosis; Parkinson's disease; rheumatoid arthritis; schizophrenia; systemic lupus erythematosus; and ulcerative colitis. The benefits are subject to limitations specified in Annexure A regarding cost-saving interventions established by the scheme (e.g., generic medication, preferred provider). Various factors influence the decision to include these conditions within the PMB cover, including prevalence, impact on quality of life years (QALY), affordability of treatment and impact on financials of medical schemes (Medical Schemes Act 133 of 1998).

List of abbreviations

3TC	lamivudine
/r	ritonavir boosting
ABC	abacavir
ADR	Adverse drug reaction
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transferase
ART	antiretroviral therapy – i.e., antiretroviral drugs, prophylaxis, and laboratory tests
ARV	antiretroviral drugs
AZT	azidothymidine / zidovudine
BMI	body mass index
CD4	CD4+ cell
d4T	stavudine
ddI	didanosine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
GART	genotypic antiretroviral resistance testing
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
LPV	lopinavir
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
PI	protease inhibitor
PMTCT	prevention of mother-to-child transmission
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
RTV	ritonavir
SOC	Standard of care

TDF	tenofovir
UCT	University of Cape Town
UNAIDS	The Joint United Nations Programme on HIV/AIDS
VL	viral load
WBC	white blood cell count
WHO	World Health Organisation

Table of Contents

Abstract	3
Acknowledgements	5
Preface	6
Glossary	9
List of Abbreviations	10
Chapter 1: Introduction	17
1.1 Introduction	17
1.2 Human Immunodeficiency Virus (HIV)	19
1.3 Antiretroviral therapy	20
1.4 Current global status of the global epidemic	21
1.5 HIV in South Africa	21
1.6 Resource allocation	23
1.7 Aims and objectives	24
1.8 Overview, context, and structure of this thesis	24
1.9 References	26
Chapter 2: Literature review	34
2.1 Overview	34

2.2 Key concepts in economic evaluations	34
2.2.1 Perspective and types	34
2.2.1 Costs	35
2.2.2 Outcomes	36
2.2.3 Decision-making tools	37
2.4 Models of ART delivery	38
2.4.1 Nurse	39
2.4.2 Pharmacist and pharmacist's assistant	40
2.4.3 Adherence clubs	41
2.4.4 General practitioner (GP)	41
2.5 Conclusions	42
2.6 References	43
Chapter 3: Methods and sources of data	50
3.1 Overview	50
3.2 General description of cohorts	50
3.2.1 Private sector cohort – Aid for Aids (AfA)	50
3.2.2 Public sector cohort – Khayelitsha	53
3.2.3 Public-private partnership cohort – BroadReach	54
3.3 Study design	54

3.4	Definitions	55
3.5	Inclusion criteria, exclusion criteria, and censoring	56
3.6	Cost data	56
3.7	Ethics	58
3.8	Conclusions	59
3.9	References	60
Chapter 4: Cohort profile: adults within Aid for AIDS (AfA) antiretroviral programme, South Africa		64
4.1	Overview	64
4.2	Why was the cohort established?	64
4.3	Which cohorts contribute to the managed-care programme?	65
4.4	What data were collected?	65
4.5	Who enrolled and what protocols were applied?	66
4.6	Clinical and other support	67
4.7	Eligibility for ART	68
4.8	ART regimens	69
4.9	Prophylactic antibiotics, laboratory and other monitoring	72
4.10	Adherence and medical support	73
4.11	Transfer in	73

4.12 What has been measured?	74
4.12.1 Clinical outcomes	74
4.12.2 Mortality ascertainment	74
4.12.3 Loss to follow-up (LTFU)	75
4.12.4 Costs/utilization	76
4.13 Conclusions	76
4.14 Can I get hold of the data?	77
4.15 References	77
Chapter 5: Early and late direct costs in a Southern African antiretroviral treatment programme: a retrospective cohort analysis	82
Chapter 6: The impact of antiretroviral therapy home-refill by courier compared to self-refill on patient clinical, immunological, and virologic outcomes: a cohort analysis in HIV-infected adults	94
6.1 Overview	94
6.2 Introduction	94
6.3 Methods	95
6.3.1 Ethics	95
6.3.2 Sources of data	95
6.3.3 Inclusion criteria	96
6.3.4 Pharmacy dispensing data	96
6.3.5 Statistical methods	97

6.4 Results	98
6.4.1 CD4 response to ART over time	99
6.4.2 VL response to ART over time	100
6.4.3 Survival analysis	101
6.5 Discussion and conclusions	105
6.7 References	107
Chapter 7: Improving the evidence base of Markov models used to estimate the costs of scaling up antiretroviral programmes in resource-limited settings	112
Chapter 8: A novel Markov model projecting costs and outcomes of providing antiretroviral therapy to public patients in private practices versus public clinics in South Africa	121
Chapter 9: Conclusion	131
9.1 Overview	131
9.2 Key findings	132
9.3 Strengths and limitations of the studies	133
9.4 Policy recommendations	134
9.5 Recommendations for future research	135
9.6 References	136
Appendix 1: Ethics approval	138
Appendix 2: Aid for AIDS registration form submitted for database registration	140

Chapter 1: Introduction

1.1 Introduction

In spite of significant progress, HIV remains a major contributor to the global burden of disease [1]. Eastern and Southern Africa (ESA) carries the highest burden of disease: 19.4 million people living with HIV/AIDS (PLWH) (53% of the global), 10.3 million accessing ART (49% of the global) [2] and 790,000 new infections (44% of global) in 2016 [3]. Access to ART has dramatically improved survival in Eastern and Southern Africa [4-6] and globally – HIV-related mortality accounted for 1.1 million (0.95–1,200 million) deaths in 2004, but only 420,000 (350,000–510,000) deaths in 2016 [2].

Given the scale of the HIV epidemic in South Africa and the need for a public sector response, there were significant challenges to establishing the infrastructure and finances for a large and intensive public sector programme [7]. Data on costs and outcomes from resource-limited settings were important [8] but limited [9, 10], yet the ambitious goal of universal access to antiretroviral treatment by 2010 was established [11]. The recent and equally ambitious “90-90-90” targets for 2020 – 90% of all PLWH knowing their HIV status, 90% of all people diagnosed with HIV receiving ongoing ART, and 90% PLWH on ART having viral suppression [12, 13] – have once again raised the importance such data. A recent review highlighted that the effects of interventions to improve adherence to ART not only lapsed with time but often required more than one intervention to achieve the desired level of effect, with effectiveness varying significantly across settings [14, 15]. Many challenges remain if we are to “close the gap” [7, 12].

South Africa bears the brunt of the of the epidemic in sub-Saharan Africa(SSA) and globally with an estimated 7.1 million or 19% of the global numbers of PLWH, 15% of new cases, and 11% of HIV/AIDS related mortality [2]. Life expectancy remains low by international standards despite large-scale ART provisions [16]. Life expectancy from birth has improved from 54 years in 2006 to 62,4 years in 2016 [17], reaching pre-HIV life expectancy rates in the early 1990s [18, 19]. However, in 2016 there were 270,000 (240,000–290,000) new HIV infections, 110,000 (88,000–140,000) AIDS-related deaths, and only 56% (50%–61%) of the estimated 7,100,000 (6,400,000–7,800,000) PLWH were accessing ART, according to UNAIDS estimates

[20]. While some of this is due to the recently implemented “test and treat” or “treat all” policy [21, 22], many remain ignorant of their status [7]. Continued ART scale-up and addressing inequalities, therefore, remain the focus in South Africa [23].

Data on the direct costs and outcomes of providing health care are important due to competing health needs and limited budgets in resource-limited settings [24], yet many of the published HIV economic models at the inception of this thesis have been developed using data from high-income countries [25, 26]. We had access to a number of cohorts in Southern Africa comprising different models of care: private, public-private partnerships (PPP), and public sector (urban and rural). These cohorts had important strengths in their data: adherence measures (private, PPP); initiating ART at varying CD4 counts (private > 200 cells/ μ L; public and PPP < 200 cells/ μ L); detailed cost data (private); long duration of follow-up (all) with significant numbers on second-line ART (private); ability to assess health care utilisation pre-ART and in patients loss to follow-up (private); and availability of national identity numbers which allowed linkage with the national death register (private, PPP). While actual costs and outcome findings from these different ART programmes were unlikely to be the same in public sector programmes, we would argue that the variables that drive costs and outcomes are likely to be generalizable even if the magnitudes of the effects differ.

This thesis, therefore, focusses on outcomes (including cost) and cost-effectiveness of different models of care, with the intention of informing future interventions and priority setting in LMICs. An improved understanding of the significant costs and poor outcomes around ART initiation, especially where a disease threshold was used, has resulted in a shift in priorities to “treat all” in LMICs, irrespective of CD4 count or WHO defined illness status. The findings in this thesis that delivering ART through a courier pharmacy and treating public sector patients through private GPs could improve outcomes (for the former) while being relatively cost-effective (for the latter) is significant and should inform resource allocation. The South Africa ART programme remains the largest public sector ART programme in the world, with over 3 million people now accessing ART in South Africa alone [20], and is, therefore, able to have a global impact [27, 28].

1.2 Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) is a sexually transmitted retrovirus caused by two lentiviruses, HIV type 1 (HIV-1) and type 2 (HIV-2) [29]. HIV resulted from zoonotic infections of the simian immunodeficiency viruses found in African primates [29]. HIV-1 is responsible for the current global epidemic whereas HIV-2 is largely confined to West Africa, is less transmissible and characterized by a slower disease progression [29]. Four groups of HIV-1 exist (M, N, O, and P) [29] – group M accounts for most of the infections, with the others being confined to West Africa [30]. In group M, there are nine subtypes (A–D, F–H, J, and K) [29] – subtype C is the most prevalent and found in Africa and India; subtype B is found within Europe, Australia, and America. Over time circulating recombinant subtypes are becoming increasingly common [30].

“Acquired immune deficiency syndrome” or AIDS was first recognized in the early 1980s, initially clustered in men who have sex with men (MSM) and intravenous drug users (IDUs) [31–36]. The Centers for Disease Control and Prevention (CDC) in 1982 defined AIDS as “a disease at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease” [33] and assigned a task force to begin surveillance and conduct epidemiologic investigations [37]. The causative virus was identified by two independent groups in 1983 [38, 39] and later named human immune deficiency virus (HIV).

HIV integrates into the cell’s genome [40] and through inexact replication with high rates of base-pair substitution evolves rapidly [41]. The body is unable to mount an adequate immune response leading to viral escape [42, 43]. High and continuous viral replication results in virus- and immune-mediated killing of CD4⁺ cell lymphocytes [44] leading to the typical progressive CD4 count decline and associated immune function deterioration [44, 45]. Furthermore, ongoing inflammation in response to HIV and direct HIV-related apoptosis contribute significantly to the deterioration in overall health [45]. Altogether, these result in complications from immunodeficiency or AIDS [32], usually once the CD4 count has fallen below 200 cells/ μ L and includes opportunistic infections, cancers and/or organ damage or wasting [37]. The WHO guidelines adopted this CD4 count level (200 cells/ μ L) as the threshold for initiating ART for many years in patients without a WHO stage III or IV illnesses [46].

1.3 Antiretroviral therapy

Combined antiretroviral therapy (cART but later referred to as ART), which consisted of a combination of three drugs from at least two different classes of drugs, proved durable in suppressing viral replication in clinical trials in high-income countries (HIC) in the mid-1990s [47, 48]. ART was therefore rolled-out in HIC despite its substantial costs [49]. Cohort studies soon confirmed the durability and impact of ART on morbidity and mortality for PLWH [50, 51] and, over time, demonstrated that CD4 counts recovered to near normal levels in those with ongoing viral suppression in LMIC and HIC settings, including in South Africa [52, 53]. Recent studies from South Africa and other LMICs have encouragingly shown that near-normal life expectancy can be achieved for certain subgroups [53, 54], in keeping with other studies from HIC settings (excluding those who inject drugs) [52, 55].

ART decreases plasma viral load concentrations below the lower limit of detection, usually within 6-months, thus allowing immune reconstitution [9, 56]. The recovery of the CD4 count in individuals on ART is variable [57, 58] and, in part, driven by a lower baseline CD4 count [59]. Importantly, impaired CD4 count recovery despite virological suppression has been shown to be associated with an increased risk of adverse outcomes [60, 61]. Later studies soon showed improved clinical outcomes in patients who started ART at CD4 count > 500 cells/ μ L [62-64] and reduced transmission within serodiscordant couples [65-70], thus establishing the case for the “treat all” that has now been widely adopted in LMICs, including South Africa [22, 71].

Adverse drug reactions (ADRs) (hepatotoxicity, hyperlactataemia and lactic acidosis, dyslipidaemia, lipodystrophy, hypersensitivity, nephrotoxicity, neuropsychiatric toxicity, dysglycaemia and gynaecomastia) [22] are not uncommon, driven in part by multi-morbidity and the higher pill-burden [72]. Early ART exposes patients to toxic effects of drugs and the development of resistance before they derive clinical benefit [73]. The recent progress towards affordable, durable, and tolerable regimens with simple dosing schedules (single tablet regimen or STR) for LMICs is, however, encouraging [22, 74].

1.4 Current global status of the global epidemic

By the end of 2015, 17 million or just under half of the 36.7 million PLWH were accessing antiretroviral therapy (ART) – well above the goal of the 2011 Political Declaration on HIV and AIDS of having 15 million on treatment by 2015 [75] but still far from the current 90-90-90 goals [76]. While incidence has flattened since 2005, total numbers on ART have continued to grow, in part due to the gradual relaxation of the eligibility criteria [77] and longer survival [78]. Further scale-up of testing and accelerated treatment are required to meet the first two of the 90-90-90 goals, and improved retention in care and access to adequate monitoring, including VL, are required to meet the last goal. In the past, where VL testing was not available, alternative strategies were developed and included CD4 count, clinical, and adherence monitoring [79]. With Roche’s Global Access Program, VL testing prices have been substantially reduced and testing is set to expand rapidly in LMICs [27]. Newer antiretroviral drugs (ARVs) are becoming available, including in LMIC settings [80], which is important given the high prevalence of ARV resistance (>10%) in naïve patients now being observed in some settings, including several SSA countries [81].

1.5 HIV in South Africa

South Africa has the largest number globally of PLWH and who are accessing ART and falls within WHO’s Southern and Eastern Africa region: nearly 4 million or 56% of the estimated 7.1 million PLWH in South Africa had started ART by 2016, according to the latest UNAIDS estimates [20]. Globally, this translates to 19% of PLWH, 15% of new HIV infections, and 11% of AIDS-related deaths in 0.7% of the world’s population [20]. HIV prevalence is high (18.9%) and varies markedly between different regions [2]. The Human Sciences Research Council’s national HIV survey in 2012 found prevalence was highest in KwaZulu-Natal (KZN) and Mpumalanga (MP) and lowest in the Northern Cape (NC) and Western Cape (WC) [82]. New infections remain high and therefore more interventions are required [83].

Addressing the HIV epidemic in South Africa to meet the 90-90-90 goals is complex [7]. A multifaceted approach, therefore, has been adopted in the National Strategic Plan for HIV, TB and STIs 2017–2022 [84]. According to the World Bank’s definition of the “food poverty line” – defined as an income above which a household can purchase “some basic-needs food bundle

and nothing more” [85] – more than 10 million people live below this line in South Africa [86]. This fact, alongside the dual burden of communicable and noncommunicable diseases, the persistent social disparities, the high burden of disease, the rising population and increasing number of refugees and economic migrants, means there are often inadequate human resources to provide the care required [86-88]. While South Africa is considered a middle-income country, the wealth remains concentrated (Gini coefficient of 0.65 for 2014): the wealthiest 20% consumed 65%, and the poorest 20% consumed 3% of the total expenditure on health care in 2014 [89].

LMICs, in particular those in SSA, were least able to respond due to the scale of the epidemic and the substantial costs of ART [90]; by 2001, AIDS was the leading cause of death in SSA. International efforts to mobilize resources – e.g. the Joint United Nations Programme on HIV/AIDS (UNAIDS); Global Fund to Fight AIDS, TB and Malaria (GFATM); the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002 (GFATM); and the US President’s Emergency Plan for AIDS Relief (PEPFAR) in 2003 [91, 92]. WHO’s ‘3 by 5’ campaign, a five-year plan to combat AIDS, primarily in countries with a high number of HIV infections, established substantial resources to fight the epidemic (\$15 billion initially). The accompanying 2003 update to the WHO guidelines [93] for resource-limited settings was rapidly adopted by many LMICs, thus allowing for expanded ART provision through a public health approach [94]. This release and its subsequent updates continued to form the basis of care in many LMIC settings, including South Africa.

The public provision of ART in South Africa was rolled out from April 2004 as part of the South African Department of Health’s “Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment” [95]. A conservative eligibility criteria for ART was initially implemented with CD4 count < 200 cells/ μ L irrespective of stage, or with WHO stage IV [95]. These conservative eligibility criteria were relaxed in a stepwise fashion in keeping with changing WHO guidelines for resource-limited settings until CD4 and WHO stage criteria were dropped completely in the current “treat all” approach [22]. The adult first line ART regimen consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI); second line ART regimen comprised of two NNRTIs and a protease inhibitor (PI) [96]. Unlike in many other resource-limited settings, viral load monitoring was implemented and patients who failed virologically (defined by two consecutive

viral loads > 1,000 copies/mL with intensive counseling) were changed to the second line ART treatment regimen [96].

The current recommended regimen for LMICs (TDF+3TC/FTC+EFV) [71], based on an accepted public health approach [97], is well tolerated [22] and effective in suppressing viral replications [98]. ADRs are less common with this regimen than with previous regimens [22], but the high prevalence of multi-morbidity in South Africa will continue to contribute to ADRs incidence [72, 99]. An estimated 60% of PLWH in South Africa are also co-infected with tuberculosis [7]. Going forward, the new “National Strategic Plan for HIV, TB, and STIs: 2017–2022” has been established for South Africa [84] and is aligned with the UNAIDS 90-90-90 Treatment Targets [76].

Knowledge of HIV status has improved substantially. In Eastern and Southern Africa, nearly twice as many adults aged 15–49 years knew their status in 2012–2016 compared to 2007–2011 [2]. HIV counseling and testing (HTC) in South Africa has been expanded through the national campaigns launched in 2010 and 2015 and resulted in 35 million HIV tests being carried out [7]. More recent modeling data suggest that 86% of people know their status, which is a significant achievement given the scale of the epidemic in South Africa [2].

1.6 Resource allocation

Ensuring adequate and appropriate resource allocation to fight the HIV epidemic is a key concern, especially within LMICs [100]. In SSA, the prevalence in some countries exceeds 10% and under this burden only middle-income countries like South Africa, Namibia, and Botswana have been able to mobilize sufficient domestic funding in conjunction with international aid organizations to establish and expand ART programmes [100]. Low-income countries, even those with low prevalence, still rely heavily on donor funding – e.g., Mozambique and Ethiopia. In a recent article, the authors argue for five key factors which influence resource allocation: disease burden, cost-effectiveness, external parties’ ability (and willingness) to pay, intertemporal trade-offs, and health equity [100].

The financing of the ART programme in South Africa is substantial – the estimated total expenditure for the 2012–2016 National Strategic plan was around R133.5 billion [7]. With

donor funding declining in recent years – historically 20% of the funding, mainly from Global Fund to Fight AIDS, TB and Malaria (GFATM) and the US President’s Emergency Plan for AIDS Relief (PEPFAR) – and projected rising future costs (driven by exchange rate, changing global economy, inflation, etc.), further pressure on resources is anticipated [7].

1.7 Aims and objectives

The overall aim of this thesis was to explore outcomes and cost-effectiveness of different models of delivery of antiretroviral therapy, using data from South African ART programmes.

The specific objectives were:

1. Describe the various cohorts included in this thesis and compare their approaches with WHO guidelines for resource-limited settings (Chapter 3).
2. Establish the cohort profile for AfA (Chapter 4).
3. Describe the costs and determinants of costs over time on ART (Chapter 5).
4. Compare outcomes of home-refill by courier versus self refill of ART, a model of care in public and private sectors in South Africa (Chapter 6).
5. Review and conduct a preliminary cost and outcome analysis of Markov models from LMIC settings (Chapter 7).
6. Establish a novel Markov model to compare the cost-effectiveness of GP versus public sector clinic for public sector patients as alternative models of care for ART in South Africa (Chapter 8).

1.8 Overview, context, and structure of this thesis

In **Chapter 2** we present a framework for an economic evaluation, together with key terminology and concepts. We then present a literature review of the cost-effectiveness of different models of HIV care in South Africa.

In **Chapter 3** we present a summary of various cohorts and their context in South Africa, including limitations and strengths, and common methodologies applied to the cohort analyses.

In **Chapter 4** we present the cohort profile of the AfA programme using the style of a paper in the *Journal of Epidemiology*. The last published update of the cohort profile was in 2004.

In **Chapter 5** we present a cost analysis exploring the direct health care costs from the healthcare sector perspective over time in a South African private sector HIV/AIDS programme. We draw attention to the high cost around ART initiation and the changing determinants of costs over time on ART. We present a full manuscript with the introduction, methods, results, discussion, and conclusions.

In **Chapter 6** we present an outcome analysis comparing patient clinical, immunological and virologic outcomes for home delivery by courier versus self-refill in a South African private sector HIV/AIDS programme. Adherence to ART is a key determinant of outcomes and costs, and inconvenience incurred by patients with self-refill may pose a significant access barrier, with implications for adherence. We present a full manuscript with the introduction, methods, results, discussion, and conclusions.

In **Chapter 7** we present a follow-on analysis identifying the determinants of direct health care costs and the likelihood of death. This is a follow-on analysis from Chapter 5 to inform the development of Markov models which can estimate lifetime costs and outcome and therefore inform scaling up of ART in a resource-limited setting. We include a literature review of Markov models from LMIC settings. We present a full manuscript with the introduction, methods, results, discussion, and conclusions.

In **Chapter 8** we present a cost-effectiveness analysis comparing the 10-year and life costs, outcomes and cost-effectiveness of using GPs in the private sector to treat public sector patients instead of primary public sector clinics. This model has been described before in Botswana and is an alternative model of care. We present a full manuscript with the introduction, methods, results, discussion, and conclusions.

In **Chapter 9** we summarize the findings and conclusions for the four analyses included in this thesis. We discuss the implications of the research and how it could inform allocation and policy in South Africa and priorities for future research on alternative models of ART delivery.

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Chapter 2: Literature review

2.1 Overview

The objective of this chapter is to briefly outline some of the key concepts used in an economic evaluation and to review the literature on the cost-effectiveness of different models of ART delivery. Public sector clinics, where doctors, nurses, and lay counselors work together, are considered the standard of care (SOC) model for ART delivery in South Africa.

2.2 Key concepts in economic evaluation

An economic evaluation is concerned with the optimal way of consuming scarce resources. Within the context of health economics, it most commonly includes a study of cost, outcomes, and cost-effectiveness. To effectively allocate scarce resources, one requires knowledge of the effectiveness and costs of a particular strategy to prevent or treat disease. Cost and outcome studies are often prioritized as they can establish whether the treatment will be effective and what resources and budget are required.

2.2.1 Perspective and types

Within a health economic evaluation, the perspective of a study should be determined upfront [1]. There are three common perspectives, and these perspectives determine which costs are collected or included in the analysis [1]:

- *Patient*, where the opportunity cost of time seeking care (including travel, waiting and consultation times), the opportunity cost of foregone work, and out-of-pocket-expenses such as transportation are all considered [2].
- *Provider or health service*, where all health care expenses are included and all costs incurred by the patient to receive the treatment are excluded. It is the most common perspective and is used within the cost analyses presented in this thesis [3]. In certain analyses, a

healthcare sector perspective can also include resources consumed in other sectors such as education or social welfare.

- *Societal*, the broadest, includes both healthcare sector and patient perspectives [1].

There are three types of economic evaluation commonly cited in the literature [4]:

- *Cost-benefit analysis* (CBA), which resolves costs and benefits to common units that are usually monetary in nature. Any net monetary benefit of an intervention is then considered favourable as it would increase social welfare [5]. It also enables comparison between health interventions and those in other sectors [4].
- *Cost-effectiveness analysis* (CEA), which is the most common analysis and is used to inform decision making within a patient group with a particular condition. Health benefits are measured in natural units whereas costs are measured in monetary units and the ratio of incremental costs to incremental outcomes provides a tool that can inform decision making [6]. Importantly, CEAs provide information which will allow interventions to be compared in terms of technical, but not allocative, efficiency [7]. In essence, this means that a CEA can compare costs and outcomes within a given patient population, but is unable to provide guidance on whether such interventions represent value for money more broadly. This is because a CEA that uses natural outcome measures can only compare interventions that produce similar outcomes (e.g., either morbidity or mortality) [6]. CEA is the approach used in Chapter 8 of this thesis.
- *Cost-utility analysis* (CUA), which is an adaptation of a CEA. In these analyses, utility based measures are used instead of natural units (e.g., QALYs and DALYs – see more below) [8]. This use of QALY (quality adjusted life years) or DALY (disability adjusted life years) enables comparisons to be made across programme or patient groups (e.g., HIV/AIDS versus malaria) and hence enables a fuller assessment of interventions in terms of whether they are allocatively efficient, meaning that their adoption will increase population health within a given health care budget constraint.

2.2.1 Costs

Costs (direct, indirect, and intangible) are defined as the opportunity costs within the context of a health economics evaluation and are the benefits that could have been realized from the best

alternative intervention [9]. This differs from the financial cost, which is the actual or accounting cost plus borrowing charges, and the economic cost, which includes the accounting cost and the opportunity cost. In most health economic evaluations, unit costs (e.g., cost per casualty visit, cost per inpatient day) are commonly established; the total cost then becomes a product of unit cost and utilization. The application of unit cost is important within the analyses presented in this thesis. The breakdown of unit costs includes all fixed/overhead and variable costs (direct labour and material costs) involved in the production of goods or services [10].

The analyses of Chapters 5, 7, and 8 use economic evaluation methods; more details are provided within each chapter about how costs and outcomes have been determined. With the private sector cohort analyses, the tariff amount (which is the amount agreed to annually following negotiations between private healthcare sector and funders) was used as a proxy for direct health care costs. We chose the tariff amount, as opposed to the amount charged by the provider or the amount reimbursed to the patient, so that similar services would take the same monetary value. We further assumed that these tariffs were a suitable proxy for opportunity costs. While this could be a shortcoming, it is common to assume that market prices are a proxy for opportunity costs in an economic evaluation given the difficulties in evaluating the latter [11].

2.2.2 Outcomes

Outcomes are often measured in natural units (viral suppression, deaths, LTFU). These units usually come from clinical trials but also are found in the literature. In the outcomes analysis in Chapter 7, we considered three common outcomes measures within HIV analyses: CD4 response, VL suppression rate, adherence levels, and death.

Within economic analyses, utility based measures are preferred as they take into account the patient's level of wellbeing [5]. The utility based measure in a CUA is therefore preferred over a CEA for decision making as it allows for a more robust comparison between interventions – e.g., higher quality of life for fewer years versus lower quality of life for more years. The most commonly reported utility based units are QALYs and DALYs. In the case of HIV, the utility based measures are particularly important and may vary significantly across age group and gender [12].

2.2.3 Decision-making tools

Decision making is an important aspect of an economic evaluation, given the scarcity of resources and the need to allocate these scarce resources appropriately. Outcome analyses are often the first analyses to be made available and can be useful in determining which treatments are effective. Cost studies, depending on the perspective taken, can also be useful in determining the budgetary requirements for a given number of patients who would receive the intervention. Neither of these by themselves will, however, gauge which treatment options are efficient [13].

Decision making within both CEA and CUA is complex in the instance that a new intervention is likely to increase both costs and outcomes. Given a constant budget, implementing this new intervention poses an opportunity cost in that other interventions will need to be scaled back. In this instance, one suggestion is to compare the positive incremental cost-effectiveness ratio, with outcomes expressed in QALYs or DALYs, to a cost-effectiveness threshold. This threshold can be expressed on the demand side as the willingness to pay to gain health or on the supply side as the opportunity cost of foregone health and health system spending. Using the supply side perspective, the cost-effectiveness threshold can be empirically established (at least in theory) by ranking programmes from most to least cost-effective in a league table and, starting with the most cost-effective, fully funding each until the budget is exhausted. The incremental cost-effectiveness ratio (ICER) of the last programme to be funded before the budget is exhausted is then the cost-effectiveness threshold. It is argued that the supply side approach is more appropriate in that it more accurately captures the decision problem of maximization within a constrained budget. Despite this, the most commonly adopted threshold for QALYs or DALYs averted is up to three times the gross domestic product per capita [14, 15]. Given that this threshold has little relationship opportunity cost of health system at the margin, it has been heavily criticized and its usage is discouraged in more recent literature [16]. Priority setting requires some pragmatism as no single method based on cost-effectiveness thresholds can be applied universally and some judgment is still required [16].

2.4 Models of ART delivery

The Khayelitsha programme, described in Chapter 4 and included in the analysis of Chapter 8, was the first public sector pilot programme in South Africa [17]. By 2004, the national public sector HIV programme had been established and HIV care of public sector patients was normalized against these guidelines [18]. Early studies raised concerns that there would be inadequate human resources to provide care for the anticipated numbers of PLWH in LMIC settings [19]. In more recent studies, limited human resources for treating PLWH remain important in LMICs, but so does the diversity of patient needs which also needs to be addressed to ensure adequate programme outcomes [18, 20, 21]. Identifying “stable patients” who could be down-referred (or even just referred for starting ART) to less intense ART delivery models has been identified as an important mechanism for improving outcomes and optimising resource allocation for those in need [18].

We have focussed our review on studies of different models of ART delivery which have included a cost-effectiveness analysis. Identifying interventions that represent value for money is important [22], especially given the ambitious 90-90-90 goals by 2020 in resource-limited settings. The number of doctors working within many public sector settings is inadequate given the disease burden in South Africa and other LMIC settings [23]. Evidence from cohort and trial data for task-shifting HIV care from doctors to other models of care is growing [24], but more research is needed and the impact these models may have on ART adherence needs to be considered as well [21].

Early cost-effectiveness studies from South Africa focussed on the use and timing of ART and antibiotic prophylaxis [25-28]. ART was argued to be cost-effective compared to no ART [25, 26, 28, 29] and more cost-effective when started at a CD4 threshold of < 200 cells/ μ L [25, 27, 29] or when only first line was made available [28]. Later studies from South Africa focussed on regimen choice [30], task-shifting [31] [32],[33] prophylactic antibiotics [34], PreP [35], eligibility criteria [36, 37], and monitoring strategies [38]. In terms of ART provision, Granich et al. (2012) and Eaton et al. (2014) concluded that extending the CD4 eligibility criterion to $CD4 < 350$ cells/ μ L would be cost-saving; Rosen et al. (2008) concluded that switching from stavudine to tenofovir would be cost neutral; and Keebler et al. (2014) concluded that both CD4 and VL monitoring should only be recommended once high ART coverage was

established. Few studies have focused on the cost-effectiveness of different models of care [13], which is the focus of this thesis.

2.4.1 Nurse

We found two cost-effectiveness analyses of nurse-based models of ART delivery [39, 40]. Previous studies had shown that nurse-led care was not inferior and improved access to ART through expanded capacity [31, 41-45]. An earlier cost analysis found doctors' salaries to be a significant proportion of total clinic costs in South Africa [46]. Another study from 1993 in the United States found that a visit for routine care to an outpatient clinic run by nurses cost USD 287 compared to USD 1,400 for inpatient care, and the implementation of these nurse-led clinics resulted in 25% fewer inpatient visits. It was therefore likely that nurse-led care would be comparatively cost-saving [47].

In an analysis by Barton et al. (2013), a cost-effectiveness analysis of nurse-led versus doctor-led first line ART provision within the STRETCH trial was presented [48]. Two cohorts were established, with over 10,000 patients who were either ART naïve or had been on ART for six months or more at enrollment. The main outcome measures of the trial were death and viral suppression (<400 copies/ml) at 12 months after enrolment, and costs were estimated. The authors concluded that nurse-led ART was associated with higher mean direct health care costs than doctor-led care but outcomes were equivocal. This study, therefore, suggests that SOC dominates nurse-led care [39]. Nurse-led care was associated with positive aspects such as longer contact time with the patient and improved CD4 count response, tuberculosis detection, and weight gain on ART [42].

Using cross-sectional mixed methods study design, Foster et al. (2012) compared a pharmacist's assistant (working under a pharmacist) and a nurse-led clinic with the standard of care (a public sector clinic) in South Africa. The authors evaluated two clinics in each setting and concluded that the pharmacist assistant model and nurse model would be on average cost-saving, with a USD 2.6 and USD 3.75 reduction in cost per patient per visit respectively.

Given this evidence, nurse-led ART provision may not necessarily reduce costs. However, given the shortage of doctors in the public sector [23], nurse-led ART provision would

be needed to enhance access [47]. More research is needed as follow-up periods were only one year and the effects may be temporal; more exposure time is therefore necessary [21].

2.4.2 Pharmacist and pharmacist's assistant

Pharmacist-care models with cost-effectiveness analyses have been published by Babigumira et al. (2011) and Foster et al. (2012) (referred to earlier). The pharmacist's support model proposed by Foster et al. (2012) was the topic of a recent systematic review [49]. The WHO recommendation is one pharmacist per 2,300 population, but few LMICs can reach this level [50]. The authors of this review found only three studies [51-53] (two cluster trials from Kenya and Uganda and an individually randomized trial from Brazil) from LMIC settings which met the inclusion criteria. The conclusion of authors of this review was that the certainty for the intervention was low – pooled analysis found improved non-significant survival (RR 1.86; 95% CI 0.44 to 7.95), worsened non-significant loss to follow-up (LTFU) (RR 1.13, 95% CI 0.68 to 1.91), and improved non-significant virological response (RR 0.92; 95% CI 0.73 to 1.15) [54].

The standard model of care in Uganda at the time of the Babigumira et al. (2011) study involved monthly physician visits [55]. The intervention allowed for pharmacy-only monthly visits for 5 months out of 6 – i.e., patients were allowed to collect their medication without seeing a clinician but were asked screening questions by a pharmacy-based nurse during every visit. As with the adherence clubs in Khayelitsha, stable patients (were 12 months or more on ART, CD4 > 200 cells/ μ l, had attended clinic visits consistently for the preceding 6 months, had disclosed HIV status to spouse, were not pregnant, and had “no substantial clinical event in the preceding 6 months”) were identified and offered the option of transferring to the pharmacy-refill model. The main outcome measures were having a CD4 > 500 cells/ μ l or favourable CD4 response on follow-up after one year. The authors concluded that there was an adjusted non-significant risk (OR 0.93, 95% CI 0.55–1.58) of a non-favourable CD4 response, but a significant cost-saving (USD 520 versus USD 655 annually) with the pharmacy-refill model. The ICER was USD 13,500 per favourable CD4 response.

Given this evidence, pharmaceutical interventions for ART provision may save costs. However, given the shortage of pharmacists in the public sector in South Africa as well, novel strategies which alleviate the pharmacist medicine dispensing burden are required [50]. The Chronic Disease Unit, an out-sourced public sector centralized dispensing service, is an example

of a successful programme that has been implemented in the Western Cape [56]. More research on the impact of this service on other potential models is required [57]. We have included an analysis of pharmacy delivery to homes in Chapter 6 of this thesis.

2.4.3 Adherence clubs

Community-based interventions have been shown to improve and sustain ART adherence in LMICs [58]. In South Africa, adherence clubs were established within Khayelitsha clinics and are well described [13, 54, 59-62]. The clubs were run by trained lay health workers and supported by nurses and in essence were a combination of several interventions that have been shown to be independently effective at improving retention in care: patient support groups, task shifting to lay workers, less frequent appointments (every two months), and quicker visits [13]. Stable patients were identified and offered the option of transferring based on the following criteria: 18 months or more on ART, CD4 > 200 cells/ μ l, viral suppression (defined as two consecutive viral loads <400 copies/ml, with the most recent not more than 6 months old), no adverse drug effect, no opportunistic infections, and consistent clinic attendance. A positive relationship between adherence clubs and VL suppression and retention in care has been reported [63].

In an analysis by Bango et al. (2016), the cost-effectiveness of adherence clubs versus a public sector clinic for the management of stable patients is presented using a similar approach to that of Barton et al. (2013) above. In this analysis, the adherence clubs were found to be cost-saving, lower costs (USD 300 versus USD 200) and better but not significant retention (98% versus 95%) and viral suppression (99% versus 97%). Future trials are planned to look into the cost-effectiveness of 3- versus 6-monthly dispensing within adherence clubs [64].

2.4.4 General practitioner (GP)

The provision of ART for public sector patients through GPs in LMIC settings, including South Africa, has been described in the literature [65-67]. The impact of high patient burden in public clinics on retention in care and quality of care has also been described [68, 69]. GP models for ART delivery should be considered in South Africa given the significant potential resources and lower patient burden [70].

In the study by Igumbor et al. (2014), a GP down-referral model was established at the request of the North West Provincial Department of Health, South Africa, to evaluate the feasibility of the model for areas where public sector resources were limited [65]. The national guidelines were followed and support mechanisms, including quarterly meetings with public hospital clinicians, were established to promote consistency of care. In the study by Innes et al. (2012), a GPs model for initiating ART was established in a managed-care environment (i.e., with clinical and programme support from the Aurum Institute). The model proposed by Innes et al. (2012) was similar to the GP model presented in Chapter 8 of this thesis, except that in Chapter 8 the managed-care provider was AfA.

We contrast the Aurum supported and AfA supported programme outcomes in Chapter 8 in more detail. The subsequent analysis of a down-referral model for ART delivery by Igumbor et al. (2014) is, however, more difficult to compare given that it was a down-referral model. Encouragingly, at 48 months, viral suppression rates were 88.4%, survival was 89.0% (95% CI: 87.1%–90.0%), and patient retention was 94.3% (95% CI: 93.0%–95.7%). These findings were consistent with the analysis of the AfA-managed model presented in Chapter 8, but retention was substantially worse in the Aurum-managed programme, with retention rates of less than 60% at 3 years [67].

Given the evidence presented in Chapter 8, a GP model for ART delivery would be cost-effective and should be considered in South Africa. More research is needed, however, given the limited cost data, ongoing concerns regarding the quality of care, and the alternative models being proposed (including contracting private GPs to work part-time in government clinics) [65, 71].

2.5 Conclusions

South Africa has adopted WHO's "treat all" [72] to reach the 90-90-90 goals [73], which according to latest estimates means a further 3.1 million or 44% of PLWH will need to start ART over the next few years [74]. New HIV infections remain significant in South Africa (110,000 in 2016) and, therefore, it is anticipated that large numbers of PLWH will need to be started and maintained on ART for many years to come [71]. Recent studies suggest that most PLWH in South Africa now know their status [75] and most rely on public sector services for

their health care [23]. Addressing factors influencing ART initiation, ART adherence, and retention in care are therefore paramount [76-78].

We present outcome and cost-effectiveness analyses for two models of ART provision in South Africa in Chapters 6 and 8 respectively that contribute significantly to the literature on models of ART delivery in South Africa. The White Paper on the South African National Health Insurance (NHI) framework was updated in 2017 [79]. Within this framework, all health care professionals are considered potential providers of care for all people in South Africa, thus removing the distinction between the public and private sector and the associated inequalities [23, 71]. To achieve the goal of establishing an NHI in South Africa, it is essential to include considerations of cost-effectiveness and budget impact in order to move towards allocations that maximize health within the budget constraint [80].

2.6 References

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Chapter 3: Methods and sources of data

3.1 Overview

We have included data from three different HIV programmes in the various studies presented in this thesis. Public sector cohorts are the main providers of HIV care in LMICs, yet these data have several limitations, particularly in relation to analysing detailed costs and/or outcomes. Within public sector programmes in South Africa, electronic medical records (EMRs) were limited to CD4 count, VL, clinic visits, status and, in some cases, dispensing events [1, 2]. HIV care has been standardized to contain costs and conform with the National Department of Health (NDoH) guidelines from 2004, inclusive of several pilot studies [3, 4]. Within the private sector, substantially more data are available, allowing for more detailed cost and outcome analyses where possible. The intention of this chapter, therefore, is to briefly describe these cohorts and contextualize them within the broader health care sector in South Africa.

3.2 General description of cohorts

3.2.1 Private sector cohort – Aid for AIDS (AfA)

In many LMICs, the private sector (which includes non-governmental organisations, international funders, and independent practitioners) has played a significant role in both health financing and health delivery. This was especially the case in the early 2000s when public sector programmes were still being piloted in South Africa and other LMICs [5-8]. A recent review estimated that 16% of South Africans belonged to a medical scheme in 2014 and a further 21% (i.e., 25% of the uninsured) pay “out of pocket” for health care expenses within the private sector [9].

For those who belong to a medical scheme, HIV care has been included within the list of medical conditions in Annexure A (along with diabetes, hypertension, etc.) which were classified under the prescribed minimum benefit (PMB) clause, Medical Schemes Act 131 of 1998 [10].

For PMB conditions, the Act stipulated that medical insurances were required to cover all reasonable costs and, therefore, HIV care soon became standard of care in South Africa. In terms of the Act, medical insurers were also able to identify a designated service provider (DSP) for a specific aspect of care. This is relevant to this thesis as, in later years when courier pharmacy dispensers were established, some companies and, later, even the Western Cape Department of Health appointed courier pharmacy dispensers as their DSP for ART and chronic medication, respectively [11]. A comparison of outcomes and cost of courier versus collect pharmacy is presented in Chapter 6.

AfA is a private sector programme operating in Southern Africa as a comprehensive disease management programme that is responsible for the oversight of HIV-related care for contracted private medical schemes and companies in the region. The programme has been described in several published studies [12-21] and was established in June 1998 [22]. At the time of AfA's establishment, increased HIV-related hospitalization in particular was driving up costs within the public and private sectors in South Africa. Many of the patients who presented with AIDS did not know their status [23]. A managed-care model was adopted within the AfA programme and a pragmatic clinical guideline, aligned with WHO guidelines for resource-limited settings, was established, given that both medical scheme financial resources and provider knowledge were limited. Over time, the guidelines and approach to care have evolved in conjunction with local and international guidelines. AfA has incentivized standardized care through a reimbursement model aligned with these guidelines. Moreover, members were able to have their blood tests (CD4 count and VL) performed regularly at their initiative at any of the private pathology laboratories in South Africa.

As of August 2015, the programme had enrolled over 200,000 members from nine countries, including South Africa, Malawi, Botswana, Zimbabwe, Namibia, Zambia, Mozambique, Lesotho, and Swaziland, noting that more than 80% of these had commenced ongoing ART while enrolled with AfA. The AfA programme, therefore, represents a significant proportion of the population accessing HIV care through the private sector in South Africa. We have included data from the AfA cohort in several studies included in this thesis, with varying inclusion and exclusion criteria (see "inclusion criteria and censoring" below). We have included a cohort profile paper in this thesis as Chapter 4, where we cover the history of the programme in more detail than was possible in previous publications [12-21, 24, 25]. In Chapter 5, we present a detailed analysis of the changing determinants of costs over time on ART, as well as

the impact of adherence on costs over time on ART. In Chapter 6, we compare the costs and outcomes of courier pharmacy versus collect pharmacy within AfA.

Key contributions to published literature from this cohort are described in Chapter 4 in more detail, and have resulted from the cohort being largely black South Africans, accessing WHO-aligned HIV care, high levels of digitalization of HIV-related care with a centralized data system, long follow-up compared with other public sector programmes in South Africa, and large numbers in HIV care. The use of electronic records within the private health-care sector is a key strength when it comes to economic and outcome studies as presented in this thesis. The timely authorization of health care expenses within the private sector has been essential, especially when identifying the need for co-payment or up-front payment by members. These electronic systems have continued to evolve within the South African private sector, often outpacing public sector systems. Centralization and standardization of health-related data within private sector programmes like AfA have allowed for detailed analyses of large numbers of patients for cost analyses (e.g., tariff rate), adherence (using pharmacy refill data), morbidity (hospitalization and other clinical events), and mortality [21]. Moreover, the active tracking of AfA members across schemes, together with accurate and extensive capturing of South African national identity numbers (RSAIDs), is a key benefit when estimating mortality and loss to follow-up (LTFU) accurately [26-28]. Studies from South African public sector HIV programmes have shown that reported mortality and LTFU are often inaccurate, and linkage with the national death registry, while accurate, was only possible for around half of the patients attending public sector clinics in these studies [26-28].

3.2.2 Public sector cohort – Khayelitsha

The Khayelitsha cohort stems from a Médecins Sans Frontières (MSF) pilot study established in 1999 in Khayelitsha, a thriving urban township in Cape Town with a population over 500,000 persons [29, 30]. Khayelitsha started as an Apartheid era dormitory town to house migrant workers in the 1980s. The community remains vulnerable given the high levels of unemployment, informal housing [30] and the highest HIV prevalence in the Western Cape Province [31]. Alarming, 34.3% of the pregnant women attending public sector antenatal clinics in the area were HIV positive in 2012 [31]. A recent cohort profile publication from 2016 describes the cohort in significantly more detail [29]. The focus of this section will, therefore, be on specifics relevant to the analysis only. The Khayelitsha cohort consists of a prevention of mother to child transmission (PMTCT) programme started in 1999. The first patients to be enrolled in ongoing ART were from 2001, making it one of the oldest public sector cohorts in South Africa and one of several pilot studies internationally. The establishment of EMRs early on is important for this study, as the clinic visit and dispensing data could be used to determine health care utilization data. In Chapter 8, we present an analysis in which we used these data to compare the cost-effectiveness of public and private-public partnerships using GPs. For this analysis, the dataset used was part of an existing publication in 2010 [2], together with cost estimates from a previous cost-effective study within the same programme in 2006 [32].

In the public sector pilot programmes, including Khayelitsha, the initial regimen consisted of zidovudine (ZDV) and lamivudine (3TC) together with nevirapine (NVP) or efavirenz (EFV). From late 2003, stavudine (d4T) replaced ZDV in the standard first-line regimen in late 2003 to align with the proposed South African national programme and guidelines [29, 33], which were implemented in April 2004 [34]. Virological failure was used to determine treatment failure, unlike in many LMICs [12], and was defined as two consecutive viral loads $> 5,000$ copies/ml. The standard second-line regimen consisted of stavudine (d4T), didanosine (ddI) and indinavir. Over time these regimens were altered: from 2008, lopinavir/ritonavir (LPV/r) and 3TC replaced indinavir and ddI respectively; from 2010, TDF replaced d4T in the first-line regimen; from 2012, FTC replaced 3TC in first line regimen; and from 2013, fixed-dose combination ART was introduced. The CD4 count threshold for initiating ART was CD4 count < 200 cells/ μ L until 2010 which was concerning given the significant early mortality observed in South African cohorts [35, 36]. The CD4 count and WHO stage thresholds for initiating ART was increased in a stepwise manner in keeping with changing

WHO guidelines for developing countries [37], and eventually dropped in favour of “treat all” [38, 39].

3.2.3 Public-private partnership cohort – BroadReach

Various models of HIV care have been implemented in South Africa, including public-private partnerships (PPPs). In a recent review [5], the authors refer to a form of “public-private engagement” (PPE); given the diversity of models that have been implemented for HIV care in South Africa and other LMICs, they felt that PPE better represented the need to focus on health financing and delivery rather than on who is providing the care. Nevertheless, given the history of disenfranchisement in South Africa, many remain concerned that an unintegrated private sector results in more harm than good as it silos resources for more affluent individuals [9]. In the proposed 2017 White Paper for NHI for South Africa, all providers will be integrated through a central payment system and free access to healthcare services would be provided through accredited health facilities (i.e., clinics, hospitals, and private health practitioners) [40]. The model evaluated in the above review is very relevant as it falls within the proposed parameters for NHI (i.e., harnessing private/independent practitioners to provide care for public sector patients) and therefore contributed significantly to the literature.

In Chapter 8, we presented an analysis in which we compared the cost-effectiveness of public and private-public partnership using GPs. The BroadReach or PPP cohort stems from a BroadReach health care initiative funded by PEPFAR, where public sector patients from public sector clinics were enrolled in a programme in which HIV care was provided by private GPs in the community, ART medication was provided by the state, and laboratory tests were undertaken by private laboratories. The GPs were supported by AfA clinical support structures and included physicians, pharmacists, and counsellors. Where complications arose requiring further work-up at specialized clinics or hospitals, the patients were referred to secondary and tertiary state facilities within their areas.

3.3 Study design

The studies included in this thesis are all longitudinal. Individuals who started ART within the AfA, BroadReach, and Khayelitsha programmes were prospectively enrolled.

3.4 Definitions

ART initiation

For the analyses in this thesis, ART initiation was defined as the date on which ongoing ART was first dispensed. While dispensing data were not generally available within the public sector programmes in LMICs, including South Africa, they were available within all the cohorts included in this thesis.

LTFU

The way loss to follow-up is accounted for in HIV cohort analyses can substantially impact the findings [41, 42]. Various definitions of LTFU have been proposed within the literature with varying timeframes and data requirements (clinic visit versus dispensing events). Thus, we proceeded with the following standardized definition of LTFU to ensure comparability between the various cohorts and other programmes: a patient has “run out” of the recorded dispensed antiretroviral drugs (ARVs) for at least 6 months (i.e., 7 months or 7 x 28 days from last dispensed date).

Death

The availability in South Africa of an efficient national vital registration system is an important resource within cohort studies as it allows for the correction of under-ascertainment of mortality observed in cohort studies (usually misclassified as LTFU) [2, 26, 28, 43]. The process required linkage to the South African death registry to ascertain deaths and dates of death using RSAIDs and was facilitated by the South African Medical Research Council (MRC). Reported deaths within cohorts studies from LMICs have been shown to be inaccurate and difficult to distinguish from LTFU [2, 26-28, 43]. A previous study using the Khayelitsha cohort dataset found that between 90% and 95% of known deaths could be identified using RSAIDs to link with the death registry [2]. We repeated this in Chapter 4 and found similar results when looking at the broader medical scheme population.

3.5 Inclusion criteria, exclusion criteria, and censoring

The following inclusion criteria were applied across all studies (Chapters 5–8) to ensure our findings would be more generalizable (i.e., aligned with WHO guidelines for resource-limited settings):

- *Adult*: 19 years or older when first dispensed ongoing ART, i.e., excluding PMTCT
- *Initiated first line therapy*: A dispensing event including NNRTI together with two NRTIs
- *Baseline*: CD4 count < 200 cells/ μ L or AIDS-defining illness or WHO stage III/IV illness

Regarding the specific studies, the following additional criteria were applied or relaxed:

- **Chapter 4**: We included all members who enrolled before 30 August 2015. The purpose of this analysis was to describe the programme and members it has served since its inception in 1998.
- **Chapters 5 and 7**: We included members from the AfA cohort who were enrolled in two of the medical schemes and initiated (first dispensed) ongoing combination ART between November 1998 and November 2007. The chosen schemes were South African medical schemes, with large numbers of patients and similar treatment benefits, requiring no co-payment for ART. This was important as the goal was to describe costs and drivers of costs without relation to patients' ability to pay, which has been reported to influence outcomes on ART in LMICs [44].
- **Chapter 6**: We included members from the same schemes in Chapters 5 and 7, who enrolled between January 2002 and July 2010.

3.6 Cost data

Health care costs were analysed from the healthcare sector's perspective, i.e., direct costs. Indirect costs and direct non health care costs, while often significant in South Africa and other similar settings [45], were not accounted for in the analyses presented in this thesis.

Sources of data

For the AfA and BroadReach cohorts, health care claims were captured centrally by Medscheme and BroadReach Healthcare, the administrators responsible for authorizing, receiving, and reimbursing medical claims related to HIV care. In most cases, the providers submitted the claims directly and, therefore, patients could access care without any upfront costs. For the Khayelitsha data, the utilization (clinic visits, ART dispensing, CD4 count and VL monitoring) was recorded at the time of the visit on a centralized computer system established for the clinic, which has subsequently been expanded [46].

Scope of data for AfA cohort analyses

For the AfA cohort analyses (Chapters 4, 5, 6, and 7), we included all direct medical costs submitted to the medical scheme. These include health care practitioner visits, medication dispensed (acute, chronic), hospitalization costs (medication, surgical, accommodation, health care practitioner) and other outpatient procedure costs (medication, surgical, accommodation, health care practitioner). The tariff amount (which is the amount agreed to on an annual basis following negotiations between private health care providers and funders) was used in most cases as a proxy for direct health care costs, as opposed to the amount charged by the provider or the amount reimbursed to the patient. In Chapter 5, over 49,517 unique claim categories were identified. Of these, 4,000 accounted for over 95% of total costs and these were grouped into the following categories:

- ART medication
- other medication
- maternity-related care (antenatal services, delivery, caesarean section, and post-delivery paediatric care)
- GP care
- specialist care
- hospital accommodation and procedures
- CD4 count and VL monitoring
- other investigations (e.g., laboratory tests and radiology)

Scope of data for Khayelitsha and BroadReach analyses

For the analysis in Chapter 8, we included all costs related to the direct provision of ART. This included antiretroviral drugs (ARVs), CD4 count and VL monitoring, other laboratory monitoring (e.g., alanine transferase, lipogram, creatinine, full blood count) and clinic visits. The net costs were determined by multiplying the utilization by the cost price for all items.

For both cohorts, we were provided with actual utilization data for ARVs, CD4 count and VL monitoring, and clinic visits. We estimated the other laboratory monitoring from the guidelines, which was reasonable as most of these costs were incurred when the patient first started ART.

We estimated the costs differently for each cohort. For the clinic visits in the Khayelitsha cohort, we inflated the estimated costs from a recently published bottom-up analysis within the same programme [32]. For the GP visits in the BroadReach cohort, we were provided with the actual reimbursed rate for a GP visit by the administrator. ARV and laboratory monitoring costs were determined from the government tender rate at the time of the visit.

Adjustments

The prices of antiretroviral drugs had fallen dramatically over the period of the studies in Chapters 5, 7, and 8. To account for this decrease, we deflated ARV drug prices prior to the April 2007 level to 2011 drug prices. All other health care costs have increased; these were inflated to the April 2007 level using the consumer price index net of mortgage payments (CPIX) [47]. The average ZAR to USD exchange rate in April 2007 (ZAR 7.14 to USD 1) was used to convert costs to USD equivalents [48].

3.7 Ethics

The study was approved by the Research Ethics Committee, University of Cape Town, on the basis that it was a retrospective cohort analysis and all patient-level identifiers were removed in the data extraction process. The approval for 2017 is included in Appendix 1.

Concerning the AfA data (including BroadReach data), the study was approved by the Board of Directors of AfA and by BroadReach. All patients within AfA signed consent for their information to be captured in the AfA clinical management database and for anonymized extracts to be used for research studies to drive improvements in patient care. A specific application was sought for the cohort registration. The approval for 2015–2018 and the AfA registration form, which was included in the ethics application, are included in Appendix 2.

Concerning the death register, an addendum was sought that granted permission to link with a copy of the national death register managed by the regional Medical Research Council's offices in Cape Town. The approval from 2017 is included in Appendix 1.

3.8 Conclusions

In summary, the various cohorts included in the analyses of this thesis would be considered to be a fair representation of different types of programmes in South Africa. Key strengths of the AfA cohort are described in Chapter 4 in more detail, and have resulted from the cohort being largely black South Africans, accessing WHO-aligned HIV care, high levels of digitalization of HIV-related care with a centralized data system, long follow-up compared with other public sector programmes in South Africa, and large numbers in HIV care. The key strengths of the Khayelitsha cohort are described briefly in Chapter 8 and comprehensively in a recent cohort profile paper [29], and include long duration of follow-up (the pilot study was started in the early 2000s), capturing of visits (dispensing, laboratory tests, and clinic visits) electronically, and the adequate recording (50%) of RSAIDs, from which status death and LTFU rates could be estimated. Key strengths of the BroadReach cohort are described briefly in Chapter 9, where it is noted that it was a PPP in which ART was initiated (rather than a down-referral), that providers were independent general practitioners within communities, the patients were recruited from public sector clinics, the patients remained integrated within the public sector system (for hospital admissions or complications), and it involved an independent programme administration to facilitate the care.

3.9 References

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Chapter 4: Cohort profile: Adults within Aid for AIDS (AfA) antiretroviral programme, South Africa

4.1 Overview

The intention of this chapter is to provide an overview of the AfA cohort – a cohort profile.

This chapter is presented in the style of other cohort profile papers published in the *International Journal of Epidemiology*.

4.2 Why was the cohort established?

AfA was established in June 1998 as a comprehensive disease management programme, responsible for the oversight of HIV care for contracted private medical schemes, companies, and PPPs in Southern Africa (South Africa, Malawi, Botswana, Zimbabwe, Namibia, Zambia, Mozambique, Lesotho, and Swaziland) [1]. The surge in HIV/AIDS-related morbidity and mortality at the time meant that facilities and budgets within the public and private sectors were taking significant strain [1-3]. Emerging evidence from high income country (HIC) settings suggested that ART, while costly, would be effective in reversing disease progression, reducing morbidity, and improving patient survival [4]. ART, therefore, was desperately needed in LMICs [5]. Moreover, a reduction in HIV related morbidity and mortality had potential social and financial benefits that would supercede the absolute costs of ART [5].

Regarding the public sector, HIV care including ART was initially only available through a few pilot programmes in South Africa [6, 7], i.e., PMTCT from 1999 and ART from 2001 [8]. The eligibility criteria for ongoing ART was conservative: baseline CD4 count < 200 cells/ μ l or WHO stage IV conditions other than extra-pulmonary tuberculosis. At the time, an estimated 1,600 new infections were occurring daily, with nearly 90% of infected individuals being unaware of their status, resulting in late presentation [4]. Given that South Africa was still an emerging democracy with significant hurdles to overcome, especially within the fragmented health care sector, private sector and workplace HIV programmes soon overtook public sector initiatives [2, 9]. For those with private health insurance, the 1998 implementation of the Medical Schemes Act

ensured that several chronic illnesses and emergency care were classified as PMBs [10]. AfA implemented a managed care approach with conservative treatment guidelines, outcome monitoring, patient counselling, and clinical support for providers. Numbers registering with AfA soon swelled [2]. In essence, the AfA programme was aligned with the public health approach to HIV care, which was later advocated by WHO for resource-limited settings [11].

4.3 Which cohorts contribute to the managed-care programme?

The population accessing care through the AfA programme included closed (company or government) and open schemes, along with PPPs within Southern Africa. Recruitment was continuous and voluntary; members were able to access HIV-related care without being registered with AfA, using personal funds or medical insurance fund savings, but reimbursement of HIV related expenses was subject to registration with AfA and authorization by AfA staff. Some flexibility was allowed where patients presented late and were started in a hospital or around a hospitalization event. Patients completed an enrollment form with their treating medical practitioner and gave consent for prospective studies to improve patient care.

4.4 What data were collected?

Data were collected prospectively. Patient-level data included sex, date of birth, family structure, and region. Identifiers (names, addresses, family units, and policy numbers), physical address, and RSAID number (for principal members only in the earlier years) were available within patient information systems held by the medical fund and its administrator and shared with AfA to avoid duplication errors. AfA captured additional RSAID numbers from the registration form.

Clinical events, including events before registration with AfA, were captured within the same central system and made available to the clinicians and pharmacists. They included events such as WHO stage-defining illnesses, pregnancy, tuberculosis, and others which would have impacted outcomes or HIV care. ART exposure and HIV-related laboratory monitoring results, including before registration with AfA, were captured within the same central system.

Laboratory tests included CD4 count, VL, full blood count, cholesterol, genotypic antiretroviral resistance testing (GART), and liver and renal function tests. Increasing digitization

has helped improve ascertainment of laboratory results and, over time, nearly all laboratories were allowing digital laboratory result transfers on a monthly basis. Moreover, AfA established a system allowing patients to do the laboratory monitoring tests themselves (e.g., 6-monthly CD4 count and VL tests) to improve monitoring.

Detailed information on HIV-related medication was collected and included prior antiretroviral exposure and context (PMTCT, PrEP, PEP, and/or ongoing), authorization within AfA and context, dispensed medication with date, quantity, dose and methodology (collect or courier pharmacy). Before 2002, combination ART was not available to all members across all schemes due to the high costs of ARVs and VL tests. Some patients elected to privately purchase a third drug and, therefore, knowledge around the exact regimen those members were on was uncertain. From 2002, combination ART was available universally without co-payment across all schemes. ART-related toxicities or adverse events which may have impacted either the choice of ARVs or required authorization for additional medication were also captured.

4.5 Who enrolled and what protocols were applied?

The first patients enrolled with AfA in 1998. Membership swelled rapidly in the first few years and again with the establishment of the Government Employment Medical Scheme (GEMS) for public servants in 2005. By 2009, GEMS was the second largest private medical scheme in South Africa, providing for over a million public servants in South Africa, many of whom had not been eligible for private medical insurance before its formation [12]. By 31 August 2015, more than 180,000 PLWH had been authorized for ongoing ART, and over 40,000 had enrolled with AfA, though they had not yet initiated ongoing ART.

Table 4.1: Characteristics of patients initiating ART, 1998–2015

	Total	Calendar period					
		1998-2000	2001-2003	2004-2006	2007-2009	2010-2012	2012-2015
N	233 114	8 437	22 429	23 183	61 205	95 273	22 564
Adult (19+ years on registration)	95%						
N	221 407	7 814	20 936	21 943	58 118	90 761	21 835
Median age (IQR) in years	36.6 (30.7-43.3)	33.8 (28.5-39.5)	34.7 (29.4-40.7)	36.2 (30.6-42.7)	36.3 (30.6-42.9)	37.4 (31.2-44.1)	37.7 (31.7-45.2)
Male (%)	35%	38%	38%	39%	34%	32%	46%
Median baseline CD4 (ICQ) in cells/mm ³	195 (94-302)	172 (75-252)	147 (60-226)	140 (59-218)	187 (92-289)	221 (113-324)	267 (138-405)
Child (<19 years on registration)	5%						
N	11 707	623	1 493	1 240	3 087	4 512	729
0-4 years	4 286	351	850	584	1 189	1 152	160
(5-9 years)	3 081	83	283	341	940	1 280	154
(10-15 years)	2 118	37	84	128	517	1 135	217
(15-18 years)	2 199	152	276	187	441	945	198
Median age (IQR) in years	7.4 (2.9-13)	3.8 (1.4-14.9)	3.9 (1.3-9.6)	5.4 (1.8-10.1)	6.7 (2.9-11.3)	9.4 (4.9-14.1)	11.1 (5.4-15.4)
Male (%)	44%	40%	42%	44%	46%	43%	42%

4.6 Clinical and other support

All scheme members received ongoing HIV education via their respective medical schemes. Additionally, any member who tested positive for HIV was encouraged to register with AfA. Medical doctors who registered with AfA and support staff received ongoing communication through newsletters, updated clinical guidelines (more recently through a mobile app as well), access to continuous medical education (CME) via online learning modules and regular clinical meetings. The clinical guidelines were developed by the AfA Clinical Advisory Committee in conjunction with the academic and private sector collaborators.

An important intention of the AfA programme was to identify and capture clinical events relevant to the care of an HIV positive person. These events would “unlock” benefits (e.g., Bactrim prophylactic antibiotics for CD4 count < 200 cells/ μ L). The effectiveness was therefore dependent on private doctors and patients informing AfA staff, and thereby enabling authorization for event-related expenses related to benefits. Clinical and claims data were used to support patient-level decisions on programme outcome monitoring.

In summary, AfA did not manage clinics but reimbursed patients’ HIV related expenses either directly or, where the member had already paid, with a refund. If members had depleted their general medical funds, AfA would authorize up to two additional visits to the doctor registered with AfA for providing their annual HIV related care to ensure continuity of care.

Most patients accessed private practice and hospital services within their regions, although there were some specialist HIV practices.

4.7 Eligibility for ART

At the time of the formation of the AfA programme, internationally accepted guidelines were already recommending that ART is started when CD4 count dropped below 500 cells/ μ l with the “hit early hard” approach [13]. Financial constraints within an LMIC setting meant that ART was not affordable if started too soon[1] and, furthermore, the benefit for an asymptomatic patient starting ART that early was unclear within the literature at the time [2]. Therefore, the CD4 count threshold for initiating ART was set at ≤ 350 cells/ μ l (two occasions, 6 to 12 weeks apart) and an AIDS defining illness or WHO stage III/IV illness was also included in the criteria for being eligible for ART.

AfA’s threshold was less conservative than the subsequent 2003 WHO guidelines for resource-limited settings broadly adopted in LMICs [11] and the subsequent 2004 South African National Department of Health (NDoH) [14]: CD4 count ≤ 200 cells/ μ l or a WHO stage IV or AIDS defining illness. Moreover, eligibility for ART in discordant couples was already allowed before it became WHO or NDoH policy to promote supportive environments. Soon afterwards, the evidence for treating at higher CD4 counts was established [15, 16] and the threshold in the WHO guidelines [17, 18] and NDoH guidelines [19] changed. From 2014, the CD4 count threshold for ART in AfA was formally moved to < 500 cells/ μ l (or any staging illness [20]), and from 2015 the threshold was formally abandoned completely [21]; where patients had requested to start at a higher CD4 count, a similar incremental approach of increasing CD4 count and decreasing stage was echoed within WHO and NDoH guidelines. The impact of changing CD4 count threshold and earlier initiation of ART over time is shown in Figure 4.1 below.

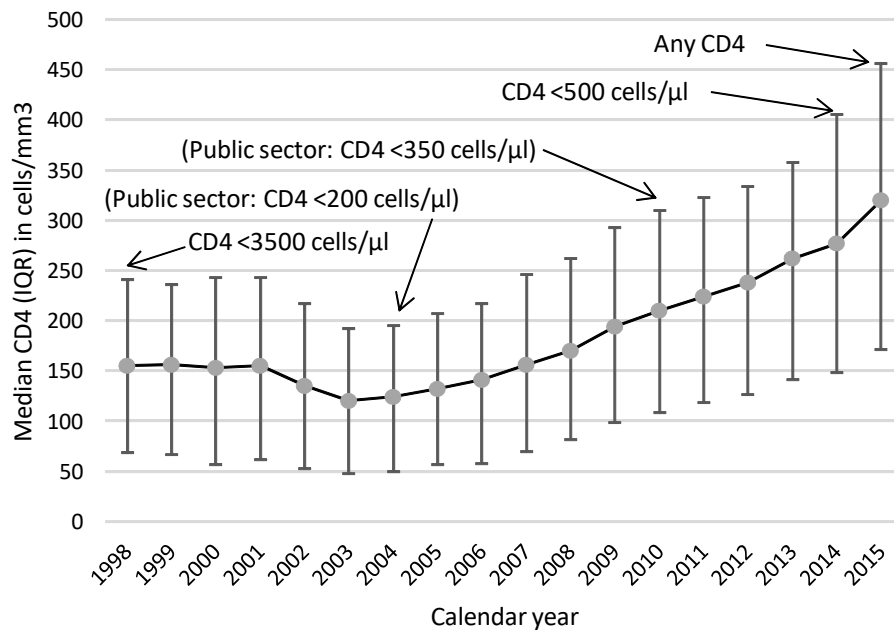


Figure 4.1. Median baseline CD4+ cell count time by calendar year, indicating changes in Afa (and public sector) CD4+ threshold over time.

4.8 ART regimens

At the launch of the Afa programme in 1998, the internationally accepted guidelines promoted triple therapy or combination ART in any patient with a CD4 count < 500 cells/ μ l. Given the high costs of drugs (PI with 2 NNRTIs) and monitoring, this was not affordable even within the private sector schemes in South Africa [1, 22]. Afa, therefore, recommended levels of cover be established within medical schemes: PMTCT (level 1) with either dual therapy (level 2) or triple therapy (level 3) [1, 2]. Initially, they focused on rolling out level 1 without co-payment and, by 2002, nearly all schemes were covering triple therapy without co-payment while NDoH negotiations with pharmacies had resulted in a reduction in dispensing fees. Additionally, international pressure had ensured reduced drug costs through access pricing for LMICs [5].

As NNTIs became widely available from the 2000s, the recommended initial regimen for LMICs including Afa evolved to a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) for individuals and medical schemes that could afford them. Afa guidelines, however, continued to allow for more flexibility in terms of initial regimen – both NNRTI- and PI-containing regimens were allowed, with some exceptions. Efavirenz (EFV)-containing regimens were recommended for

those patients on rifampicin for tuberculosis; nevirapine (NVP)-containing therapy was recommended for women of childbearing potential who did not commit to using two reliable methods of contraception initially (e.g., condoms and hormonal contraceptives) due to concerns about the risk of teratogenicity with efavirenz [23]. In keeping with other pilot ART programmes in South Africa [6, 24], Afa recommended AZT+3TC as the preferred initial NNRTI backbone; many of the public pilot studies later switched to d4T+3TC to align with the first NDoH guidelines in 2004. The preferred NNRTI backbone soon switched to TDF+FTC/3TC and the use of NVP in women was soon dropped as studies from observation cohorts did not provide evidence for EFV causing harm during pregnancy [21]. The changes to the dispensed first line regimens by calendar year are shown in Figure 4.2 below.

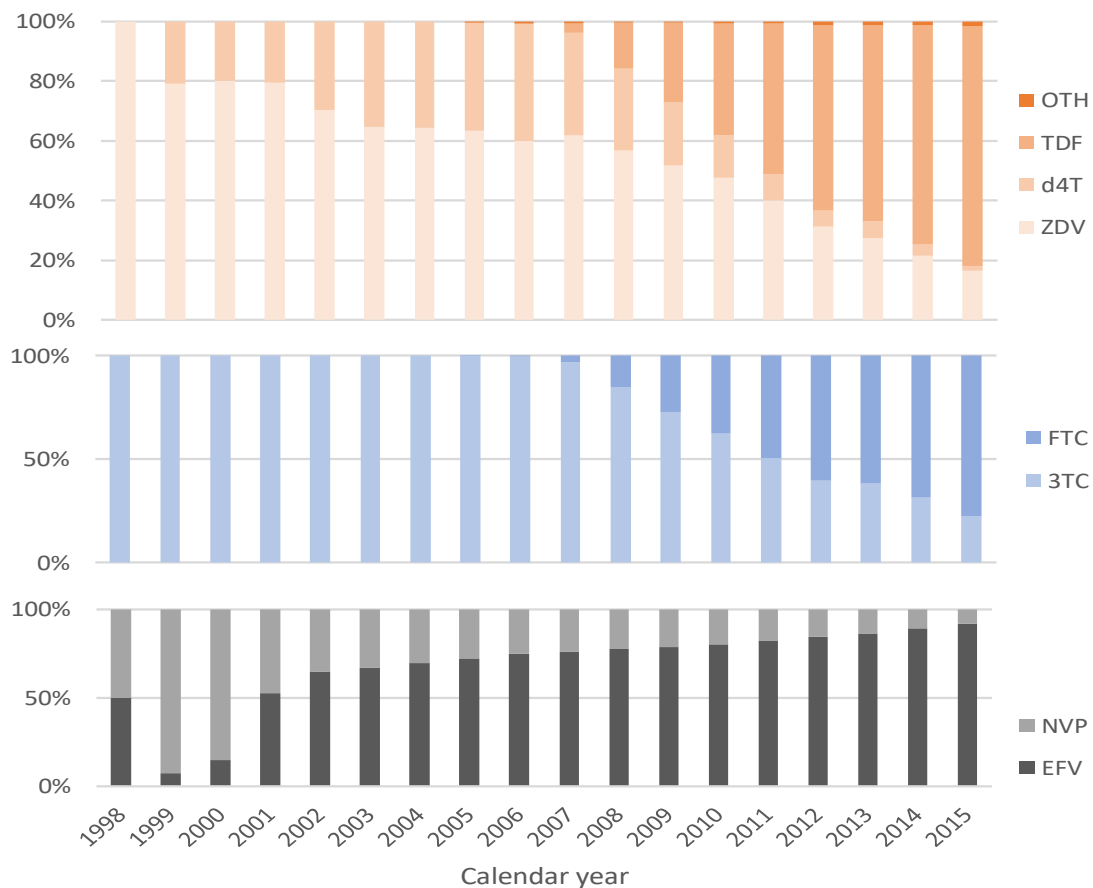


Figure 4.2: Changing composition of first line therapy by calendar year

As NNRTIs became available, the recommended second line therapy became a PI (later boosted PI) with two NRTIs. Up to 10% of patients in the early phase of the programme started treatment with a PI-containing regimen, but this trend gradually abated as confidence in

the WHO approach grew. Furthermore, ritonavir-boosted saquinavir, indinavir, or lopinavir were all initially available as PIs. Ritonavir-boosted lopinavir soon replaced other PIs due to its superior effectiveness and tolerability.

Third line or salvage regimens have been made available since 2007 to patients failing second line therapy and consist of either darunavir/ritonavir-, tipranavir/ritonavir-, raltegravir-, or etravirine-containing regimens. After an intensive adherence to counselling, those with a repeat 3-month VL > 1,000 copies/ml and a history of a possible infection with a resistant strain (e.g. from partner) were offered a genotype antiretroviral resistance test (GART); at least one major PI mutation was necessary, with regimens individualized on the basis of GART results. Patients were then contacted by AfA clinical staff before being switched to assess commitment to educating them about the new regimen. After that, adherence support through monthly telephonic counselling was implemented until the VL was suppressed. The outcomes were encouraging as shown in the recent publication: 82.9% had a VL ≤400 copies/ml and the Kaplan-Meier estimate for survival at 2000 days was 87% [25]. The relative proportion of exposure per regimen line over time is shown in Figure 4.3 below.

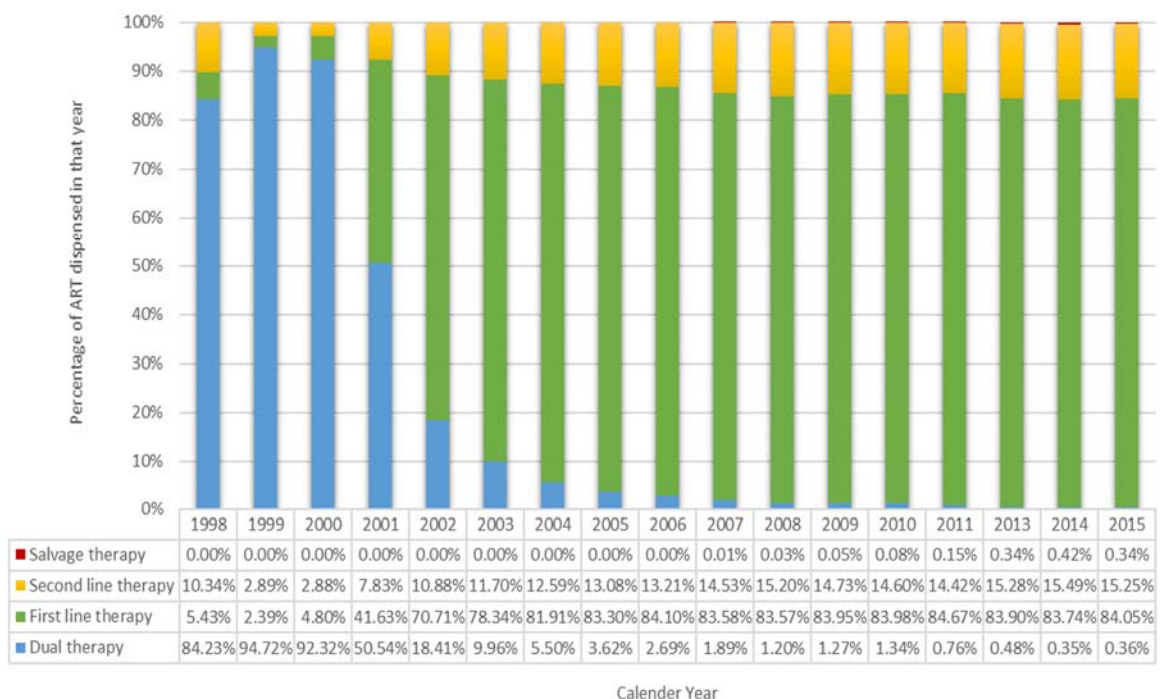


Figure 4.3: Regimen exposure per calendar year in adults, 1998–2015.

Drugs are collected monthly from private pharmacies (collect pharmacy). As courier pharmacy became available, patients increasingly switched to courier pharmacy. Some medical aids appointed a courier pharmacy as the preferred supplier as their large purchasing power lowered the medical costs for the scheme; patients could still collect medication from their local pharmacy but would have to make a co-payment. Others offered both alternatives.

In summary, the AfA guidelines have allowed for more individual choices regarding the regimens and monitoring frequency and intensity than is typically found in LMIC settings. However, a public sector approach was strongly influential given the resource-constrained context of South Africa. In general, the recommended regimens have, over time, more closely resembled WHO guidelines for LMIC settings [26] and South African guidelines [27] than HIC guidelines [28-31].

4.9 Prophylactic antibiotics, laboratory, and other monitoring

The AfA clinical guidelines defined which aspects of care related to HIV treatment would be covered over time; certain laboratory tests were subject to review and approval by AfA clinical staff to ensure that costs were reimbursed. Important baseline investigations, apart from CD4 count and VL (quantitative PCR), included: full blood count (FBC) and differential count (diff), Pap smear, alanine transferase (ALT), Mantoux (tuberculin skin test), syphilis serology, serum creatinine (Cr) and estimated glomerular filtration rate (eGFR), hepatitis B surface antigen, hepatitis C surface antigen (if ALT is elevated), pregnancy test, urine dipstick (proteinuria), serum cryptococcal antigen test, and chest x-ray results.

Nutritional support was not routine [32] but AfA later recommended a multivitamin and Vitamin BCo [33]. Prophylaxis included pneumococcal vaccine repeated every 5 years initially [34], though this was found later to be controversial and after that reserved for individuals who had had a splenectomy or a chronic lung disease [32]. Annual influenza was recommended as well as Hepatitis B immunization for antibody negative members. Cotrimoxazole/dapsone prophylaxis was recommended for those with a CD4 < 200 cells/ μ l, which was only stopped once the CD4 count was consistently > 250 cells/ μ l for at least 6 months (version 1), thereafter > 200 cells/ μ l. Given that tuberculosis was endemic in South Africa, isoniazid (INH) prophylaxis was initially recommended for 6 months in patients who had a Mantoux test, which

was positive [34], then later for those who had had recent contact with open tuberculosis [32] and those at risk (e.g., miners) [33].

CD4 count and VL monitoring can be done 2–3 months after starting ART and after that every 4–6 months [34]. This was aligned with the adopted 2003 WHO [11] and 2004 NDoH [14] guidelines. The recent shift towards more targeted CD4 count monitoring (only while CD4 count < 200 cells/ μ l or while failing virologically (VL > 1,000 copies/ml) is in keeping with HIC guidelines [28], and is broadly reflected in both the 2016 WHO [35] and 2015 NDoH [27] guidelines. Both NDoH and WHO guidelines, however, also advocated for more targeted VL monitoring, which is not reflected in the AfA guidelines.

4.10 Adherence and medical support

Given concerns around confidentiality and the complexity of HIV care, a dedicated unit was established from the beginning to provide patients, doctors, pharmacists, and hospitals with a centralized management and communication portal [1]. For patients, telephonic counselling, pharmacist (and specialist) services were provided by AfA on a demand basis. This was particularly relevant when salvage therapy was introduced as all patients received intensive counselling before commencing treatment [25].

For medical staff, reimbursement was subject to authorization by AfA clinical staff; decisions to start/alter regimens or HIV related medications (e.g., antibiotics) were therefore communicated to AfA clinical staff and authorization established before prescribing. More complex decisions (e.g., salvage therapy regimens) were referred to weekly clinical expert meetings, where additional input from academic staff and professional organizations/associations was available.

4.11 Transfer in

Some patients transferred from other schemes or public sector ART programmes (especially in later years). Excluding these patients from analyses proved difficult as the baseline VL data and baseline questionnaire data, which asked for details on previous ART exposure, proved only partially informative [36].

4.12 What has been measured?

4.12.1 Clinical outcomes

Extensive data are available for patients enrolled in the AfA programme. Patients complete the registration form (usually with their doctor) at enrollment. This information, which includes demographics, prior medication and illness, and HIV-related information (ART exposure, AIDS defining or WHO stage illness, CD4 count, and VL monitoring results) is captured digitally and presented to the medical team for review for authorization. The medical scheme provides information on hospitalization and other outpatient events, including medication dispensed. Initially, pathology results were captured manually, but over time links have been established with private pathology laboratories to facilitate electronic medical records transfers instead. Specific events are tracked over time that may impact HIV care and include pregnancies, infections (meningitis, tuberculosis), and adverse drug reactions.

4.12.2 Mortality ascertainment

During follow-up, deaths were communicated to AfA by the attending medical practitioner, hospital case manager (for in-hospital deaths), medical fund administrator, medical scheme, and designated treatments. Other studies from the South African public sector have reported that administrator deaths substantially underestimated true deaths when compared with deaths ascertained through linkage with the vital registry [37] and between 90% and 95% of known deaths have been shown to be identified by the registry [38]. AfA had collected significantly more RSAID numbers (as part of the registration process) than either the scheme administrator or scheme itself, particularly for non-principal members; reported mortality ascertainment improved over time. Most missed deaths were misclassified as censored – i.e., as having left the medical scheme. Furthermore, determining mortality from RSAIDs allowed for an improvement in LTFU status ascertainment as well [37-40].

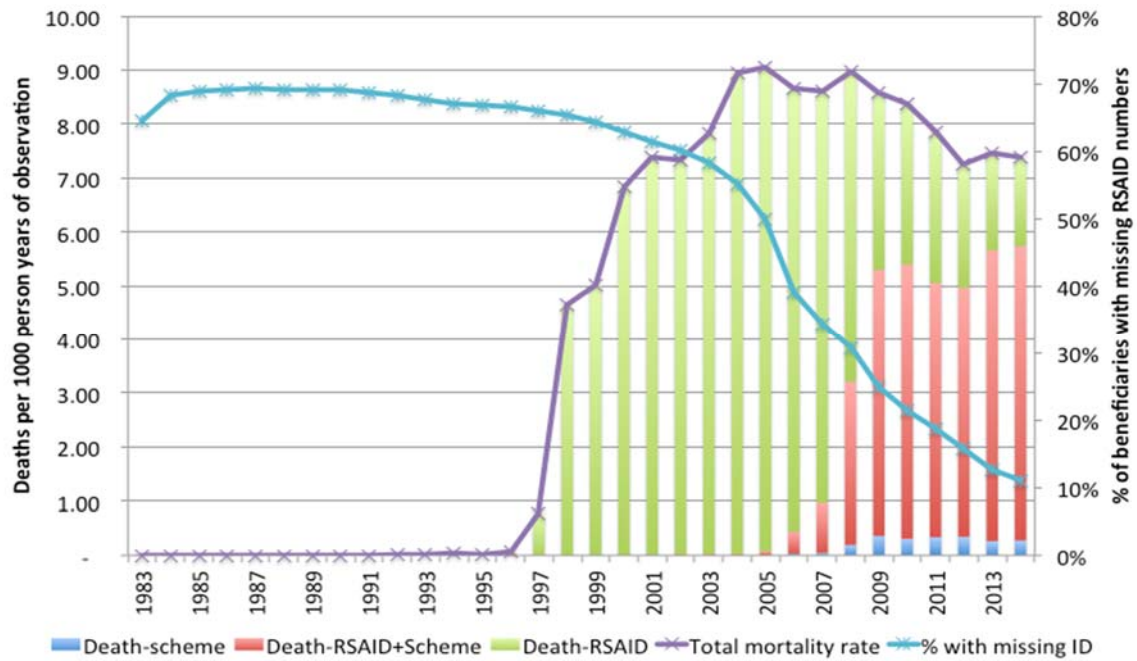


Figure 4.4: Trends in missing RSAID numbers and mortality rates within large medical scheme subsets (all lives), illustrating the deaths known to the scheme versus deaths ascertained via the RSAID linkage to the South Africa National Death Register

4.12.3 Loss to follow-up (LTFU)

The manner in which LTFU is incorporated into HIV cohort analyses can substantially impact findings on programme effectiveness [41, 42]. Many studies defined LTFU in a similar manner to death, as a terminal state [38], yet many patients were subsequently found to return to care. Furthermore, while many studies classify members as being LTFU once they have left the programme, many of these may have been seeking treatment elsewhere [43]. Finally, courier pharmacy, where medicine is delivered on a regular basis to the member's designated location, has been implemented broadly within the private sector (usually the patient's home). More recently, courier pharmacy has been implemented in the public sector (home or community adherence clubs) in South Africa [44]. Determining whether members have received their medication, especially in the case of adherence clubs, has proved to be logistically challenging.

Most studies have treated LTFU as an alternative state to alive or dead for patients who have started ART [45], without taking into account whether the patient is adherent to ART or not. With the increasing availability of digital dispensing systems, particularly within the private sector as dispensing events generated claims, we defined LTFU in our setting as not having received antiretroviral (ARV) medication for 6 months while alive. Given the incentive of suppliers to report dispensing events to get paid, and the low barrier for members with no co-payment for HIV related care and the convenience of using a local private sector doctor, we anticipated that this is a more accurate representation of LTFU numbers than in most settings.

4.12.4 Costs/utilization

The availability of claims data is unique within the South African context. In previous analyses [46, 47], we found 49,517 unique claim categories within the scheme administrators database, of which 4,000 accounted for over 95% of total costs and were grouped as follows: ARVs, other medication, maternity-related care (antenatal services, delivery, caesarean section, and postdelivery paediatric care), general practitioner care, specialist care, hospital accommodation and procedures, CD4 count and VL monitoring, and other investigations (e.g., laboratory tests and radiology).

4.13 Conclusions

AfA is one of the larger cohorts in South Africa, with substantial follow-up on ART at higher baseline CD4 counts. The extensive digitization of health systems within the private sector is a distinct advantage for analysts, patients, and providers. Each claim contained information about the service date, specific medication or care received (and quantity supplied for a drug), thus allowing for costs to be determined down to a granular level. The National Strategic Plan on HIV, STIs, and TB (2002–2016) [48] highlighted the importance of a unique health sector identifier while the increasing reliance on RSAIDs to uniquely identify patients allows for the accurate ascertainment of LTFU and death.

4.14 Can I get hold of the data?

The cohort dataset is curated by the Center for Infectious Disease at the University of Stellenbosch and the Division of Clinical Pharmacology at the University of Cape Town. The analyses are produced in collaboration with AfA and its various partners (e.g., medical schemes, suppliers). Going forward, the cohort will contribute to collaborative analyses, including the International Epidemiological Databases to Evaluate AIDS (IeDEA) Southern Africa collaboration. For these analyses, the data were stripped of all identifiers. Patient consent was sought at registration with AfA, and all data were considered routinely collected data as part of standard-of-care service provision with HIV. Approval to perform routine data analysis has been granted by the Human Research Ethics Committee at the University of Cape Town. Requests for external collaboration are welcomed, and decisions about participation in analyses and the sharing of data are taken jointly by the collaborators on the cohort study. Enquiries related to data access or collaborative studies should be directed to the principal investigators [mcot@sun.ac.za and gary.maartens@uct.ac.za].

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Chapter 5:

Early and late direct costs in a Southern African antiretroviral treatment programme: a retrospective cohort analysis

Early and Late Direct Costs in a Southern African Antiretroviral Treatment Programme: A Retrospective Cohort Analysis

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Abstract

Background: There is a paucity of data on the health care costs of antiretroviral therapy (ART) programmes in Africa. Our objectives were to describe the direct health care costs and establish the cost drivers over time in an HIV managed care programme in Southern Africa.

Methods/Findings: We analysed the direct costs of treating HIV-infected adults enrolled in the managed care programme from 3 years before starting non-nucleoside reverse transcriptase inhibitor-based ART up to 5 years afterwards. The CD4 cell count criterion for starting ART was <350 cells/ μ l. We explored associations between variables and mean total costs over time using a generalised linear model with a log-link function and a gamma distribution. Our cohort consisted of 10,735 patients (59.4% women) with 594,497 mo of follow up data (50.9% of months on ART). Median baseline CD4+ cell count and viral load were 125 cells/ μ l and 5.16 log₁₀ copies/ml respectively. There was a peak in costs in the period around ART initiation (from 4 mo before until 4 mo after starting ART) driven largely by hospitalisation, following which costs plateaued for 5 years. The variables associated with changes in mean total costs varied with time. Key early associations with higher costs were low baseline CD4+ cell count, high baseline HIV viral load, and shorter duration in HIV care prior to starting ART; whilst later associations with higher costs were lower ART adherence, switching to protease inhibitor-based ART, and starting ART at an older age.

Conclusions: Drivers of mean total costs changed considerably over time. Starting ART at higher CD4 counts or longer pre-ART care should reduce early costs. Monitoring ART adherence and interventions to improve it should reduce later costs. Cost models of ART should take into account these time-dependent cost drivers, and include costs before starting ART.

Please see later in the article for the Editors' Summary.

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Abbreviations: ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

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Introduction

Access to combination antiretroviral therapy (ART) is rapidly expanding in resource-limited settings. Data on the costs of providing HIV health care and how these change over time are important for guiding resource allocation. However, there are few good quality studies of the direct health care costs of HIV infection, as illustrated by a recent systematic review that found only nine studies from the ART era that fulfilled inclusion criteria [1]. Data on costs prior to starting ART are limited as most cost studies only report costs once ART has been commenced. A recent South African study reported that health care costs were almost twice as high in the first year on ART in comparison with the second year [2]. However, the sample size was small, patients had advanced disease, follow up was relatively short, and the period of higher costs in the first year on ART was not defined.

Delays in establishing public ART programmes in South Africa until 2003 [3], together with studies highlighting the detrimental effects of HIV in the workplace [4], resulted in the scaling up of access to ART through private medical insurance funds from as early as 1998 [5]. Given the level of need for improved access to ART in South Africa, which has the world's largest number of HIV-infected people [6], the government has identified partnerships with the private sector as a key mechanism for enhancing access [7]. In the private sector, starting ART is encouraged earlier than current WHO guidelines for resource-limited settings [8], thus enabling exploration of the cost implications of starting ART earlier.

The objective of this study was to explore health care costs in a South African private sector HIV/AIDS programme, with a special focus on the determinants of costs around the period of ART initiation, as well as the determinants of costs during the later phases of ART.

Methods

Ethics Statement

The study was approved by the Research Ethics Committee, University of Cape Town and by the Board of Directors of Aid for AIDS (AfA). Informed consent was not required as the data were analyzed anonymously, but all patients signed consent for their information to be entered into the AfA database.

Data Source

Data for this study were extracted from a database of patients enrolled with AfA, a group that manages HIV-related care for a number of medical insurance funds and companies in the private sector in Southern Africa [9]. Registration of eligible patients with AfA is done by the private doctor looking after the individual patient (i.e., there are no clinics, but some private doctors run exclusive HIV practices). Demographic data, CD4+ cell count, viral load, and previous ART history is captured centrally. Patients are managed according to a clinical guideline and any decision to start ART, change ART regimen, and treat certain opportunistic infections is subject to review and approval by AfA clinical staff. The antiretroviral guidelines are similar in many respects to WHO guidelines for resource-poor settings [8] and the South African public sector programmes, but ART is initiated earlier and there is room for choice of individual antiretroviral drugs. For example several ritonavir-boosted protease inhibitors (PIs) are available rather than the single one available in the South African public sector. ART can be initiated at CD4+ cell counts <350 cells/ μ l rather than <200 cells/ μ l in the South African public sector, but similar to WHO guidelines that recommend initiation with CD4+ cell counts <350 cells/ μ l with symptomatic disease. The recom-

mended initial regimen is a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). Second line therapy consists of a boosted PI with two NRTIs. CD4+ cell counts and viral loads are monitored 6 monthly. There is a telephonic counselling service provided by AfA, although counselling is not routine but done on demand. Drugs are collected monthly from private pharmacies.

Inclusion Criteria

Two of the medical insurance funds contracted to AfA were selected on the grounds that they had large numbers of patients, similar treatment benefits, and required no co-payment for ART. This selection allowed us to describe costs and drivers of costs without relating to the patient's ability to pay, which has been reported to influence outcomes on ART [10–12]. Patients were included in the study if they were ART naïve at entry (women who had received prophylaxis for prevention of mother-to-child transmission were not excluded); adult (19 y or older at the time of approval for ART); and if ART was started between November 1998 and November 2007. Patients were excluded if they had missing cost data over the entire period. To make our findings more generalisable, we only included patients starting ART with an NNRTI plus two NRTIs, as recommended by the WHO for resource-limited settings [8].

Cost Data

Direct health care costs were analysed from the provider's perspective [13], and indirect costs were not assessed. Submitted health care claims were captured into a central database. The tariff amount (which is the amount agreed to annually following negotiations between private healthcare providers and funders) was used as a proxy for direct health care costs, as opposed to the amount charged by the provider or the amount reimbursed to the patient. Of the 49,517 unique claim categories in the AfA database, 4,000 accounted for over 95% of total costs. These 4,000 claim categories were grouped into the following categories: ART, other medication, maternity-related care (antenatal services, delivery, caesarean section, and postdelivery paediatric care), general practitioner care, specialist care, hospital accommodation and procedures, CD4+ cell count and viral load monitoring, other investigations (e.g., laboratory tests and radiology).

The prices of antiretroviral drugs have fallen dramatically over the period of our study. To account for this decrease we deflated ART prices to the April 2007 level. All other health care costs have increased; these were inflated to the April 2007 level using the consumer price index net of mortgage payments (CPIX) [14]. The average South African rand to US\$ exchange rate in April 2007 (R7.14 to US\$1) was used to convert costs to US\$ equivalents [15].

Exploratory Cost Analysis

The mean total cost and its components were explored from 36 mo before starting ART to 60 mo on ART. Costs were broken down into the following components: ART, other medication, hospitalisation, investigations, CD4+ cell count and HIV viral load monitoring, general practitioner consultations, specialist consultations, maternity, and auxiliary care. This exploratory analysis revealed a marked peak in cost from 4 mo before starting ART until 4 mo on ART. This 8-mo interval is denoted the "peri-ART" period in this study.

Statistical Methods

Even though health care costs are often right-skewed, with a minority of patients incurring very high costs, the health

economics literature argues that health care policy decisions are best guided by analyses of arithmetic mean costs, as the mean provides information on the costs of treating the entire population [16]. Thus ordinary least squares (OLS) regression models and generalised linear models (GLM) were considered [16,17]. The month in which patients started ART was set as the zero month for all patients, which provided a common reference point for all the patients in our analysis. We divided the period from 4 mo before to 60 mo after starting ART into 4-mo intervals and determined the mean total cost in each interval. As many months had zero costs (>10%), using the mean cost over 4 mo intervals resulted in few zero values in the outcome variable, thus avoiding the need for zero-inflated models. A GLM with a gamma distribution and a log-link function was selected on grounds that it could describe the distribution of the data. An OLS model was abandoned because it was unable to adequately account for the patients with very high costs, which was a significant proportion of total costs. With a log-link function, the variables are associated with a proportional change in total mean costs. Improved residual diagnostics, lower Akaike Information Criteria (AIC), and improved trend prediction were used in the model development and refinement.

The time-varying associations between mean total cost and the variables was modelled using three methods: a separate model for each 4-mo time interval using categorical variables, and two models with categorical or continuous variables over the entire interval with time included as a variable, which also interacted with the other variables. Effect estimates and their significance at the 95% level were assessed using robust standard errors with clustering at an individual level. Data storage, basic calculations, and data extraction was handled in Microsoft Access 2003 [18] and statistical analysis was performed in Stata 10 [19].

The following variables were considered in our analysis: baseline CD4+ cell count and HIV viral load (baseline was defined as the most recent result within 6 mo before starting ART), ART adherence assessed by monthly pharmacy claims, age, sex, the NNRTI and the NRTI combination used in patients on first line therapy, whether the patient switched to PI-based second line ART, and the duration of CD4+ cell count monitoring (as a proxy for being in HIV care) prior to starting ART. Patients with less than 4 mo of claims data after starting ART were excluded on the grounds that we were unable to assess their ART adherence over shorter time intervals. We split the continuous variables into the following categories: (1) Baseline CD4+ cell count was divided into four groups: 0–49, 50–199, 200–349, and ≥ 350 cells/ μl . (2) HIV viral load was categorised as $\geq 100,000$ copies/ml or $< 100,000$ copies/ml. (3) The mean ART adherence was determined using pharmacy refill data and divided into quartiles. (4) The NNRTI was included as a binary variable (either efavirenz or nevirapine); whereas (5) the NRTI combination in first line was divided into three groups: zidovudine and lamivudine, stavudine and lamivudine, or any other combination. (6) A binary variable was used to reflect whether or not the patient was on second line ART. (7) Age was divided into quartiles. (8) Sex was included as a binary variable. (9) Patient follow-up for HIV prior to starting ART was measured by the length of time between the first CD4+ cell count and the date of starting ART, and was categorised as less than 6 mo and more than 6 mo.

Results

10,735 patients met our eligibility criteria. The characteristics of the cohort are described in Table 1. There were almost 600,000

patient months of observation, about half of which were on ART. Median follow-up on ART was 26 mo. Baseline body mass index (BMI) was only available for 4,416 of the patients: 13% were < 18.5 kg/m², 52% were ≥ 18.5 kg/m² and < 25 kg/m², and 35% were ≥ 25 kg/m². The most common first line and second line antiretroviral regimens were zidovudine, lamivudine, and efavirenz and lopinavir/ritonavir, zidovudine, and didanosine, respectively. CD4 and viral load monitoring were done 1.5 times per annum on average. Hospitalisation rates were 441 d per 100 patient years of observation (PYO) in the first 6 mo of ART and 179 d per 100 PYO subsequently. Hospitalisation incidence was highest in patients in the lowest CD4 count stratum.

The proportion of patients who left the scheme was 31% overall and 24% at 2 y. Patients who left the scheme either changed their employment, switched to a different medical insurance scheme, or voluntarily stopped their contributions to the insurance scheme. Patients who left the scheme differed from those who did not leave in the following baseline characteristics (established using the Wilcoxon rank sum test for continuous variables and Chi-squared test for categorical variables): viral load (median of 5.2 versus 5.1 log₁₀, $p = 0.0016$), proportion female sex (57% versus 60%, $p = 0.0001$), and age (37.4 y versus 37.0 y, $p = 0.0006$). Importantly, these baseline differences are not clinically significant and the CD4+ cell count did not differ significantly (median of 127 versus 123 cells/ μl , $p = 0.137$).

Exploratory Cost Analysis

The cost data were highly skewed with 10% of the population accounting for 90% of the costs. Figure 1 shows the mean monthly cost and its components. The mean monthly cost rose from a plateau of around US\$100 per month before ART, to a peak of around US\$500 in the peri-ART period, before dropping down to a new higher plateau of around US\$200 on ART. Median (IQR) monthly costs are shown in Figure S1.

Multiple Regression Analysis

After excluding patients with missing demographic and baseline viral load and CD4+ cell count data, 7,427 patients were included in this analysis, and their characteristics are shown in Table 1. The summary statistics for this subset were comparable with the full dataset.

In our first analysis, we modelled each 4-mo time interval separately. We found that lower baseline CD4+ cell counts and high HIV viral loads were associated with increased mean total cost predominantly from 4 mo before to 8 mo after starting ART. In contrast, the highest ART adherence quartile was increasingly associated with lower mean total cost over time when compared with the lowest quartile (Figure 2A). When ART-related costs were excluded (on the grounds that high adherence would result in more ART-related costs), the association was more marked. In a subanalysis, the effect of lagged ART adherence (adherence in the prior 4 mo) on costs per 4-mo period was assessed. Again higher adherence in the prior 4 mo was associated with lower costs (Figure 2B). Being on second line (PI-based) ART was associated with higher costs throughout the time period. The other variables were associated with small effects (<10%), which were largely not significant. In a subanalysis, we excluded maternity (which is associated with high costs as nearly all women deliver by caesarean section) and ART costs (a lower proportion of women started efavirenz, which is teratogenic and more expensive than nevirapine) and found the association between sex and mean total cost was not consistent and marginal (<10%).

Mean total costs fell over the first 24 mo on ART and thereafter cost remained constant. Similarly, the associations between many variables and mean total costs changed over the first 24 mo and

Table 1. The characteristics of the cohort.

Characteristics		Overall <i>n</i> = 10,735	Regression Subset <i>n</i> = 7,427
Patient months included in analysis	Overall	594,497	282,141
	On ART	302,579 (50.9%)	252,433
Duration on ART (mo)	Median	26	33
	IQR	(9–44)	(16–50)
Age at starting ART (y)	Median	37	37
	IQR	(32–43)	(32–43)
Sex	Female	6,379 (59.%)	4,557 (61%)
	Male	4,356 (41%)	2,897 (39%)
Patient status at end of study period	Active	6,339 (59%)	4,217 (56%)
	Left scheme	3,329 (31%)	2,669 (36%)
	Dead	1,067 (10%)	1,067 (8%)
Baseline CD4+ cell count	Median	125 cells/ μ l	125 cells/ μ l
	IQR	(49–203)	(55–204)
	Missing	1,726	N/A
Baseline viral load (log₁₀)	Median	5.20	5.16
	IQR	(4.70–5.60)	(4.66–5.59)
	Missing	2,031	N/A
NNRTI used in first line	Nevirapine	2,655 (28%)	2,432 (28%)
	Efavirenz	6,711 (72%)	6,127 (72%)
NRTI combination in first line	AZT+3TC	6,950 (65%)	4,945 (67%)
	D4T+3TC	1,564 (15%)	1,684 (23%)
	Other	2,221 (20%)	798 (10%)
Duration of CD4+ cell count monitoring before starting ART (mo)	Median	1.5	1.5
	IQR	(0.7–4.2)	(0.7–4.2)

3TC, lamivudine; AZT, zidovudine; D4T, stavudine; IQR, interquartile range; N/A, not applicable.
doi:10.1371/journal.pmed.1000189.t001

thereafter remained constant. We found that splitting time into four periods (–4 to 4 mo, 5–12 mo, 13–24 mo, and >24 mo) described time-dependent association between time and total mean cost and its interaction with the other variables. The results from this multiple regression analysis are found in Table 2.

We found that costs were very high in the peri-ART period. Mean monthly costs were more than 3 times higher in this period and the association between costs and baseline CD4 count and baseline viral load were more marked in the peri-ART than in later time periods. In the above analysis, we excluded patients who died within the first 4 mo on ART because we could only estimate ART adherence over a period of 4 mo or longer. However given that patients who died might incur significant costs, we performed an additional subanalysis including these early deaths. This subset included 8,559 patients. The findings were similar but the associations between variables and total mean costs diminished marginally when we repeated the multiple regression analysis with the ART adherence variable excluded (unpublished data).

Finally, we explored continuous models for ART adherence, age at starting ART, baseline viral load, and baseline CD4+ cell count (only counts <350 cells/ μ l were analysed as patients with higher counts were started on ART for serious HIV-related morbidity): polynomial functions of the 2nd degree were used for all the variables except ART adherence (4th degree polynomial) and baseline HIV viral load (3rd degree polynomial) were used. We felt that the duration of CD4+ cell count monitoring before starting ART was better handled as a categorical variable. Time

and its interactions with the other variables displayed nonlinear associations with total mean cost for the first 24 mo; thereafter trend was approximately linear. A restricted cubic spline (a cubic spline with linear tails) with three knots placed –4 to –1 mo, 4–7 mo, and 16–19 mo fitted the observed trends in our data; we experimented with the placement and number of knots using the Akaike Information Criteria and predictive plots to guide the final model selection. An interaction with the spline function for time was used for all variables except ART (first line versus second line) as the trend over time was difficult to quantify. Overall, the model was able to describe the trends in the data well, though in some intervals the trends in the baseline viral load and age variables were not well approximated at the extremes. While the main findings from this analysis using continuous variables did not differ from the previous analysis using categorical variables, some subtleties not previously shown were found in the relationships between costs and baseline CD4+ cell count and ART adherence. The association between baseline CD4+ cell count and mean total costs over time is shown in Figure 3; costs within each interval were compared with a referent group (CD4+ cell count = 200 cells/ μ l). Initially, the association with mean total cost followed a j-shape, with low CD4 counts associated with very high costs but also a modest increase in costs in patients with high counts. Over time the association between CD4+ cell count and mean total costs became less marked but costs were lowest for patients with higher CD4 counts. The association between ART adherence and mean total costs is shown in Figure 4; costs within

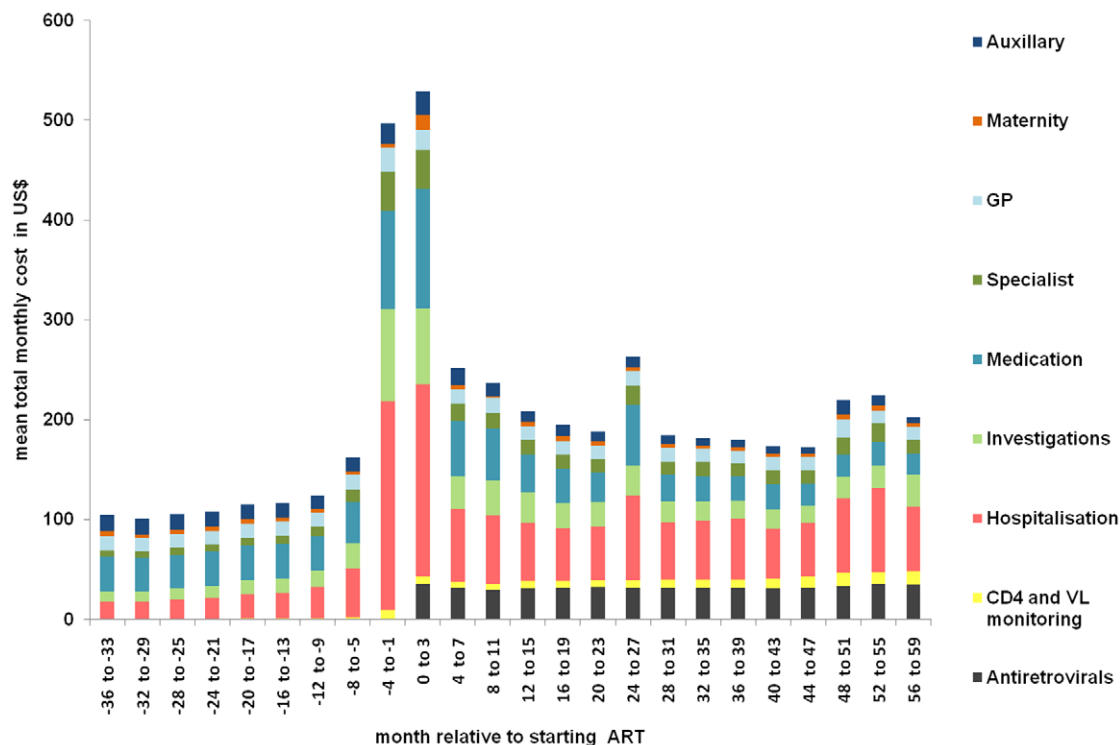


Figure 1. Mean categorised total monthly costs from 36 mo before starting to 60 mo on ART.
doi:10.1371/journal.pmed.1000189.g001

each interval were compared with a referent group (ART adherence 75%). Initially, the model found three peaks: one around highly adherent patients, another around 50% adherence, and a smaller peak at very low adherence. Over time the lower peak fell away, the middle dominant peak moved to be centred at around 30% adherence, while the highly adherent patients were now associated with the lowest costs. Very low ART adherence was associated with low costs in all time intervals except in the peri-ART period. The association between mean total cost and baseline viral load (Figure S2) age at starting ART (Figure S3) are found in the supporting information (Figures S1–S3).

Discussion

We analysed the direct health care costs of treating over 10,000 HIV-infected adults enrolled in a Southern African managed care ART programme with almost 600,000 patient months of follow-up, spanning 3 y before ART to 5 y on ART. We found a peak in costs in the period around the time of ART initiation, thereafter total mean costs dropped off to a plateau that persisted for 5 y. An important and novel feature of our study was the presentation of time-dependent associations between total mean costs and relevant variables. We identified lower baseline CD4+ cell count, higher baseline viral load, and shorter duration of CD4+ cell count monitoring before starting ART (as a proxy for HIV care) as being independently associated with higher costs in the early time periods. Lower ART adherence, being on second line ART, and starting ART at a younger age were most strongly associated with lower mean costs in later time periods, and the association with ART adherence became more marked over time.

The peak in costs in the peri-ART period we observed was largely driven by the high proportion of patients requiring hospitalisation. High rates of early morbidity, often resulting in hospitalisation or death, are characteristic of antiretroviral

programmes in resource-limited settings. Patients on ART in low-income countries have higher early mortality compared with high-income countries, even after correcting for baseline differences in CD4+ cell counts [20]. A strength of our study is the analysis of cost data before starting ART. Few ART cost analyses include the period before starting ART. Higher costs in the first year on ART compared with later years with high rates of hospitalisation was reported in another South African study of a public sector ART programme, but they only assessed costs for 1 mo before starting ART and did not attempt to more accurately define the period of high cost [2]. Given our finding of high costs in the 4-mo period before starting ART, which was equivalent to 1.5 y of cost in patients on ART after the first year, other studies might have significantly underestimated the costs of providing HIV care just prior to starting ART.

We found that higher ART adherence was associated with lower costs particularly after removing antiretroviral drug costs. The magnitude of this association becomes greater as duration on ART increases. However, the continuous model showed that while highly adherent patients (>92%) were associated with the lowest total mean costs in later time intervals, they were associated with higher costs in the early time intervals. A similar association was found with high baseline CD4+ cell counts (>300 cells/ μ l) being associated with higher costs initially. These findings could be attributed to increased health-seeking behaviour leading to increased costs initially, but reduced costs over time. Very low ART adherence was associated with low total mean costs in all time intervals as these patients are presumably accessing minimal services. Our group has previously reported that ART adherence assessed by pharmacy refills in this cohort predicted both virological suppression [21] and survival [22]. Poor adherence limits the effectiveness of ART, drives resistance to first line regimens, and thus leads to earlier switching to costly second line ART. Despite the important role of ART adherence, existing economic models fail to include it.

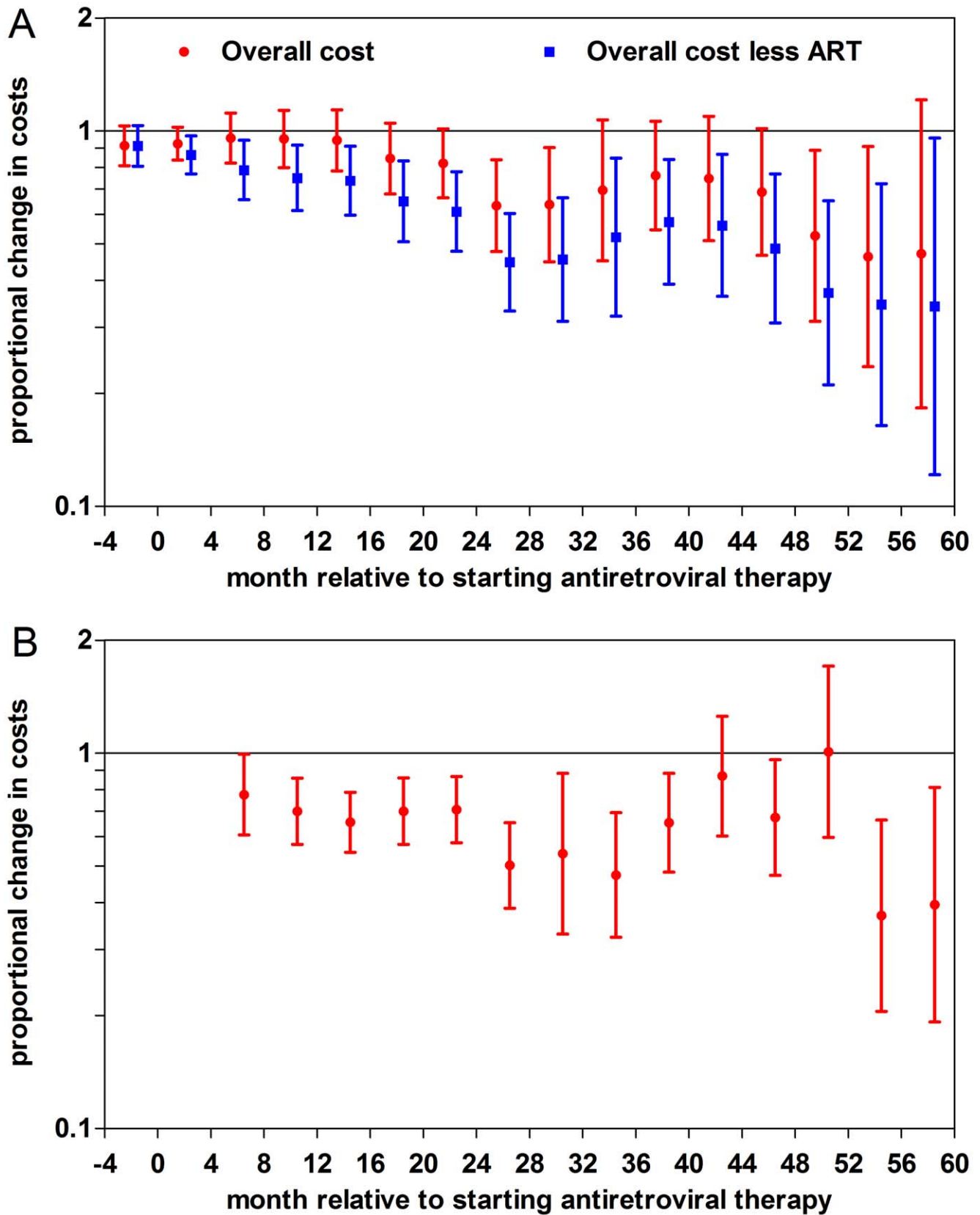


Figure 2. The proportional change in mean total costs associated with ART adherence with 95% confidence intervals. (A) The highest overall ART adherence quartile was compared with the lowest adherence quartile within each time interval (ART costs included and excluded) from 4 mo before starting ART to 60 mo on ART. (B) The highest lagged ART adherence group was compared with the lowest group (≥ 3 monthly versus ≤ 1 monthly refills in the previous 4-mo period) within each time interval from 4 mo before starting ART to 60 mo on ART. doi:10.1371/journal.pmed.1000189.g002

Table 2. The proportional change in mean total cost modelled using a multiple generalised linear model regression.

Variable	Time Intervals (mo)				
	—	–4 to 4	5–12	13–24	>24
Mean monthly total cost (US>¥)	—	377 (337–418)	183 (160–206)	161 (138–183)	115 (98–131)
Baseline CD4 count (cells/μl)	<50	1.98 (1.74–2.22)	1.35 (1.07–1.63)	1.28 (1.05–1.51)	1.23 (0.97–1.48)
	50–199	1.34 (1.20–1.48)	1.08 (0.94–1.21)	1.02 (0.87–1.17)	1.31 (1.11–1.51)
	200–349	1 (referent)	—	—	—
	\geq 350	1.57 (1.21–1.92)	1.39 (0.97–1.8)	1.43 (0.96–1.89)	1.12 (0.78–1.45)
Baseline viral load (copies/ml)	\geq 100,000	1.24 (1.10–1.37)	1.08 (0.93–1.23)	1.08 (0.94–1.23)	1.09 (0.95–1.23)
	<100,000	1 (referent)	—	—	—
Age at starting ART (y)	<25	1.03 (0.81–1.26)	0.82 (0.64–0.99)	0.83 (0.60–1.06)	0.85 (0.59–1.12)
	25–49	1 (referent)	—	—	—
	\geq 50	1.20 (0.97–1.43)	1.14 (0.87–1.42)	1.01 (0.79–1.23)	1.52 (0.72–2.32)
Sex	Male	0.98 (0.87–1.10)	1.00 (0.83–1.17)	0.91 (0.77–1.06)	0.91 (0.75–1.06)
	Female	1 (referent)	—	—	—
NNRTI	Nevirapine	0.87 (0.77–0.96)	0.89 (0.78–1.00)	1.11 (0.96–1.27)	1.02 (0.86–1.18)
	Efavirenz	1 (referent)	—	—	—
NRTI combination	D4T/3TC	1.05 (0.88–1.22)	1.01 (0.80–1.22)	0.95 (0.74–1.16)	0.96 (0.61–1.32)
	Other	0.91 (0.81–1.02)	0.98 (0.82–1.14)	1.05 (0.88–1.22)	1.06 (0.84–1.27)
	AZT/3TC	1 (referent)	—	—	—
Duration CD4+ cell count monitoring	\geq 6 mo	0.76 (0.67–0.85)	0.98 (0.84–1.12)	1.01 (0.87–1.16)	1.30 (1.06–1.54)
	<6 mo	1 (referent)	—	—	—
Therapy	Second line	1.65 (1.09–2.2)	3.10 (0.43–5.76)	1.94 (1.45–2.44)	2.06 (1.53–2.58)
	First line	1 (referent)	—	—	—
Mean overall ART adherence	<38%	0.84 (0.75–0.94)	1.00 (0.86–1.14)	1.17 (0.98–1.35)	1.54 (1.21–1.86)
	38%–73%	1.08 (0.97–1.20)	1.25 (1.01–1.49)	1.12 (0.97–1.27)	1.28 (1.07–1.50)
	74%–92%	0.85 (0.77–0.94)	1.25 (1.06–1.44)	1.06 (0.92–1.21)	1.09 (0.92–1.26)
	>92%	1 (referent)	—	—	—

A log-link function with a gamma distribution was used in the model. Numbers in parentheses are the 95% confidence intervals. 3TC, lamivudine; AZT, zidovudine; D4T, stavudine.

doi:10.1371/journal.pmed.1000189.t002

Our analysis of the time-dependent associations with increased costs has several important public health implications. The high early costs of ART programmes could be reduced by starting ART at a CD4+ cell count of <350 cells/ μ l rather than <200 cells/ μ l (for patients without major symptomatic HIV disease). Our cohort does not allow for an evaluation of starting ART in patients with baseline CD4+ cell counts \geq 350 cells/ μ l because AfA guidelines only allow these patients to start ART following an AIDS-defining illness or with other serious comorbidity: costs were actually higher in this group compared with those starting ART with baseline CD4+ cell counts 200–349 cells/ μ l, presumably reflecting the costs of treating the morbidity that was the criterion for starting ART. The second intervention that could reduce early costs would be the earlier identification of HIV infection, illustrated by our finding that being in HIV care for more than 6 mo prior to starting ART reduced costs in the peri-ART period. The key driver of later costs with public health implications is ART adherence. Higher adherence prolongs time on the cheaper first line regimen, but also reduces non-ART direct costs in our study. The third intervention that might reduce costs would be to encourage ART programmes to invest in systems to monitor ART adherence and implement effective interventions if adherence is suboptimal.

ART adherence could be monitored over short time periods of 3 to 4 mo, which identifies patients incurring higher costs and those at risk of virological failure [23].

We estimate that annual total direct health care costs are approximately US\$2,400 (after the peak in costs in the peri-ART period) for patients accessing ART in the private sector. Lower costs were reported in two other South African studies. Harling reported costs of \$2,502 in year one and \$1,372 in year two of a donor-funded public sector program [24]. Rosen estimated the ART component of care to be US\$757–US\$1,126 in the first year of several different models of ART delivery to public sector patients, but non-ART-related clinic visits and hospitalisations were not included [25]. The incidence rate of hospitalisation we found in the first 6 mo on ART was similar to that reported in a South African public sector ART programme in the first 48 wk on ART, but our incidence was higher in later periods, which would increase costs [24]. Higher rates of hospitalisation in the private sector compared with the public sector after the initial period of ART probably reflect greater access in the private sector. Other factors driving higher costs in the private sector compared with public sector are higher costs for hospitalisation (US\$340 versus US\$202 per day, respectively) and viral load tests (US\$62 versus US\$42, respectively) [26].

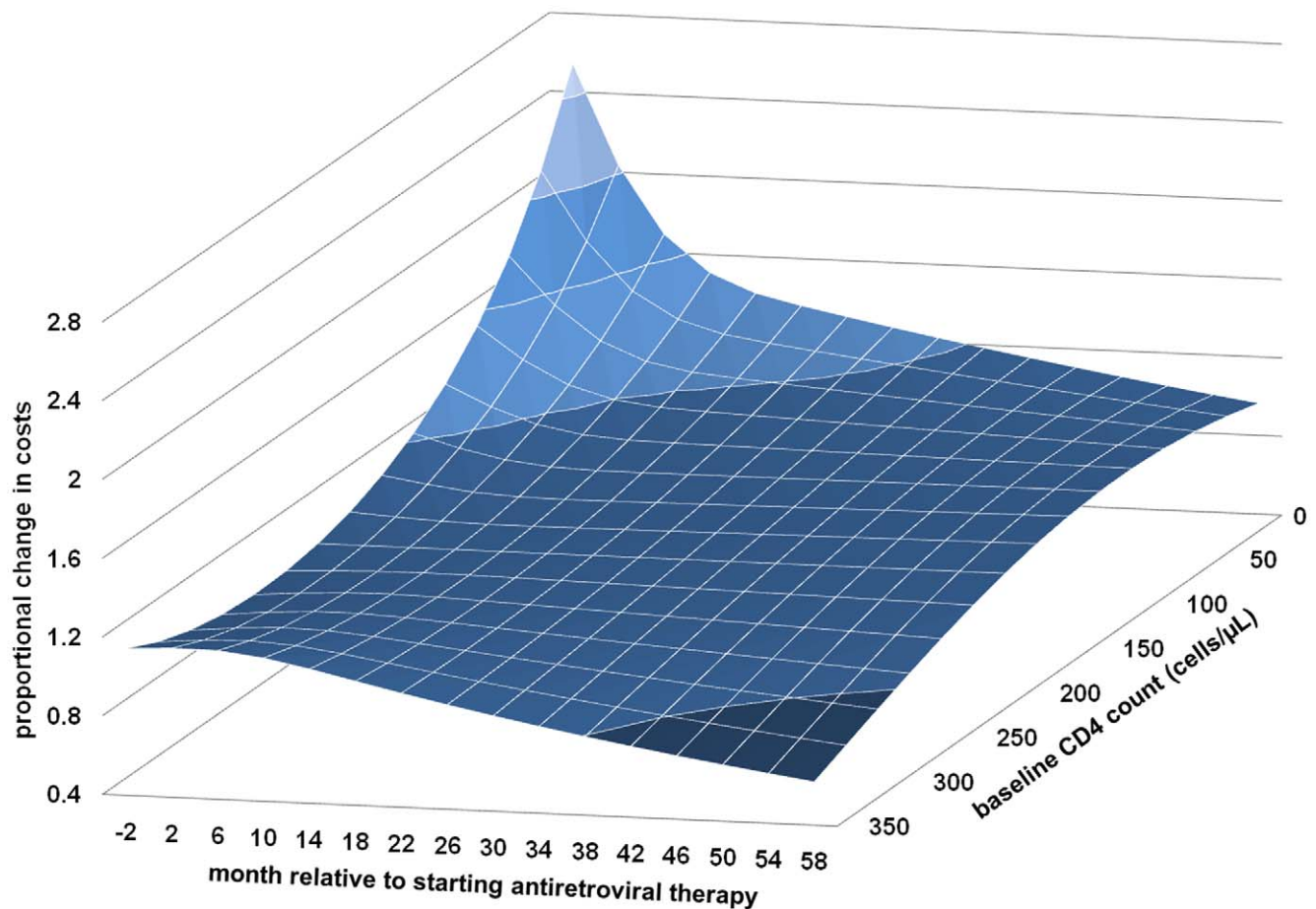


Figure 3. The proportional change in mean total monthly costs over time associated with baseline CD4 cell count. Baseline CD4 count was compared with the referent group (200 cells/ μ L) within each time interval from 4 mo before starting ART to 60 mo on ART with lighter blue indicating higher relative costs.
doi:10.1371/journal.pmed.1000189.g003

Some findings of other ART programme cost studies differed from our analysis. We found that the ART component of costs was relatively small compared with other studies in resource-limited settings [2,25,27], which could be related to higher hospitalisation and other costs in our private sector setting. Younger age has been found to be associated with increased costs in some [28,29], but not all studies [2]. We found a significant age effect with younger age (<25 y) associated with lower early but higher later costs and older age (\geq 50 y) associated with higher early and especially later costs. Finally, unlike the finding of another South African study [2], sex was not independently associated with costs, even after controlling for pregnancy-related costs and the higher proportion of men being on efavirenz. It is possible that our inclusion of ART adherence in our multiple regression model adjusted for sex differences, as we have previously shown that men have lower ART adherence than women [30].

There are a number of limitations to this analysis. First, our cohort consisted of private sector patients when the majority of patients in resource-limited settings are treated in the public sector. However, the baseline characteristics of our cohort (CD4+ cell count, proportion of females, and age) are comparable with cohorts from low-income countries [20,31]. The BMI was <18.5 kg/m² in 13% of our cohort compared with 19% in a South African public sector cohort [32], but their patients had more advanced disease as evidenced by their lower baseline CD4+

cell counts. These baseline nutritional differences would likely impact outcomes. We restricted our analysis to patients receiving NNRTI-based first line ART regimens, in keeping with WHO recommendations for resource-limited settings [8]. While we would not claim that our actual cost findings are generalisable to public sector settings or to other countries, we would argue that the variables that drive early and late costs are likely to be relevant even if the magnitude of the effect could differ.

Second, the impact of specific AIDS-defining illnesses on outcomes and costs was not included in this analysis because these data were not available. Third, as a provider's perspective was chosen for this analysis, the cost to society is not fully represented because we did not have data on direct non-health care costs and indirect costs. However, a provider's perspective is more appropriate for the aim of this study, which was to unpack the key drivers of health care costs in order to inform appropriate budgeting and planning. Fourth, the characteristics of the patients who left the scheme were different from those who remained, which may have affected our findings. However, there was no significant difference in the key baseline characteristic of CD4+ cell count and many of the other differences (e.g., age, difference of 0.1 log₁₀ viral load) were small and are of questionable importance. Fifth, we chose to use the tariff amount as opposed to the amount claimed or reimbursed so that similar services would take the same monetary value and have further assumed

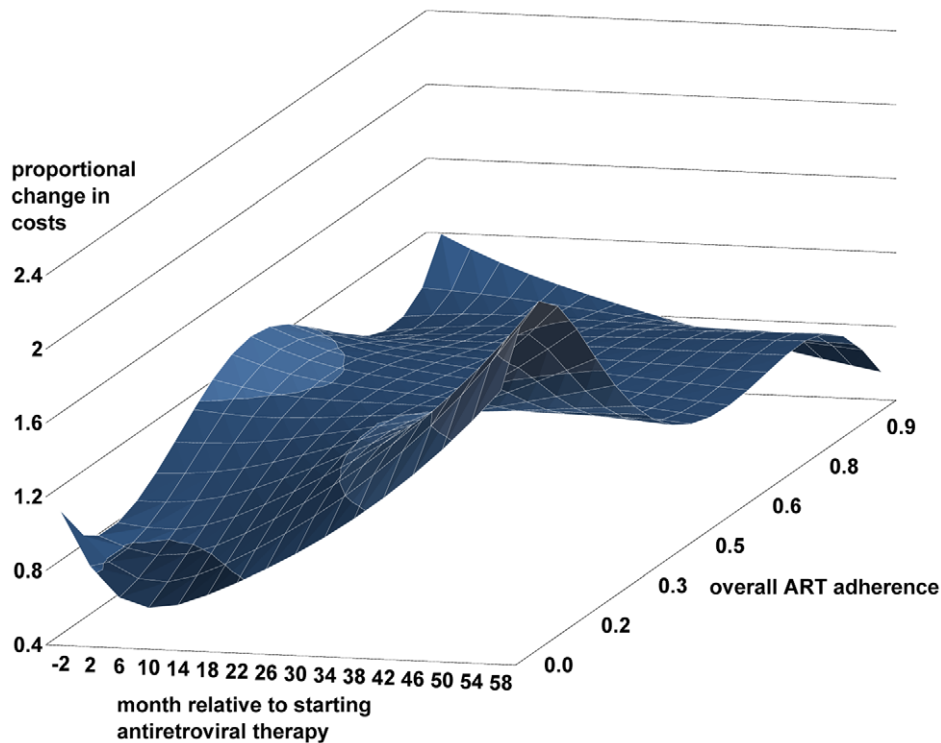


Figure 4. The proportional change in mean total monthly costs over time associated with overall ART adherence. Overall ART adherence was compared with the referent group (75%) within each time interval from 4 mo before starting ART to 60 mo on ART with lighter blue indicating higher relative costs.
doi:10.1371/journal.pmed.1000189.g004

that these tariffs are a suitable proxy for opportunity costs. While this could be a shortcoming, it is common to assume that market prices are a proxy for opportunity costs in economic evaluation given the difficulties in evaluating the latter [33]. Finally, cost minimisation should not be the only goal of health care providers, and other important aspects of care such as quality and outcomes are not addressed by our analysis.

In conclusion, we have described the temporal trends of costs of a large private sector HIV disease management programme in Southern Africa and shown that associations with costs change over time. Interventions that should reduce early costs include starting ART at higher CD4 counts and being in HIV care for longer periods before starting ART. Our results also indicate that systems to detect suboptimal ART adherence and interventions that improve adherence would reduce later costs. The increasing impact of ART adherence on costs over time suggests that this variable should be incorporated in economic models of ART.

Supporting Information

Figure S1 Total monthly costs from 36 mo before starting ART to 60 mo on ART. Median and interquartile range, mean, and running-line least squares smooth are shown.
Found at: doi:10.1371/journal.pmed.1000189.s001 (0.15 MB TIF)

Figure S2 The proportional change in mean total monthly costs over time associated with baseline HIV viral load. Baseline HIV viral load was compared with the referent group ($\geq 100,000$ copies/ml) within each time interval from 4 mo before starting ART to 60 mo on ART with lighter blue indicating higher relative costs.
Found at: doi:10.1371/journal.pmed.1000189.s002 (0.31 MB TIF)

Figure S3 The proportional change in mean total monthly costs compared over time associated with age at starting ART. Age at ART was compared with the referent group (37 y) within each time interval from 4 mo before starting ART to 60 mo on ART with lighter blue indicating higher relative costs.
Found at: doi:10.1371/journal.pmed.1000189.s003 (0.40 MB TIF)

Author Contributions

ICMJE criteria for authorship read and met: RL SC MH AD LR FL GM. Agree with the manuscript's results and conclusions: RL SC MH AD LR FL GM. Designed the experiments/the study: RL GM. Analyzed the data: RL MH AD FL. Collected data/did experiments for the study: MH. Wrote the first draft of the paper: RL. Contributed to the writing of the paper: SC MH AD LR FL GM. Contributed to the overall study design and methodology: SC. Collection and preparation of data used in the study: MH. Provided input into data analysis methodology: MH. Statistical consultant to the revision of this paper: FL. Reviewed various drafts of the paper: FL.

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Editors' Summary

Background. About 30 million people (22 million people in sub-Saharan Africa alone) are infected with the human immunodeficiency virus (HIV), the cause of acquired immunodeficiency syndrome (AIDS). HIV destroys immune system cells (including CD4 cells, a type of lymphocyte), leaving infected individuals susceptible to other infections. Early in the AIDS epidemic, on average HIV-positive people died within 10 years of infection. Then, in 1996, highly active antiretroviral therapy (ART; combinations of powerful antiretroviral drugs) was developed. For people living in affluent, developed countries HIV/AIDS became a chronic, treatable condition, but for the millions of HIV-infected people living in low- and middle-income countries, effective treatment was unavailable and HIV/AIDS remained a fatal illness. In 2003, this situation was declared a global health emergency and governments, international agencies, and funding bodies began to implement plans to increase ART coverage in developing countries. By the end of 2008, of the 9.5 million people in need of ART in low- and middle-income countries, more than 4 million people were receiving treatment.

Why Was This Study Done? Good progress is being made towards achieving universal access to ART, partly because the cost of antiretroviral drugs has plummeted in developing countries. But the provision of antiretroviral drugs is not the only direct cost associated with ART. General practitioner, specialist, and maternity-related care for patients receiving ART, hospital accommodation when necessary, and the investigations that are needed to monitor the progress of HIV infection such as CD4 cell counts and viral load measurements all incur considerable costs. To use their limited resources effectively, public-health officials in developing countries need to know as much as possible about the direct costs of HIV health care but few studies have investigated these costs, particularly those incurred before an individual starts taking ART. In this study, the researchers explore health care costs in a South African private-sector HIV/AIDS program and examine the variables that drive the costs of HIV health care around the time of ART initiation and during later phases of ART.

What Did the Researchers Do and Find? The researchers analyzed the direct costs of treating more than 100,000 HIV-infected adults enrolled in a private HIV care program in South Africa from 3 years before they started ART until up to 5 years after ART initiation; within this program, individuals began to receive ART when their CD4 cell count fell below 350 cells/ μ l of blood. The researchers found a peak in direct health costs from 4 months before to 4 months after starting ART (the "peri-ART" period), which was driven mainly by

hospital costs. After the peri-ART period, costs dropped (although not to the levels seen before this period) and stabilized at an intermediate level for the next 5 years. Detailed statistical analyses suggest that the key variables associated with higher costs in the peri-ART period were a low baseline CD4 cell count, a high baseline HIV viral load, and a shorter time in HIV care before ART initiation. The key variable associated with higher costs later in ART was lower adherence to the drug therapy. That is, costs were higher among patients who did not take their antiretroviral drugs regularly.

What Do These Findings Mean? This study involved patients enrolled in a private health care program in which the criteria for initiating ART differed somewhat from those recommended by the World Health Organization for ART initiation in resource-limited settings. Thus, the absolute mean total costs calculated by the researchers are unlikely to be generalizable to public HIV care systems in South Africa and in other resource-poor settings. However, the finding that the drivers of mean total costs change considerably over time may be generalizable and provides some useful information for public-health planners that can now be tested in other, more resource-limited patient populations. In particular, the findings of this study suggest that the high early costs of ART programs could be reduced by starting ART at higher CD4 cell counts or by providing longer pre-ART care. In addition, the findings suggest that monitoring ART adherence and introducing interventions to improve ART adherence could reduce the later direct costs of ART programs.

Additional Information. Please access these Web sites via the online version of this summary at <http://dx.doi.org/10.1371/journal.pmed.1000189>.

- Information is available from the US National Institute of Allergy and infectious diseases on HIV infection and AIDS
- HIV InSite has comprehensive information on all aspects of HIV/AIDS
- Information is available from Avert, an international AIDS charity on many aspects of HIV/AIDS, including information on the HIV and AIDS in Africa, and on universal access to AIDS treatment (in English and Spanish)
- The World Health Organization provides information about universal access to AIDS treatment, including the September 2009 progress report (in English and French)
- The US Centers for Disease Control and Prevention also provides information on global efforts to deal with the HIV/AIDS epidemic

Chapter 6: The impact of antiretroviral therapy home-refill by courier compared to self-refill on patient clinical, immunological, and virologic outcomes: a cohort analysis in HIV-positive adults

6.1 Overview

The intention of this Chapter is to present an outcome analysis of home-refill (by courier) versus self-refill. The structure is consistent with a publication in an academic journal.

6.2 Introduction

Adherence to ART is an important factor driving key outcomes in antiretroviral programs, including viral suppression [1-6], the emergence of drug resistance [7-11], disease progression and death [4, 12, 13], hospitalization rates [4], and direct health care costs [14-16]. There are numerous barriers to adherence, many of which are unique to LMICs, e.g., structural barriers, including long waiting time at the clinic and cost of transport to collect antiretroviral drugs (ARVs) [17-19], and few interventions are consistent across settings [20-22]. Improving adherence is, however, critical if we are to achieve the UN's 90-90-90 goals, namely to ensure that 90% of PLWH know their HIV status, 90% of all people diagnosed with HIV receive ongoing ART, and 90% of PLWH on ART will have viral suppression by 2020 [23].

The importance of adherence in chronic illness was highlighted by WHO in 2003 [1]. Adherence is driven by several factors, including patient, medication and prescriber factors [3-5]. In recent systematic reviews and network meta-analysis [22], two-way short message service (SMS) was found to be effective in many settings, and effects were additive when a combination of interventions was applied (e.g., peer-support). Importantly, effects waned over time, suggesting that several parallel and/or staggered interventions may be needed if we are to achieve the 90-90-90 targets.

Indirect costs remain a significant and largely unaddressed barrier to HIV care [18, 24] and ART adherence [25-27]. Travel costs represent a significant component of indirect costs and are

particularly important to people who live far from clinics and have a limited income [24, 28]. Home-refill represents a potential intervention to reduce substantial indirect costs and has already been implemented in the Western Cape province, South Africa, for clinically stable patients on medication for chronic diseases such as hypertension and diabetes [29]. We hypothesized that ART delivery by courier to the patient's home would improve ART adherence and, therefore, lead to better outcomes. We compared outcomes between patients with home-refill (central pharmacy) and self-refill (local pharmacy) in a South African private sector HIV/AIDS programme.

6.3 Methods

6.3.1 Ethics

We obtained approval for this study from the Research Ethics Committee, University of Cape Town. All patients consented for their information to be entered into the AfA database.

6.3.2 Sources of data

We analyzed patients enrolled with AfA, a disease management group that manages HIV-related care for a number of medical insurance funds and companies in the private sector in Southern Africa [30]. The cohort has been described in detail in several earlier publications [5, 12, 15, 16, 30-38]. In brief, doctors working within their private practices registered patients with AfA, after completing online training and registration themselves, and continued to manage patients in their private practices. Demographic data, CD4+ cell count, viral load, and previous ART history were captured into a central database on registration and made available to the staff, who then authorized ART initiation and switches, in addition to other components of HIV care (e.g., prophylaxis of opportunistic infections, infant formula feeding, and some specialized investigations). The criteria for the initiation of ART at the time of the study were CD4+ cell counts <350 cells/ μ L or WHO stage III/IV illness. The recommended initial regimen was a combination of two NRTIs and a NNRTI but some flexibility was allowed. The recommended second line therapy consisted of a boosted PI with two NRTIs and the recommended salvage therapy consisted of either darunavir/ritonavir-, tipranavir/ritonavir-, raltegravir-, or etravirine-containing regimens. CD4+ cell counts and viral loads were recommended for monitoring every

6 months. The vital status of a member was determined by linking with the National Death Register using the RSAID number , as described in previous publications [36, 38, 39].

6.3.3 Inclusion criteria

We included open medical funds (i.e., not closed which were restricted to employees) for this analysis only, with no co-payment for ART. Patients were included if they were ART naïve (women who had received prophylaxis for PMCT were not excluded), were 19 years or older on starting ART, started ART between January 2002 and July 2010, and started first line ART.

6.3.4 Pharmacy dispensing data

ART dispensing data were collected by the medical schemes from electronic submissions by pharmacies. For each dispensing event, the medical administrator (Medscheme) recorded the date, details of the medication, quantity dispensed, and dispensing pharmacy. Courier pharmacies were identified and dispensing marked accordingly.

We found that patients often collected their medication in the first month on ART while the courier pharmacy was appointed. We, therefore, assigned patients who started home-refill by courier pharmacy during the second month of ART to the home-refill group from the start of the analysis. Most patients did not self-select but were instead assigned to courier pharmacy proactively by the scheme on registration with AfA. The schemes did allow for non-courier pharmacies, but this would incur a co-payment in some schemes and therefore, over time, courier pharmacies became the preferred providers.

6.3.5 Statistical methods

The following baseline variables were considered in our analysis: CD4+ cell (CD4) count, body mass index (BMI), VL, age, sex, and initial ART regimen. For CD4 count, VL, and weight, the baseline level was defined as the most recent result within 12 months before starting ART. We divided patients into three groups based on their mode of ART delivery: those that received all their ART through courier services (home-refill), those who collected their ART from private

pharmacies (self-refill), and those who initially collected ART from private pharmacies and then switched or were switched to courier services (mixed-refill).

Some data were missing for baseline CD4 count, baseline VL, baseline weight, and height (see Table 1). For the missing variables, we imputed five datasets using multiple imputations by chained equations (MICE). The imputation model included the following baseline variables: sex, baseline weight, height, age, CD4 count, VL, death, time on ART. CD4 count and VL were actively imputed, and BMI was passively imputed (using actively imputed baseline weight and height). We checked the results of the imputation model by comparing the imputed data with the actual data [40, 41].

Our primary endpoint was all-cause mortality; secondary endpoints were viral suppression (VL < 400 copies/ml) and median CD4 response (from baseline) at 6-month intervals. We assessed differences in baseline characteristics with 2-sample Student t-tests (continuous variables) and Chi-Square tests (categorical variables). We compared the crude survival of self-refill and home-refill groups using a Kaplan–Meier plot and a log-rank test. We used Cox proportional hazards regression to model the individual and simultaneous effects of baseline variables and mode of ART delivery on all-cause mortality. We used plots of $-\log[-\log(\text{survival})]$ against $\log(\text{analysis time})$ and analysis of scaled Schoenfeld residuals to assess the proportionality assumption (data not shown). We included the following variables based on significance in the univariate analyses in multivariate models, stratified into discrete categories: age, sex, CD4 count, VL, year of starting ART, NNRTI, and NRTI. We considered a model with the propensity score included as a covariate to adjust for possible confounding in observational studies and compared the results [42]. All statistical analyses were performed using Stata, version 14.2 (StataCorp, College Station, Texas).

6.4 Results

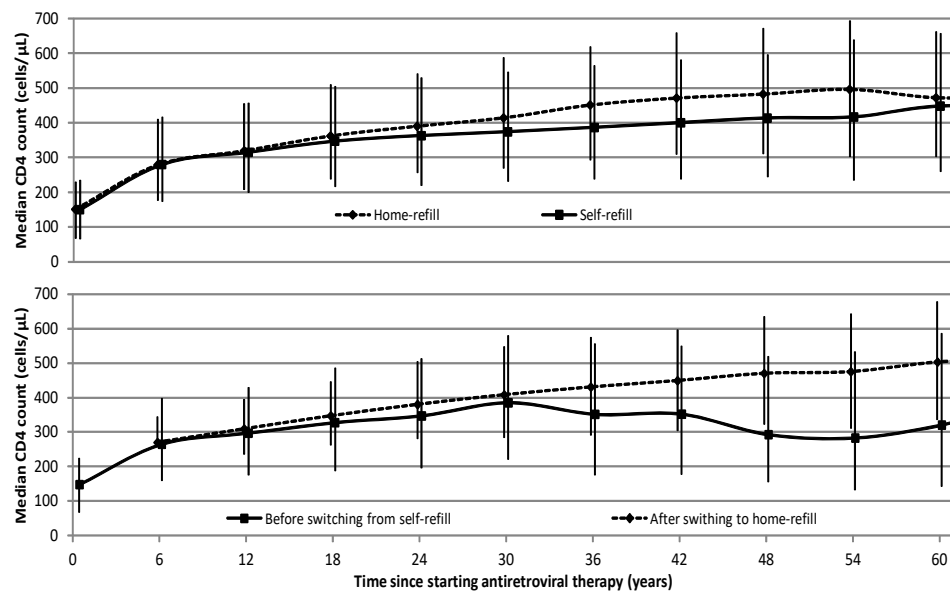
Table 6.1 shows baseline socio-demographics and clinical characteristics. Between January 2002 and June 2011, 40,939 patients met our eligibility criteria. In total, 66,204 years of follow-up were recorded. The most common first line regimens were EFV+3TC+ZDV initially, followed by EFV+FTC+TDF in later years. CD4 and viral load monitoring were done 1.5 times per annum on average. Given the high numbers of entrants towards the end of the study period, the median follow-up on ART was less than 2 years for both self- and home-refill groups; the patients who switched had had significantly longer exposure to ART. Other baseline variables were similar between groups but statistically significantly different.

Table 6.1: Baseline characteristics

Categories		Overall	Switched (self- to home-refill)	Self-refill (control)	Home-refill
Cohort size		33 822	7 117	19 202	14 620
Time on antiretroviral antiretroviral therapy (years)	Total	106 461	40 257	31 983	34 220
	Median (IQR)	1.83 (0.91 to 3.63)	5.33 (2.28 to 7.05)	1.48 (0.79 to 2.55)	1.77 (0.88 to 3.14)
Baseline CD4+ cell count (cells/ μ L)	Median (IQR)	150 (167 to 230)	148 (68 to 224)	150 (65 to 235)	151 (68 to 229)
	n (missing)	39 496 (1 443)	7 005 (112)	18 158 (1 044)	14 333 (287)
Baseline viral load (log ₁₀ copies/ml)	Median (IQR)	4.84 (4.01 to 5.39)	4.97 (4.35 to 5.47)	4.85 (3.94 to 5.41)	4.83 (4.04 to 5.38)
	n (missing)	37 845 (3 094)	6 811 (306)	17 343 (1 859)	13 691 (929)
Baseline body mass index (log ₁₀ copies/ml)	Median (IQR)	24.4 (21.4 to 28.1)	24.4 (21.5 to 28.2)	24.3 (21.4 to 28.1)	24.3 (21.3 to 28.1)
	n (missing)	37 845 (3 094)	6 811 (306)	17 343 (1 859)	13 691 (929)
Age at starting antiretroviral therapy	Median (IQR)	38 (33.1 to 44.1)	37.3 (32.5 to 42.9)	37.6 (32.9 to 43.5)	39.1 (33.7 to 45.4)
Calendar year at starting antiretroviral therapy	Median (IQR)	2007 (2005 to 2008)	2004 (2003 to 2007)	2008 (2005 to 2008)	2007 (2006 to 2008)
Sex (% female)		60	63.7	59.1	60.0

6.4.1 CD4 response to ART over time

We compared the CD4 response on ART over time in two analyses. In Figure 6.1 below we (a) compare the median and interquartile range (IQR) CD4 response over time between the home-refill by courier and self-refill groups from baseline until 60 months on ART and (b) repeat the analysis for those who switched from self- to home-refill by courier. There was a clear trend toward a better CD4 response over time in the home-refill by courier group than in the self-refill group, with curves separating already from 2 years on ART (e.g., at 36-month median CD4: 451 versus 387, $p < 0.0$). After 5 years, these two groups merged. Again, in (b) those who switched to home-refill by courier had better CD4 responses after switching than those remaining in the self-refill group (60-month Median CD4: 503 vs. 321; $p < 0.001$).

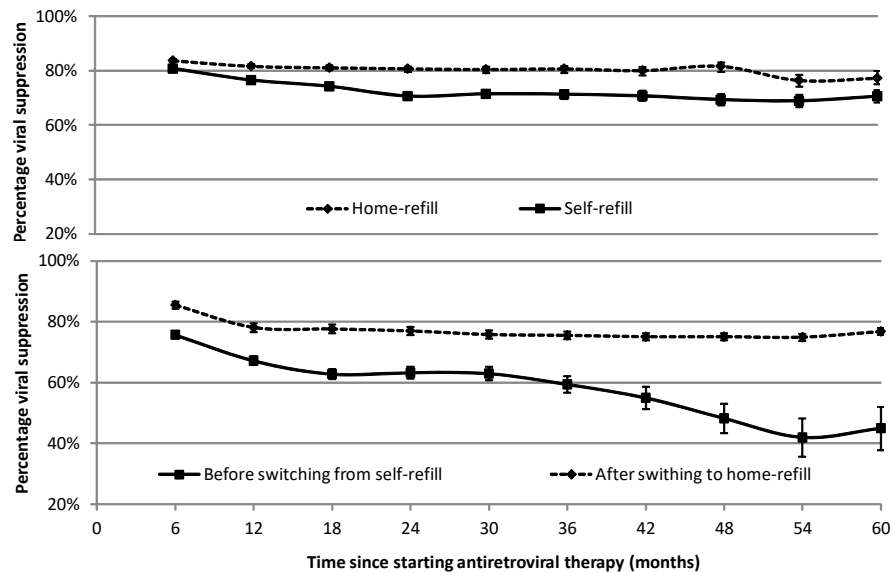


Months since starting antiretrovirals		0	6	12	18	24	30	36	42	48	54	60	
Control - self-refill from start	Median (IQR)	150 (68 to 235)	280 (176 to 417)	315 (208 to 457)	347 (238 to 504)	363 (256 to 530)	374 (270 to 546)	387 (292 to 565)	400 (309 to 580)	414 (310 to 596)	417 (302 to 639)	448 (302 to 657)	
	n (missing)	()	6855 (7447)	4752 (5977)	3439 (4344)	2291 (3372)	1569 (2535)	1108 (2210)	878 (1870)	736 (1697)	636 (1506)	550 (1322)	
Home refill from start		Median (IQR)	151 (68 to 229)	279 (176 to 410)	319 (208 to 454)	362 (238 to 509)	390 (256 to 542)	414 (270 to 587)	451 (292 to 619)	471 (309 to 658)	483 (310 to 671)	496 (302 to 693)	472 (302 to 662)
		n (missing)	()	6756 (5101)	5071 (4227)	3915 (3443)	3096 (2779)	2447 (2103)	1851 (1584)	1289 (1190)	950 (750)	570 (410)	297 (366)
Switched from self- to home-refill	Before	Median (IQR)	148 (68 to 224)	265 (159 to 397)	297 (176 to 429)	328 (188 to 486)	347 (196 to 512)	385 (221 to 579)	352 (176 to 556)	352 (178 to 550)	293 (156 to 519)	283 (133 to 533)	321 (143 to 586)
		n (missing)	()	2279 (68)	1671 (51)	1304 (31)	1005 (20)	781 (18)	570 (14)	357 (6)	231 (4)	151 (2)	114 (2)
	After	Median (IQR)	0 (0 to 0)	270 (196 to 413)	309 (224 to 442)	347 (248 to 495)	380 (257 to 524)	408 (269 to 566)	431 (286 to 611)	449 (302 to 643)	470 (306 to 667)	475 (307 to 678)	503 (328 to 718)
		n (missing)	()	977 (5502)	1077 (5026)	1173 (4516)	1237 (4047)	1372 (3606)	1512 (3233)	1664 (2895)	1797 (2561)	1869 (2211)	1710 (1863)

Figure 6.1: Comparing median CD4+ cell count (cells/ μ L) response from baseline to 60 months on antiretroviral therapy with interquartile ranges for home-refill by courier with (a) self-refill and (b) switching from self-refill to home-refill by courier

6.4.2 VL response to ART over time

We compared VL suppression on ART over time in two similar analyses. In Figure 6.2, we (a) compared the percentage with VL suppression (<400 copies/ml) over time between the home-refill by courier and self-refill groups from 6 months until 60 months on ART and (b) repeated the analysis for those who switched from self- to home-refill by courier. VL suppression was significantly better over time in the home-refill by courier compared with the self-refill group, with curves separating already from the first year on ART (e.g., at 36-month VL suppression: 81% versus 71%, $p < 0.001$). Again, in (b) those who switched to home-refill by courier had better VL suppression after switching than those remaining in the self-refill group (e.g., at 60-month VL suppression, 77% versus 45%, $p < 0.001$).



Months since starting antiretrovirals		6	12	18	24	30	36	42	48	54	60	
Control - self-refill from start	% suppressed (95% CI)	81 (80 to 81)	77 (76 to 77)	74 (73 to 75)	71 (69 to 72)	71 (70 to 73)	71 (70 to 73)	71 (69 to 73)	69 (67 to 71)	69 (67 to 71)	71 (68 to 73)	
	n (missing)	5360 (7665)	3525 (6122)	2453 (4478)	1565 (3447)	1084 (2587)	763 (2248)	601 (1898)	495 (1719)	416 (1538)	379 (1335)	
Home refill from start	% suppressed (95% CI)	84 (83 to 84)	82 (81 to 82)	81 (80 to 82)	81 (80 to 82)	80 (80 to 81)	81 (80 to 82)	80 (79 to 81)	82 (80 to 83)	76 (74 to 78)	77 (75 to 80)	
	n (missing)	5469 (5324)	4028 (4365)	3082 (3559)	2433 (2862)	1909 (2178)	1457 (1630)	1002 (1228)	748 (784)	425 (424)	228 (368)	
Switched from self- to home-refill	Before	% suppressed (95% CI)	76 (75 to 77)	67 (66 to 69)	63 (61 to 64)	63 (61 to 65)	63 (61 to 65)	59 (57 to 62)	55 (51 to 59)	48 (43 to 53)	42 (36 to 48)	45 (38 to 52)
		n (missing)	1660 (154)	1086 (105)	784 (86)	611 (59)	474 (46)	323 (40)	189 (19)	106 (15)	62 (5)	49 (7)
	After	% suppressed (95% CI)	85 (84 to 87)	78 (77 to 80)	78 (76 to 79)	77 (76 to 78)	76 (74 to 77)	75 (74 to 77)	75 (74 to 76)	75 (74 to 76)	75 (74 to 76)	77 (76 to 78)
		n (missing)	812 (5525)	809 (5066)	880 (4555)	919 (4086)	1013 (3637)	1100 (3285)	1206 (2949)	1309 (2613)	1372 (2239)	1283 (1894)

Figure 6.2: Comparing median HIV viral load (copies/ml) response from baseline to 60 months on antiretroviral therapy with interquartile ranges for home-refill by courier with (a) self-refill and (b) switching from self-refill to home-refill by courier

6.4.3 Survival analysis

We identified 5,150 (12.6%) deaths over 106,461 patient-years of follow-up (PYFU), giving a crude incidence of 48.3 deaths per 1000 PYFU. The Kaplan Meier analysis together with log-rank tests of all-cause mortality in self-refill versus home-refill is shown in Figure 6.3 below. The curves diverge and remain so with a significant ($p < 0.001$) difference between home-refill via courier and self-refill.

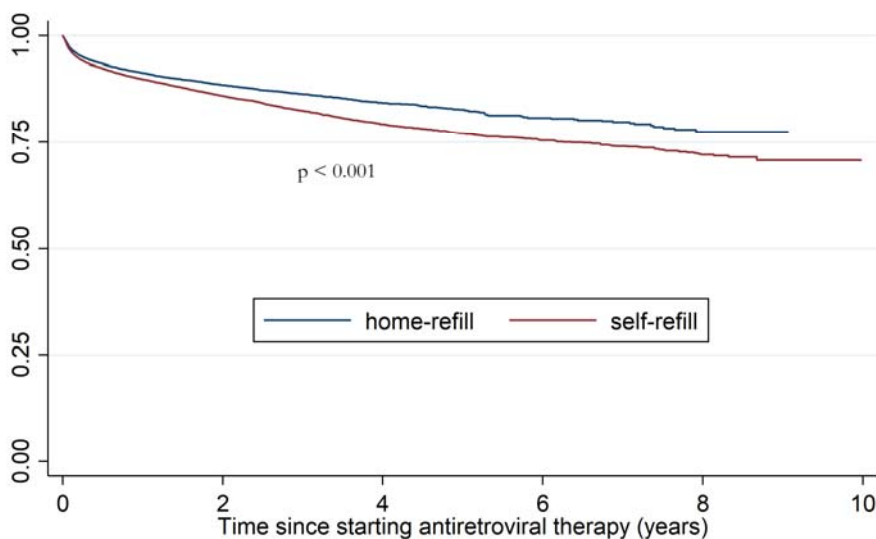


Figure 6.3: Kaplan-Meier plot of home-refill versus self-refill with log-rank test

The results of the multivariable analysis are shown in Table 6.2 below. In this analysis, home-refill was associated with a lower hazard of all-cause mortality than self-refill, adjusted hazard ratio (aHR) 0.90 (95% confidence interval (CI): 0.84-0.96). NRTI backbones other than tenofovir or zidovudine, EFV-containing regimens, male, were all associated with an increased adjusted hazard of all-cause mortality. Increasing age, increasing baseline VL, decreasing baseline CD4, and decreasing year of starting ART, decreasing BMI were also all associated with an increased adjusted hazard of all-cause mortality.

Table 6.2: Cox regression table comparing univariate and multivariate regression analyses

Variables		Univariate		Multivariate	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Antiretroviral dispensing	home-refill	0.86 (0.83 to 0.88)	<0.001	0.9 (0.84 to 0.96)	0.003
	self-refill	referent		referent	
Baseline NNRTI	efavirenz	1.42 (1.3 to 1.55)	<0.001	1.14 (1.04 to 1.25)	0.006
	nevirapine	referent		referent	
Baseline NRTI	tenofovir	referent		referent	
	other	2.28 (1.5 to 3.46)	<0.001	1.91 (1.24 to 2.94)	0.003
	zidovudine	1.1 (1 to 1.2)	0.051	0.87 (0.78 to 0.96)	0.008
	stavudine	1.35 (1.23 to 1.49)	<0.001	0.99 (0.88 to 1.1)	0.813
Sex	female	referent		referent	
	male	1.51 (1.42 to 1.6)	<0.001	1.15 (1.08 to 1.23)	<0.001
Age on starting antiretroviral therapy (years)	<25	0.73 (0.57 to 0.93)	<0.001	0.74 (0.58 to 0.94)	0.014
	25-49	referent		referent	
	>50	1.48 (1.36 to 1.61)	<0.001	1.58 (1.45 to 1.73)	<0.001
Baseline viral load (copies/ml)	<100,000	0.61 (0.5 to 0.74)	<0.001	0.73 (0.44 to 1.21)	0.217
	100,000-999,999	referent		referent	
	>1,000,000	3.43 (2.89 to 4.08)	<0.001	1.85 (1.2 to 2.85)	0.005
Baseline CD4 category (cells/ μ L)	0-49	5.39 (5.16 to 5.64)	<0.001	4.38 (3.92 to 4.89)	<0.001
	50-199	2.26 (2.16 to 2.36)	<0.001	referent	
	200-349	referent		2.02 (1.81 to 2.26)	<0.001
	>350	0.6 (0.55 to 0.66)	<0.001	1.09 (0.85 to 1.39)	0.494
Year of starting antiretroviral therapy	2002-2003	2.72 (2.62 to 2.82)	<0.001	2.25 (2.03 to 2.49)	<0.001
	2004-2005	1.85 (1.77 to 1.92)	<0.001	1.55 (1.39 to 1.73)	<0.001
	2006-2007	1.31 (1.27 to 1.36)	<0.001	1.19 (1.09 to 1.31)	<0.001
	2008+	referent		referent	
Body Mass index (kg/m ²)	<18	1.86 (1.56 to 2.23)	<0.001	1.56 (1.33 to 1.83)	<0.001
	18-24	referent		referent	
	25-34	0.64 (0.58 to 0.72)	<0.001	0.8 (0.7 to 0.91)	0.003
	35+	0.47 (0.36 to 0.61)	<0.001	0.67 (0.51 to 0.88)	0.006

Finally, the results of the Cox-proportional hazard regression which included the propensity as a covariate is presented in Table 6.3. The propensity score (2.66 95% CI: 1.07-6.62) attenuated the effect of baseline NRTI (stavudine and zidovudine) and sex, but the effect of home-refill by courier remained similar.

Table 6.3: Cox regression table comparing multivariate analyses with or without propensity score

Variables		Multivariate with p-score		Multivariate	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Antiretroviral dispensing	home-refill	0.88 (0.82 to 0.95)	<0.001	0.9 (0.84 to 0.96)	0.003
	self-refill	referent		referent	
Baseline NNRTI	efavirenz	1.13 (1.03 to 1.23)	0.012	1.14 (1.04 to 1.25)	0.006
	nevirapine	referent		referent	
Baseline NRTI	tenofovir	referent		referent	
	other	1.95 (1.26 to 3)	0.003	1.91 (1.24 to 2.94)	0.003
	zidovudine	1 (0.85 to 1.19)	0.957	0.87 (0.78 to 0.96)	0.008
	stavudine	1.09 (0.94 to 1.26)	0.255	0.99 (0.88 to 1.1)	0.813
Sex	female	referent		referent	
	male	1.04 (0.92 to 1.17)	0.562	1.15 (1.08 to 1.23)	<0.001
Age on starting antiretroviral therapy (years)	<25	0.81 (0.63 to 1.06)	0.121	0.74 (0.58 to 0.94)	0.014
	25-49	referent		referent	
	>50	1.5 (1.35 to 1.66)	<0.001	1.58 (1.45 to 1.73)	<0.001
Baseline viral load (copies/ml)	<100,000	0.71 (0.43 to 1.18)	<0.001	0.73 (0.44 to 1.21)	0.217
	100,000-999,999	referent		referent	
	>1,000,000	1.78 (1.15 to 2.76)	0.19	1.85 (1.2 to 2.85)	0.005
Baseline CD4 category (cells/ μ L)	0-49	4.04 (3.53 to 4.62)	0.009	4.38 (3.92 to 4.89)	<0.001
	50-199	1.96 (1.75 to 2.2)	<0.001	referent	
	200-349	referent		2.02 (1.81 to 2.26)	<0.001
	>350	1.11 (0.87 to 1.42)	0.415	1.09 (0.85 to 1.39)	0.494
Year of starting antiretroviral therapy	2002-2003	2.4 (2.13 to 2.71)	<0.001	2.25 (2.03 to 2.49)	<0.001
	2004-2005	1.53 (1.38 to 1.71)	<0.001	1.55 (1.39 to 1.73)	<0.001
	2006-2007	1.16 (1.06 to 1.28)	0.002	1.19 (1.09 to 1.31)	<0.001
	2008+	referent		referent	
Body Mass index (kg/m ²)	<18	1.52 (1.3 to 1.78)	<0.001	1.56 (1.33 to 1.83)	<0.001
	18-24	referent		referent	
	25-34	0.82 (0.72 to 0.93)	0.007	0.8 (0.7 to 0.91)	0.003
	35+	0.7 (0.53 to 0.92)	0.013	0.67 (0.51 to 0.88)	0.006

6.5 Discussion and conclusions

The main finding of this analysis is that home-refill of ARVs by courier was associated with significant improvements in CD4 count, viral suppression, and overall survival over a 10-year period relative to self-refill in AfA, a large managed-care programme in the private sector in South Africa. Moreover, in patients who switched from self-refill to home-refill while enrolled with AfA, significant improvements in CD4 count and viral load suppression were observed as well post switching. To our knowledge, this is the first large-scale study investigating home-based delivery of ARVs by courier in the healthcare system [43, 44]. This study has important implications for LMICs as home-refill represents a potential model for ART delivery in LMICs that could reduce patient burden while simultaneously improving outcomes [45].

Home-based ART, which included clinical management, laboratory monitoring, and ARV delivery has been shown to be effective in a systematic review [46], but only one study has looked purely at ARV delivery, this time in a HIC setting [47]. In this study, home delivery of ARVs was associated with improved non-significant outcomes: lower virologic failures, lower outpatient attendances, less frequent laboratory monitoring, and less frequent abnormal liver function tests [47]. In terms of survival, the positive relationship between treatment outcome and year of treatment initiation has been described in previous analyses [48, 49], together with improved outcomes for females [34, 50], lower baseline VL [34], higher baseline CD4 count [34, 48, 49], and higher BMI [51]. The choice of NNRTI and NRTI has been shown to impact outcomes on ART but usually favours efavirenz-containing first line regimens and first line regimens which do not contain stavudine [52].

Our data have important clinical and public health implications. First, given the burden that can be associated with self-ART refills (travel to a clinic, long waiting time, loss of a day job, etc.) [24, 53], home delivery of ART represents a possible effective intervention to improve clinical outcomes while reducing patient burden in clinics in LMICs. Second, such an ART delivery model can be considered as part of the emerging DSD, a patient-centred approach that simplifies and adapts services across the HIV cascade to reflect the preferences and expectations of different PLWH subpopulations, while reducing unnecessary burdens on the health system [54]. Third, with the aging of the HIV population and increasing incidence of NCD co-morbidities [55], such home delivery models can include other chronic medication (e.g., hypertension, diabetes) [38]. Finally, home-based care and support strategies have been found to

achieve retention and treatment outcomes that are comparable and even superior to those reported by mainstream health facilities, further underscoring the need to increase community service delivery [45, 56].

This is the first large-scale study to evaluate the impact of home-refill by courier versus self-refill and switch from self- to- courier refill in LMICs, with a large sample size and well-defined and documented clinical, immunological, and virological outcomes. While the study is informative and innovative, its limitations include its retrospective and observational nature, limited confounder variables in our multivariate analysis, the data being from a private-sector and not a public-sector cohort, and that the analysis was based on baseline characteristics. Most patients were adherent and remained on their initial regimen for several years. We did not include time-updated values (e.g., regimen, CD4, or VL), including patients who switched to home-refill by courier at this stage in the regression analysis, but the findings would support the development of a marginal structural model to confirm the results [57]. Further analyses are needed to address these and other limitations.

In summary, this analysis of data from a South African private-sector programme suggests that home delivery of ART is associated with improved clinical, immunological, and virologic outcomes for PLWH in Southern Africa. As ART programmes continue to expand in LMICs and in aging HIV populations with an increased incidence of NCD co-morbidities, such community-based ART delivery models add to the growing number of differentiated service delivery models in LMICs and need to be investigated further and scaled-up in these settings, if proved cost-effective. An existing public sector initiative within the Western Cape, South Africa, where a central pharmacy already prepares chronic medication “packs” to speed up existing clinic-based dispensing, could be adapted to include home delivery for patients to alleviate clinic congestion and patient costs incurred in clinic attendance [29].

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RESEARCH

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Improving the evidence base of Markov models used to estimate the costs of scaling up antiretroviral programmes in resource-limited settings

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Abstract

Background: Despite concerns about affordability and sustainability, many models of the lifetime costs of antiretroviral therapy (ART) used in resource limited settings are based on data from small research cohorts, together with pragmatic assumptions about life-expectancy. This paper revisits these modelling assumptions in order to provide input to future attempts to model the lifetime costs and the costs of scaling up ART.

Methods: We analysed the determinants of costs and outcomes in patients receiving ART in line with standard World Health Organization (WHO) guidelines for resource poor settings in a private sector managed ART programme in South Africa. The cohort included over 5,000 patients with up to 4 years (median 19 months) on ART. Generalized linear and Cox proportional hazards regression models were used to establish cost and outcome determinants respectively.

Results: The key variables associated with changes in mean monthly costs were: being on the second line regimen; receiving ART from 4 months prior to 4 months post treatment initiation; having a recent or current CD4 count <50 cells/ μ L or 50-199 cells/ μ L; having mean ART adherence <75% as determined by monthly pharmacy refill data; and having a current or recent viral load >100,000 copies/mL. In terms of the likelihood of dying, the key variables were: baseline CD4 count <50 cells/ μ L (particularly during the first 4 months on treatment); current CD4 count <50 cells/ μ L and 50-199 cells/ μ L (particularly during later periods on treatment); and being on the second line regimen. Being poorly adherent and having an unsuppressed viral load was also associated with a higher likelihood of dying.

Conclusions: While there are many unknowns associated with modelling the resources needed to scale-up ART, our analysis has suggested a number of key variables which can be used to improve the state of the art of modelling ART. While the magnitude of the effects associated with these variables would be likely to differ in other settings, the variables influencing costs and survival are likely to be generalizable. This is of direct relevance to those concerned about assessing the long-term costs and sustainability of expanded access to ART.

Introduction

With access to antiretroviral therapy (ART) now rapidly expanding in low and middle-income countries, attention is increasingly turning to the affordability and sustainability of these programmes [1]. Given the potential effectiveness of treatment coupled with the scale of the

response needed, it is important that planning takes a long term perspective. While many studies have focussed on the effectiveness of ART in resource-limited settings, cost studies are limited, especially those documenting costs in routine and established programmes and over longer periods of time. In recent years, the management of ART programmes in low and middle income countries has increasingly conformed to the World Health Organization (WHO) guidelines for

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resource-limited settings [2]. These include guidelines for when to start ART based on the patient's CD4 count or WHO stage, guidelines for monitoring ART as well as guidelines regarding which antiretrovirals (ARVs) should be administered within distinct first and second line regimens. These guidelines therefore provide a good framework for understanding disease progression and the costs of patients in ART programmes.

Because ART has only recently been available in resource-limited settings, lifetime costs – a key input into the costs of scaling up – are calculated through extrapolating primary data, with the Markov model being the most common framework used for this extrapolation. Many models include the baseline and current CD4+ cell count (i.e. the most recent test value), viral load and WHO staging, but other potential determinants of costs such as adherence have been excluded. This raises questions of the accuracy of the resulting estimates which could have implications for attempts to plan for expanded access to ART.

A Markov model consists of a number of mutually exclusive and collectively exhaustive Markov states, with at least one of these being an “absorbing state” (e.g. death). Patients remain in each state for an equal increment of time, called a Markov cycle, before being allowed the option of moving to a different state (or staying in the current state) as determined by one or more transition probabilities. In addition to time (or survival) increments, health care costs are attached to each state. Over a large number of cycles, lifetime costs and life expectancy is estimated [3,4].

To establish appropriate Markov states it is thus necessary to estimate which variables have a sizeable impact on the costs associated with being in a state together with the transition probabilities determining movements between states. While many types of transition probabilities are possible, the most important is the probability of dying as this determines overall life expectancy. Because the majority of the costs of ART are associated with ARV drugs, accurate calculation of life expectancy is crucial for the estimation of lifetime costs which in turn is a key input into calculations of the costs of scaling up [5].

This paper seeks to identify the variables that have an impact on direct health care costs and the likelihood of dying with a view to informing the development of Markov models for estimating lifetime costs and the costs of scaling up ART in resource-limited settings. We initially review the ART Markov model and cost determinant literature to establish the variables and variable categories that have been used to date. Thereafter, we assess the importance of these through the analysis of a large cohort from a private health care disease management programme. While this analysis would ideally be

conducted using data from individuals receiving ART in a range of routine models of care, including those found in the public health care sector, these routine data are not available. We have attempted to improve the generalisability of our findings by restricting our analysis to those patients in the private disease management programme that receive ART in line with the WHO guidelines for resource-limited settings [2].

Methods

Literature review

Our literature review included all cost, cost-effectiveness and cost-utility analyses of HIV-treatment including ART in resource-poor settings. While most economic analyses of ART focus on the annual per patient cost or the cost per specified outcome measure (e.g. per patient virally suppressed), we restricted our review to studies that had used Markov modelling to extrapolate available data to calculate lifetime costs and life expectancy. The reason for this is that the life expectancy of a patient on ART is a key determinant of lifetime costs and of the number of patients surviving and remaining in care over any projection period; it is therefore one of the most important inputs into any estimation of the costs of scaling up. A previous study by our group showed that 20% more patients would be remaining in care after a scale-up period of 10 years if life expectancy on ART of 13 years were assumed instead of 8.5 years [6]. However, we also included studies that attempted to ascertain the variables influencing costs over shorter time frames given that these could provide input into the construction of Markov states. A Pubmed search using the keywords “cost”, “resource-poor”, “low-income country/countries”, “middle-income country/countries”, “developing” and “antiretroviral” was conducted for all papers published before 1 May 2009.

Model comparison and refinement

Data source

The determinants of costs and survival on ART were evaluated using a large database of patients enrolled with Aid for AIDS (AfA), a group that manages HIV-related care for a number of medical insurance funds in the private health care sector in Southern Africa. Aid for AIDS does not manage patients directly, but rather provides guidelines for private medical practitioners' care of its participants and reimburses claims. Medical care is provided via patients' own general practitioner, therefore there are no formal “sites” but rather several thousand general practitioners and specialist practices taking care of patients, including those participating in Aid for AIDS. Treatment is funded by contracted companies or medical aid funds (composed of pooled monthly contributions from members) which

substantially cover co-morbid conditions including those not related to HIV. Data collected by AfA include demographics and previous medical history, CD4+ cell count, viral load and claims (including ART dispensing data). These claims are captured monthly by AfA from the medical insurance funds, pathology laboratories or from the patients or treating doctors directly using routine electronic administrative systems. Claim reimbursement is subject to established AfA protocols, including protocols for ART initiation, change of ART regimen, and the treatment of certain opportunistic infections. Despite this being a private sector programme, antiretroviral guidelines are similar in many respects to WHO guidelines for resource-poor settings as well as the South African public sector guidelines [2,7]. The recommended initial regimen is a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). Second line therapy consists of a boosted protease inhibitor (PI) with two NRTIs. Health services provided for patients within AfA include additional primary care doctor visits for patients that have exceeded their routine medical insurance benefits, telephonic counseling services and antiretroviral drugs dispensed monthly from private pharmacies or delivered via courier to the patient's home. While ART can be initiated at CD4 <350 cells/ μ L rather than CD4 <200 cells/ μ L, we restricted the analysis to the latter group as this is the more common starting criterion in resource poor settings, including the South African public sector at the time of this study (these guidelines have recently been revised to recommend ART initiation at CD4 <350 cells/ μ L [8]). Furthermore, we only included patients starting ART with a NNRTI plus two NRTIs, as recommended by the WHO for resource-limited settings [2].

We determined average adherence to ART using monthly pharmacy refill data. This approach has been shown to correlate well with adherence assessment by therapeutic drug levels [9,10], and has been found to reliably predict virologic suppression [11], development of HIV drug resistance [12], and survival [13]. Previous analyses of these AfA data have in addition shown that this measure of adherence is a determinant of costs [14,15]. We expressed pharmacy claim adherence as a percentage and calculated it as the number of months with ART claims submitted divided by the number of complete months from ART initiation to death, withdrawal from the Aid for AIDS program, or study end.

Two of the medical insurance funds that contract AfA were selected on the grounds that they had large numbers of patients, similar treatment benefits, and no co-payment for ART. This allowed us to describe determinants of costs and outcomes without biases associated with the patient's ability to pay, which has been reported

to influence access to health care and outcomes on ART [16,17]. Patients were included in the study if they were ART naive at entry (the exception being women who had received prophylaxis for prevention of mother-to-child transmission), adult (19 years or older at the time of approval for ART) and if ART was started between November 1998 and November 2007.

Direct health care costs were analysed from the provider's perspective. The tariff amount was used as a proxy for these costs, as opposed to the amount charged by the provider. This is because providers may charge different rates for services with the same tariff code. The use of the tariff rate allows for the same cost to be assumed for the same type of service.

The prices of antiretroviral drugs have fallen dramatically over the past ten years. To account for this we deflated ARV prices to the April 2007 level. All other health care costs have increased; these were inflated to the April 2007 level using the Consumer Price Index net of mortgage payments (CPIX) [18]. The average South African Rand to United States Dollar (US\$) exchange rate in April 2007 (R7.14 to US\$1) was used to convert costs to US\$ equivalents [19].

Establishment of Markov states

As the distribution of mean health care costs was right-skewed in our data, ordinary least squares regression was not appropriate [20,21]. Generalised linear regression models (GLM) have been proposed as they determine the impact of variables on the arithmetic mean and thus provide a method for identifying variables strongly associated with varied costs [20]. A GLM with a log-link function and a gamma distribution described the trends in the data well. To account for multiple measures within an individual as well as potentially strong correlations between the variables, we used generalised estimated equations with an unstructured correlation matrix. Variable coefficients and their 95% confidence intervals were determined using robust standard errors and the model fit was evaluated using deviance residuals [20].

Multiple Cox proportional hazard regression analysis was used to identify variables associated with a likelihood of dying. Based on the findings of both the cost and outcome analyses, a pragmatic decision on which Markov states to include in the final model is needed; as the number of states increases, so the model complexity increases exponentially. Data storage, basic calculations and data extraction was handled in Microsoft Sequel Server 2008. Statistical analysis was performed in Stata 10.

Ethics statement

The study was approved by the Research Ethics Committee, University of Cape Town and by the Board of Directors of Aid for Aids. All patients signed consent

for their information to be entered into the AfA database.

Results

Existing models in literature

Over 300 cost, cost-effectiveness and cost-utility analyses of ART were found via a Pubmed search, but these included only 6 different Markov models of ART in low and middle income countries, some of which were used in more than one publication [6,22-27]. A number of variables were used in these studies to define Markov states, as outlined in Table 1. These included the baseline (i.e. pre-ART) CD4 count category, the current CD4 count category, baseline and current viral load categories, time on ART, being on a first or second line ARV regimen, opportunistic infections or WHO staging; and adverse events on ART. These variables could be combined in a variety of ways to create distinct Markov states depending on the model.

Model comparison and refinement

Dataset

The characteristics of the cohort are described in Table 2. After exclusions, 5,177 patients met our eligibility criteria, with over 136,600 patient months of observation, about half of which were on ART. Median follow-up on ART was 19 months (IQR: 10 to 32). The proportion of patients who left the medical insurance fund was 34%. These patients either changed their employment, switched to a different medical insurance

scheme or voluntarily stopped their contributions to the insurance scheme. The most common first line antiretroviral regimen was zidovudine/lamivudine/efavirenz (65 %). Lopinavir/ritonavir/zidovudine/didanosine was the most common second line regimen. CD4 and viral load monitoring was done 1.5 times per annum on average.

Markov states

To determine the most important variables on which to base Markov states, we assessed whether variables had a sizeable effect on costs or on the likelihood of dying. The literature review identified a number of differences in the ways that variables were categorised. Using the categories described in the literature as a starting point, we determined the most appropriate categories for the variables in our dataset guided by residual diagnostics, whether overall model fit improved with a changed categorisation, and whether the p-value was significant at the 95% confidence interval. The variables included in the analysis were: (1) baseline CD4+ cell count (categorised as 0-49, 50-199 cells/ μ L) (following Cleary et al [6,22] and Goldie et al [25]); (2) current or most recent (carried forward for up to 12 months) CD4+ cell count (0-49, 50-199, 200 to 349, 350 to 499, and \geq 500 cells/ μ L) (similar categories as Bachman [24], Badri et al [23] and Goldie et al [25]); (3) baseline viral load (categorised below or above 100,000 copies/ml) (Goldie et al [25] include this variable, but use far more categories); (4) Current or most recent viral load (categorised as <400, 400-10,000, 10,000-100,000, >100,000 copies/ml) (Goldie

Table 1 Determinants of Markov states in the literature

Markov states defined by:	Bachmann 2006	Badri et al 2006	Cleary et al 2006; 2008	Goldie et al 2006	Marseille et al 2006	Vijayaraghavan et al 2007
Baseline CD4 stratum		<200, 200-350, >350	<50, 50-200	<50; 50-200; 200-500; >500		
Current CD4 stratum	<200, 200-350	<200, 200-350, >350		<50; 50-200; 200-500; >500		
Baseline viral load stratum				>100,000; 30,001-100,000; 10,001-30,000; 3,001-10,000; 501-3,000; 0-500		
Current viral load stratum				>100,000; 30,001-100,000; 10,001-30,000; 3,001-10,000; 501-3,000; 0-500		Suppressed; unsuppressed
Time on ART			0-3; 3-6; 6-12; 12-24; 24-36; >36 months			
First or second line ARV regimen		Yes	Yes	Yes	Yes	Yes
Disease staging or opportunistic infections	Tuberculosis, other opportunistic infection, no opportunistic infection	No-AIDS/ AIDS		Severe bacterial infection; severe fungal infection; severe malaria; tuberculosis; isosporiasis; cerebral toxoplasmosis; nontuberculous mycobacteriosis; other severe opportunistic infection; mild bacterial infection; mild fungal infection; other mild infection	WHO Stages (1, 2, 3, 4)	AIDS
Adverse events						Toxicity; no toxicity

Table 2 The characteristics of the cohort (IQR = interquartile range)

Total number of patients		5 197
Patient months	Overall	136 672
	On ART	116 306 (85%)
Duration on ART (months)	Median	19
	IQR	(10 to 32)
Age at starting ART (years)	Median	37.3 years
	IQR	(32.4 to 42.9)
Sex	Female	6 379 (59%)
	Male	4 356 (41%)
Patient status at end of study period	Active	2 922 (56%)
	Left the scheme	1 834 (34%)
	Dead	421 (8%)
Baseline CD4+ cell count	Median	87 cells/ μ L
	IQR	(37 to 145)
Baseline viral load (\log_{10})	Median	5.22
	IQR	(4.73 to 5.63)
NNRTI used in first line	Nevirapine	2 655 (26%)
	Efavirenz	6 711 (74%)
NRTI combination in first line	Zidovudine + lamivudine	3 339 (65%)
	Stavudine + lamivudine/other	1 225 (24%)
	other	633 (11%)
Duration of CD4+ cell count monitoring before starting ART (months)	Median	1.2
	IQR	(0.6 to 2.6)
Overall Adherence as measured by monthly pharmacy refill data	Median	74.4%
	IQR	(38.4 to 92.3)

IQR=Interquartile Range

et al [25] and Vijayaraghavan et al [26] include this variable, but use different categories); (5) ART regimen (either first line or second line) (used by all except Bachman [24]); and (6) time periods relative to ART initiation (-4 to 4, 4 to 12, 12 to 24, 24 to 48 months on treatment) (similar to Cleary et al [6,22]). In addition to the variables identified in the literature, we also considered: (7) overall adherence, as determined using monthly pharmacy claim data and divided into quartiles based on the observed distribution of adherence in the cohort (<42%, 42%-75%, 75%-92%, >92%); (8) the NNRTI included in the initial first line regimen (either efavirenz or nevirapine); (9) the duration of CD4 count monitoring prior to starting ART, a proxy for duration within pre-ART care (≤ 6 months and > 6 months); (10) age at starting ART (<25, 25 to 50 and >50 years old); and (11) sex. Our data did not allow us to include variables relating to WHO disease staging, opportunistic infections or adverse events.

All the variables were included in the analysis exploring the determinants of costs and the likelihood of dying. In the baseline, the following initial parameter states were assumed: (1) baseline CD4 cell count between 50 and 199cells/ μ L; (2) current CD4+ cell count between 50 and 199cells/ μ L; (3) baseline viral load < 100,000 copies/ml; (4) current viral load < 400 copies/ml; (5) on first line ART; (6) time period 12 to 23 months on ART; (7) overall adherence in the upper

quartile (>75%); (8) NNRTI = efavirenz; (9) >6 months of CD4 monitoring prior to starting ART; (10) age at starting ART 25 to 50; and (11) sex = female

The results from the multiple regression analysis of costs (all variables were included in the model) are found in Table 3. Mean cost per patient month is presented for each variable or variable category and is compared to a reference or baseline which is the mean cost across all patients and time periods. We found higher current CD4 counts were associated with lower costs while having a current viral load above 100,000 copies/ml was associated with increased costs. Being on efavirenz was more costly than nevirapine, and being on second line was more costly than being on first line; these findings are likely to relate to the higher costs of the ARV drugs in these states as opposed to other health care costs. Lower adherence was an important driver of costs, as was time on treatment, with monthly costs in the period from 4 months before starting ART to 4 months on ART being almost double the monthly costs thereafter. After this time, the size and significance of the association between costs and time on treatment waned dramatically. Figure 1 illustrates the full set of variables and their influence on the mean total monthly direct health care costs relative to the baseline scenario.

The results from the multiple Cox proportional hazards regression analysis of the likelihood of dying

Table 3 Multiple generalised linear regression analysis of the determinants of total mean monthly costs (US\$)

Variables		Value	% change from referent	p-value
Time period relative to ART initiation (months)	-4 to 4	384 (321 to 459)	80%	<0.001
	4 to 12	238 (204 to 277)	12%	0.158
	12 to 24		Referent	
	24 to 48	222 (182 to 270)	4%	0.705
Baseline CD4 count (cells/ μ L)	0 to 49	193 (164 to 227)	-10%	0.228
	50 to 199		Referent	
Current CD4 count (cells/ μ L)	0 to 49	352 (290 to 426)	65%	<0.001
	50 to 199		Referent	
	200 to 349	190 (161 to 223)	-11%	0.16
	350 to 499	166 (141 to 195)	-22%	0.002
Baseline viral load (copies/ml)	\geq 500	158 (123 to 202)	-26%	0.017
	<100 000		Referent	
	\geq 100 000	220 (195 to 248)	3%	0.601
Current viral load (copies/ml)	<400		Referent	
	400 to 9 999	219 (191 to 250)	3%	0.717
	10 000 to 99 999	195 (164 to 232)	-8%	0.317
	\geq 100 000	249 (209 to 296)	17%	0.082
Overall adherence	<42%	264 (235 to 297)	24%	<0.001
	42 to 74%	263 (233 to 295)	23%	0.001
	75 to 92%	244 (218 to 273)	14%	0.019
	\geq 92%		Referent	
ARV regimen	First line		Referent	
	Second line	409 (255 to 656)	92%	0.007
NNRTI in first line	Nevirapine	197 (182 to 213)	-8%	0.042
	Efavirenz		Referent	
Duration of CD4 count monitoring (months)	\leq 6	181 (161 to 204)	-15%	0.008
	>6		Referent	
Sex	Male	206 (188 to 226)	-3%	0.463
	Female		Referent	
Age at starting ART (years)	<25	194 (164 to 230)	-9%	0.282
	25 to 50		Referent	
	>50	230 (194 to 271)	8%	0.384
Referent cost		213 (178 to 256)	NA	NA

are found in table 4. The relative likelihood of dying is compared with the same referent groups as in the cost analysis, but a separate model was used for each of the time periods. We found higher current CD4 counts, higher ART adherence, and current viral loads below 100,000 copies/ml were associated with lower likelihoods of dying across all periods, with baseline values for CD4 and viral load contributing very little additional effect after the first 4 months on treatment. Longer duration of monitoring prior to starting ART was associated with a lower likelihood of dying in earlier periods and being greater than 50 years or younger than 25 years at starting ART was associated with a higher likelihood of dying in later periods. Being on second line was associated with an increased likelihood of dying across all periods.

Discussion

We analysed determinants of direct health care costs and survival in 5,197 HIV-infected adults enrolled in a South African managed care ART programme with 136,672 patient months of follow-up, spanning -4 months before ART to 4 years on ART. If each Markov state is defined to include unique combinations of these variables, thousands of states could be defined. A correspondingly large dataset would then be needed to calculate the costs and transitions associated with each of these states. For this reason, it becomes necessary to focus only on variables that have the most marked effects on costs and outcomes within reasonable confidence intervals. The key variables associated with changes in mean monthly costs were: being on the second line regimen; receiving ART from 4 months prior

Figure 1:

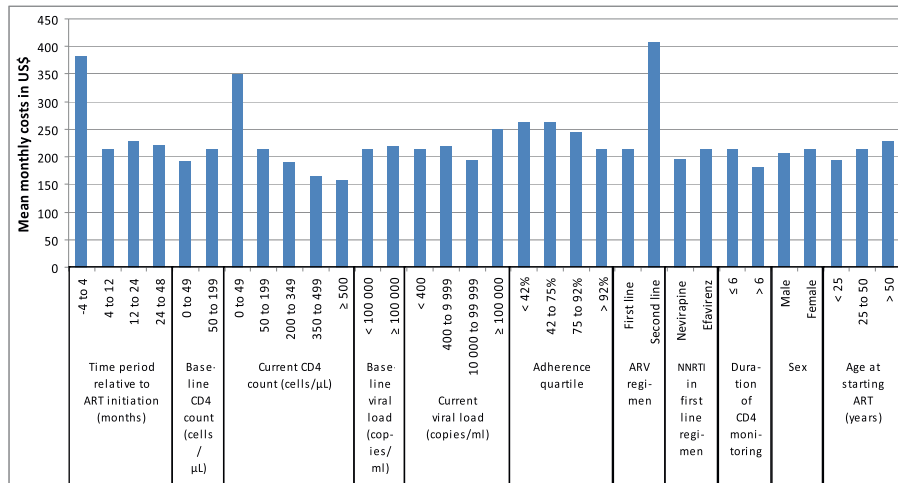


Figure 1 The influence of variables on mean monthly costs

to 4 months post treatment initiation; having a recent or current CD4 count <50 cells/ μ L or 50-199 cells/ μ L; having mean ART adherence <75% as determined by monthly pharmacy refill data; and having a current or recent viral load >100,000 copies/mL. In terms of the likelihood of dying, the key variables associated with changes in survival were: baseline CD4 count <50 cells/ μ L (particularly during the first 4 months on treatment); current CD4 count <50 cells/ μ L and 50-199 cells/ μ L (particularly during later periods on treatment); and being on the second line regimen. Being poorly adherent and having an unsuppressed viral load was also associated with a higher likelihood of dying.

The relationships between these variables and costs and outcomes were consistent with trends described in the literature, though the scale did differ in some cases: lower CD4 count, higher viral load, lower adherence, and being on second line therapy was associated with higher costs and worse outcomes. In addition, sub-optimal adherence drives resistance to first line therapy, leading to second line therapy being initiated. There was a relative small and limited association between costs and outcomes and the baseline pathology results (CD4 count and the viral load), most likely due to the current or most recent CD4 and viral load results being dominant. The finding that lower adherence is associated with higher costs (in addition to its known effects on biological variables such as CD4 count and viral load and starting second line therapy) further supports the need to include this variable in Markov models.

Based on the above, one would anticipate that Markov models that use these variables as the bases of their Markov states may have superior accuracy. However, in our literature review, the only Markov model that

specified costs and outcomes in relation to duration on ART was Cleary et al [6,22]. Most of the models separated first from second line ART to capture the cost differences, but were unable to estimate different survival transition probabilities because data on outcomes of patients on second line was limited. Bachmann [24], Goldie et al [25] and Badri et al [23] all included the current CD4 count but Cleary et al [6,22] only included the baseline CD4 count. Baseline and current viral load was only included by Goldie et al [25]. Opportunistic infections or WHO staging were included in all the models except Cleary et al [6,22]. Unfortunately these data were not available within the AfA cohort, and we were therefore unable to assess the importance of these for the construction of Markov states. None of the models included sex, ART adherence, age or duration of pre-ART care.

There are a number of limitations to this analysis. First, our cohort consisted of private sector patients when the majority of patients in resource-limited settings are treated in the public or NGO sector. However, the baseline characteristics of our cohort (CD4+ cell count, proportion female and age) are comparable with cohorts from low-income countries [28] and we restricted our analysis to patients receiving NNRTI-based first line ART regimens and starting ART at CD4 < 200 cells/ μ L, in keeping with WHO recommendations for resource-limited settings [2]. While we would not claim that our actual cost findings are generalisable to public sector settings or to other countries, we would argue that the variables that influence costs and outcomes are likely to be relevant even if the magnitude of their effects could differ. Second, the impact of specific opportunistic infections, disease staging or adverse

Table 4 Multiple Cox proportional hazard regression analysis of the relative risk of dying

Variables	0 to 4 months on ART		5 to 12 months on ART		13 to 24 months on ART		>24 months on ART		
	co-eff (95% CI)	p-value	co-eff (95% CI)	p-value	co-eff (95% CI)	p-value	co-eff (95% CI)	p-value	
Baseline CD4 cell count (cells/ μ L)	<50	2.09 (1.02 to 4.28)	0.043	1.6 (0.84 to 3.06)	0.152	1 (0.57 to 1.73)	0.992	0.79 (0.51 to 1.22)	0.279
	50-199					Referent			
Current CD4 cell count (cells/ μ L)	<50	N/A	N/A	1.89 (0.96 to 3.72)	0.065	3.88 (2.03 to 7.41)	<0.001	3.54 (2.17 to 5.75)	<0.001
	50-199					Referent			
	200-349	N/A	N/A	0.58 (0.25 to 1.34)	0.206	0.19 (0.06 to 0.55)	0.002	0.74 (0.38 to 1.44)	0.376
	\geq 350	N/A	N/A	N/A	N/A	0.36 (0.12 to 1.09)	0.071	0.42 (0.15 to 1.17)	0.098
	\geq 500	N/A	N/A	N/A	N/A	N/A	N/A	0.42 (0.15 to 1.23)	0.115
Baseline viral load (copies/ml)	<100 000					Referent			
	\geq 100 000	2.12 (0.86 to 5.21)	0.103	0.82 (0.44 to 1.53)	0.541	1.34 (0.77 to 2.33)	0.298	1.2 (0.78 to 1.85)	0.413
Current viral load (copies/ml)	<400					Referent			
	400 – 9 999	N/A	N/A	1.09 (0.44 to 2.66)	0.270	1.42 (0.57 to 3.59)	0.967	1.32 (0.56 to 3.14)	0.033
	10 000 – 99 999	N/A	N/A	0.64 (0.29 to 1.41)	0.106	1.02 (0.44 to 2.36)	0.394	2.24 (1.07 to 4.7)	0.001
	\geq 100 000	N/A	N/A	1.76 (0.89 to 3.47)	0.541	1.42 (0.63 to 3.2)	0.298	3.6 (1.68 to 7.7)	0.413
ART adherence (quartiles)	<42%	2.14 (0.69 to 6.67)	0.188	1.89 (1 to 3.57)	0.049	1.40 (0.59 to 3.29)	0.443	2.21 (0.87 to 5.63)	0.096
	42 to 75%	3.18 (1.05 to 9.61)	0.04	1.78 (0.92 to 3.43)	0.086	0.65 (0.26 to 1.64)	0.362	2.58 (1.04 to 6.39)	0.041
	75 to 92%	N/A	N/A	1.76 (0.9 to 3.46)	0.098	0.91 (0.37 to 2.23)	0.84	1.48 (0.56 to 3.91)	0.427
	>92%					Referent			
ARV regimen	First line					Referent			
	Second line	6.39 (0.85 to 47.75)	0.071	5.25 (2.11 to 13.06)	<0.001	1.4 (0.64 to 3.06)	0.402	1.67 (1.09 to 2.56)	0.018
NNRTI in first line	efavirenz					Referent			
	nevirapine	0.6 (0.28 to 1.26)	0.175	1.26 (0.8 to 2)	0.324	1.56 (0.85 to 2.85)	0.149	0.89 (0.59 to 1.34)	0.568
Duration of monitoring prior to starting ART (months)	\geq 6					Referent			
	<6	2.9 (0.28 to 1.26)	0.296	1.15 (0.8 to 2)	0.692	1.67 (0.85 to 2.85)	0.328	1.05 (0.59 to 1.34)	0.890
Sex	male	0.79 (0.38 to 1.67)	0.545	1 (0.68 to 1.46)	0.998	1.15 (0.69 to 1.91)	0.595	1.26 (0.85 to 1.86)	0.257
	female					Referent			
Age at baseline (years)	<25	0.63 (0.15 to 2.7)	0.531	2.06 (0.51 to 8.4)	0.312	1.82 (0.25 to 13.22)	0.555	2.15 (0.52 to 8.83)	0.289
	25-49					Referent			
	\geq 50	1.69 (0.32 to 9.03)	0.540	2.39 (0.52 to 10.98)	0.263	1.34 (0.14 to 13.03)	0.801	3.86 (0.81 to 18.35)	0.090

events on costs and outcomes was not included in this analysis as these data were not available. We are therefore unable to comment on the validity of this aspect of some of the Markov models in the literature.

Conclusion

In conclusion, we have analysed the determinants of direct health care costs and outcomes in a private health care sector managed ART programme. Our focus has been to use statistical techniques to determine the key variables to include in Markov states and to use these findings to inform future modelling of the costs of scaling up ART. Our results suggest that important drivers of costs and outcomes include time on ART, being on

first versus second line regimens, the current CD4 cell count, the current viral load, age at starting ART and adherence. The inclusion of these variables should be considered for future modelling of the costs of scaling up ART programmes.

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Authors' contributions

RL analyzed the data. MH collected and prepared the data used in the study and provided input into the data analysis methodology. SC, GM and RL contributed to the overall study design and methodology. SC wrote the first draft of the paper while SC and RL were responsible for revisions of the paper. All authors contributed to the writing of the paper and agreed with the manuscript's results and conclusions.

Competing interests

The authors declare that they have no competing interests.

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Chapter 8:

A novel Markov model projecting costs and outcomes of providing antiretroviral therapy to public patients in private practices versus public clinics in South Africa

A Novel Markov Model Projecting Costs and Outcomes of Providing Antiretroviral Therapy to Public Patients in Private Practices versus Public Clinics in South Africa

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Abstract

Introduction: Providing private antiretroviral therapy (ART) care for public sector patients could increase access to ART in low- and middle-income countries. We compared the costs and outcomes of a private-care and a public-care ART program in South Africa.

Methods: A novel Markov model was developed from the public-care program. Patients were first tunneled for 6 months in their baseline CD4 category before being distributed into a dynamic CD4 and viral load model. Patients were allowed to return to ART care from loss to follow up (LTFU). We then populated this modeling framework with estimates derived from the private-care program to externally validate the model.

Results: Baseline characteristics were similar in the two programs. Clinic visit utilization was higher and death rates were lower in the first few years on ART in the public-care program. After 10 years on ART we estimated the following outcomes in the public-care and private-care programs respectively: viral load <1000 copies/ml 89% and 84%, CD4 >500 cells/μl 33% and 37%, LTFU 14% and 14%, and death 27% and 32%. Lifetime undiscounted survival estimates were 14.1 (95%CI 13.2–14.9) and (95%CI 12.7–14.5) years with costs of 18,734 (95%CI 12,588–14,022) and 13,062 (95%CI 12,077–14,047) USD in the private-care and public-care programs respectively. When clinic visit utilization in the public-care program was reduced by two thirds after the initial 6 months on ART, which is similar to their current practice, the costs were comparable between the programs.

Conclusions: Using a novel Markov model, we determined that the private-care program had similar outcomes but lower costs than the public-care program, largely due to lower visit frequencies. These findings have important implications for increasing and sustaining coverage of patients in need of ART care in resource-limited settings.

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Introduction

Expanding capacity to deal with the HIV epidemic is a formidable task in low- and middle-income countries given the scale of the epidemic and the limited public health infrastructure. While much has been achieved to make antiretroviral therapy (ART) affordable, access to care is still inadequate. According to the latest UNAIDS report, only 46% of those who were in need had started ART by the end of 2010 in low- to middle-income countries [1].

One way to expand access to ART and improve retention within ART care for public sector patients is to utilize the private sector. In many low- and middle-income countries a high proportion of doctors work in the private sector [2]. Contracting private doctors to initiate ART and follow up public sector patients in their private rooms according to the public sector

guidelines has been successfully implemented in Botswana [2] and other developing country settings [3]. However, there are concerns about the ability and willingness of individual private doctors to implement the public health approach to ART management, and about high costs in the for-profit private sector. To date there have been no published comparisons of clinical and economic outcomes of the provision of ART care to public patients between the private sector and public sector.

In addition to the debates about public versus private ART care, there are also questions about how frequently patients should be followed up, and by whom. In the earlier years of ART provision, patients were required to attend facilities for regular consultations with doctors or nurses [4]. More recently, however, there has been a move towards less frequent follow-up, and towards task shifting from doctors to nurses, and from nurses to counselors [5]. It is however unclear whether this changing

intensity in follow-up will impact negatively on patient adherence and outcomes.

We assessed the costs and outcomes of providing ART care for public patients in the private versus public sector in two South African ART programs where no co-payment from patients was required: a grant-funded program providing care for public patients in private practices and a public-sector program providing care for public patients in public sector community clinics. We utilized a newly developed Markov-model, which addresses many of the limitations of existing models [6].

Methods

Study design

We assessed the costs and outcomes of ART provision in the private-care and public-care models to provide care to public sector dependent patients. We took the provider's perspective and only included ART-related costs: antiretroviral drugs, CD4+ cell count (CD4) and viral load (VL) monitoring, toxicity laboratory monitoring, and public clinic or private general practitioner (GP) visits. We used Markov modeling to extrapolate primary data in order to estimate results over 10 years and lifetime for costs, rates of loss to follow-up and life years. Zero and three percent annual discount rates were used. The model was developed using data from the public-care cohort, and validated externally using data from the private-care cohort. Uncertainty was assessed using multi-way and probabilistic sensitivity analyses.

Study setting

ART care for patients in both programs followed the 2003 South African national guidelines, which were based on the 2003 World Health Organization guidelines for resource-limited settings [7]. Patients were eligible for ART when they met the following criteria: either a CD4 below 200 cells/ μ L or a WHO stage 4 illness (other than extra-pulmonary tuberculosis) irrespective of the CD4 count. The first line ART regimen consisted of two nucleoside reverse transcriptase inhibitors (NRTI), zidovudine (ZDV) or stavudine (D4T) with lamivudine (3TC), with a non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP) or efavirenz (EFV). Viral load and CD4 counts were monitored 6 monthly. Patients with confirmed virologic failure (two consecutive viral loads \geq 5000 copies/ml) in spite of enhanced adherence promotion, were switched to a second line regimen of two NRTIs, ZDV and didanosine (DDI), in combination with a boosted protease inhibitor, lopinavir/ritonavir (LPV/r). Safety monitoring was limited to serum alanine aminotransferase (ALT), complete blood count, and lipogram for patients on NVP, ZDV, and LPV/r respectively.

Cohort Description

The public-care cohort was the Khayelitsha HIV treatment program, which is a public sector program operating in an urban area in Cape Town, South Africa. The program is jointly funded by the state and a donor, Medecins Sans Frontieres. ART care was provided at three primary care clinics. ART was initiated by doctors but routine follow up was largely done by nurses. The clinics operated on a queue system and therefore patients would spend between 1–4 hours at the clinic. Counselors and peer-educators played an important role in educating and encouraging patients while they waited to see clinical staff. Most patients returned to the clinic every month to collect medicines, attend group or individual counseling sessions, and/or for clinical assessments. We included data from the inception of the program on 15 January 2000 until 25 Jan 2008.

The private-care cohort was the BroadReach Healthcare program, a donor-funded (President's Emergency Plan for AIDS Relief (PEPFAR)) managed-care ART program. Patients were recruited into the program at several urban and rural public sector clinics in the Mpumalanga, Eastern Cape and Kwazulu-Natal provinces in South Africa. ART care was provided by local contracted general practitioners (GPs) in their private practices on an appointment basis and visit frequency was pre-specified. The private doctors had to successfully complete internet-based training on the national ART guidelines before they could enroll patients. Telephonic counseling support for the patients and clinical guidance for the doctors was provided by Aid for AIDS, a private sector disease management program. Patients collected their medication from the doctors' rooms monthly, but clinical consultations were performed less frequently. We included data from the inception of the program on 1 May 2005 until 31 July 2010. New patient enrollment was stopped in March 2008.

In both cohorts severely ill or complicated patients were referred to secondary level public sector hospitals for further management and then re-integrated back into the program once their condition had stabilized. Data were entered prospectively into databases. Deaths were ascertained by several mechanisms: (1) clinic staff or private practice practitioners who learnt of a death from family members or friends, would either complete a specific form and fax it to a central office or capture it on a computer-based system onsite; (2) staff and program administrators identified patients who had missed several appointments and contacted a family member or treatment supporter of the patient to determine whether the patient was deceased and if so the date of death; and (3) the patient's South African identity number, where available, was used to cross-reference the South African national death register to establish whether a death was recorded.

We included adult patients (19 years and older) who started first line ART within the programs and had a baseline CD4 count below 200 cells/ μ L. The study intervals differed somewhat for each cohort, although the median year of starting ART was 2005 in both cohorts. A patient's follow-up period was truncated on the date they either: transferred out of the program, died, on the study end date, or on the last date seen if they were not seen within six months of the end of the study period and their identity number was not available (and we were therefore unable to ascertain whether they had died).

Healthcare utilisation and cost data

GP or clinic utilisation was determined from the electronic database records for both cohorts. The cost in South Africa Rands (ZAR) for a public-sector clinic visit was determined from a previously published estimate [4]. In that study, the unit clinic visit costs included time allocations for nurses, doctors, and counselors, and this has changed in more recent times due to increased task shifting. Together with improved economies of scale and learning by doing, cost would have fallen substantially had it not been for substantial increases in doctor's salaries over the same period. We therefore decided to only use the consumer price index table [8] to inflate costs to April 2010 levels. Private GP visit costs were determined from contracted rates in April 2010.

Drug utilisation was divided into first line (2NRTIs and NNRTI) and second line (2NRTIs and PI) therapy, and the average utilisation of each drug was determined within each line of therapy. Because estimates of ARV drug utilization were not available within our dataset, we conservatively assumed that all patients had received their ARVs each month and therefore allocated full monthly ARV drug costs within the ART model.

ARV drug costs were set at the public sector tender prices for April 2010.

There was some under-reporting of CD4 and VL monitoring, and ARV laboratory toxicity monitoring was not recorded in both programs. We conservatively assumed all patients underwent laboratory monitoring as per the South African public-sector guidelines. The guidelines recommended six monthly CD4 and VL monitoring. Laboratory toxicity monitoring, which occurred predominant in the first six months on ART, was limited to ZDV, NVP, and LPV/r. We scaled the specific toxicity monitoring utilisation associated with a specific ARV drug in accordance with its relative proportion within the two regimen lines. All laboratory costs were set at the public sector tender prices for April 2010. All costs were converted from ZAR to United States Dollars (USD) in April 2010 (7.34 ZAR per USD).

The Markov model framework, development and uncertainty analysis

WHO stage, current CD4, and current VL were identified as key determinants of lifetime costs and outcomes [9]. Many patients categorized as “LTFU” in studies return to ART care and therefore are not truly LTFU [10]. This is important as: (a) ART-related resources are not consumed while a patient is LTFU, (b) the CD4 count falls rapidly to pre-ART levels in patients who interrupt ART [11], (c) additional resources are consumed in patients restarting ART [9], (d) treatment interruptions increase resistance to first line regimens [9][9][9][9]9(9)(8), and (e) treatment interruptions increase deaths [9] and attenuate CD4 recovery [12].

We based the structure of the Markov model on these determinants of costs and outcomes as well as on our own analysis of the public-care program – the larger of the two cohorts. We implemented this Markov model in Treeage 2009 [13] and populated it with parameter estimates derived in Stata 11 [14] using survival models for time-to-event analyses and generalized linear models for clinic/GP utilisation. We evaluated the model fit and adjusted the model design where appropriate. Then, using the data from the private-care program, we derived new parameter estimates and evaluated the ability of the model to predict outcomes and costs. This procedure allowed us to assess the external validity of the model [4,15]. The model was run for two durations: 10 years and until all members of each cohort were dead (i.e. lifetime duration). Finally, we conducted probabilistic sensitivity analysis to assess uncertainty. This entailed specifying distributions on utilization and outcome parameters, where possible and propagating uncertainty through the model by way of first and second order Monte Carlo simulations. The models were run using a 1 month cycle length [16,17].

The Markov Model

The overall Markov model was divided into two parts: an ART model and a LTFU model (see figure 1). All patients started in the ART model, and remained there until they either died or became LTFU. Healthcare utilisation and mortality has been shown to be significantly higher in the first 6 months on ART [4,6]. Therefore the ART model was divided into two phases: 0–6 months on starting or restarting ART and >6 months on ART. We defined LTFU as defaulting ART for more than 6 months. Patients entering the LTFU model remained there until they either died or restarted ART. We used parametric survival analysis with an exponential distribution to determine the transition probabilities to outcomes (death, LTFU, CD4 category change, and VL category change), and generalized regression models to determine utilisation (GP and clinic visits) within the Markov states. Covariates

included time on ART, on-ART CD4 category, on-ART VL category, and year of starting ART (normalizing findings to 2005). We assumed that non-HIV related deaths of a typical individual (34 years) were included in the recorded deaths. We modeled the increasing relative contribution of non-HIV related deaths over time using the mortality curves for South Africa (less the typical mortality for a 34 year old adult) before the onset of South Africa’s HIV epidemic (prior to 1990).

In the first 6 months after starting or restarting ART, patients were split according to their pre-ART CD4 count category (0–49 or 50–199 cells/ μ L), and remained within this CD4 category for 6 months. At the end of 6 months, the remaining patients (i.e. not LTFU or dead) were distributed into the Markov states of the >6 months on ART model using a competing risks regression model with the pre-ART CD4 category as the only covariate. The >6 months on ART phase was defined by fifteen Markov states. These included: five on-ART CD4 categories (0–49, 5–199, 200–349, 350–499, and \geq 500 cells/ μ L) and three on-ART VL categories (<1,000; 1,000–99,999; and \geq 100,000 copies/mL). Within each Markov cycle, we limited transitions between these Markov states to either a CD4 or VL category change but not both, as this reduced model complexity.

We distributed patients entering the LTFU model into the two pre-ART CD4 categories (0–49 and 50–199 cells/ μ L) with the relative proportions being derived from the observed data. Given the limited LTFU data within our cohorts, we used the transition probability from the higher to the lower pre-ART CD4 category on a previously published natural history HIV model [4], and adapted the transition probabilities from these CD4 categories to death to match the observed trends in deaths within our cohorts. We used a regression model to determine the transition probability of restarting ART for patients LTFU, with time since first starting ART as the covariate.

The transition probability from first line to second line ART was determined separately within the two phases of the ART model and the covariates for the regression model included pre-ART CD4 category, on-ART VL category, on-ART CD4 category, and time since starting ART. Within the second line ART model all transition probabilities were the same as the first line ART model, but the ARV drug utilisation and therefore costs differed. Patients within the LTFU model were assigned no ART-related utilisation and therefore no costs.

Uncertainty analysis

We assessed the uncertainty in the data and model design using probabilistic sensitivity analysis (first and second-order Monte Carlo simulations). First-order simulations were used to capture the variability in the simulated population and tracked the varying paths taken by patients moving through the model in order. Second-order simulations were used to capture the variability in the parameter estimates by randomly sampling from the triangular-shaped distribution for the parameter, which approximated the 95% confidence interval. We ran 1,000 second-order and 10,000 first-order simulations to determine the 95% uncertainty intervals around the lifetime costs and outcomes. We assessed uncertainty related to extrapolation of the data and the generalizability of the model in three ways: (1) we externally validated the model derived from public-care cohort using the private-care cohort dataset, (2) we extrapolated our estimates over 10 year and life-time durations and compared the results, and (3) we compared our outcomes and cost estimates with other published studies. Finally, we assessed the uncertainty related to analytical methods by comparing the findings with 0% and 3% annual discounting of costs and outcomes.

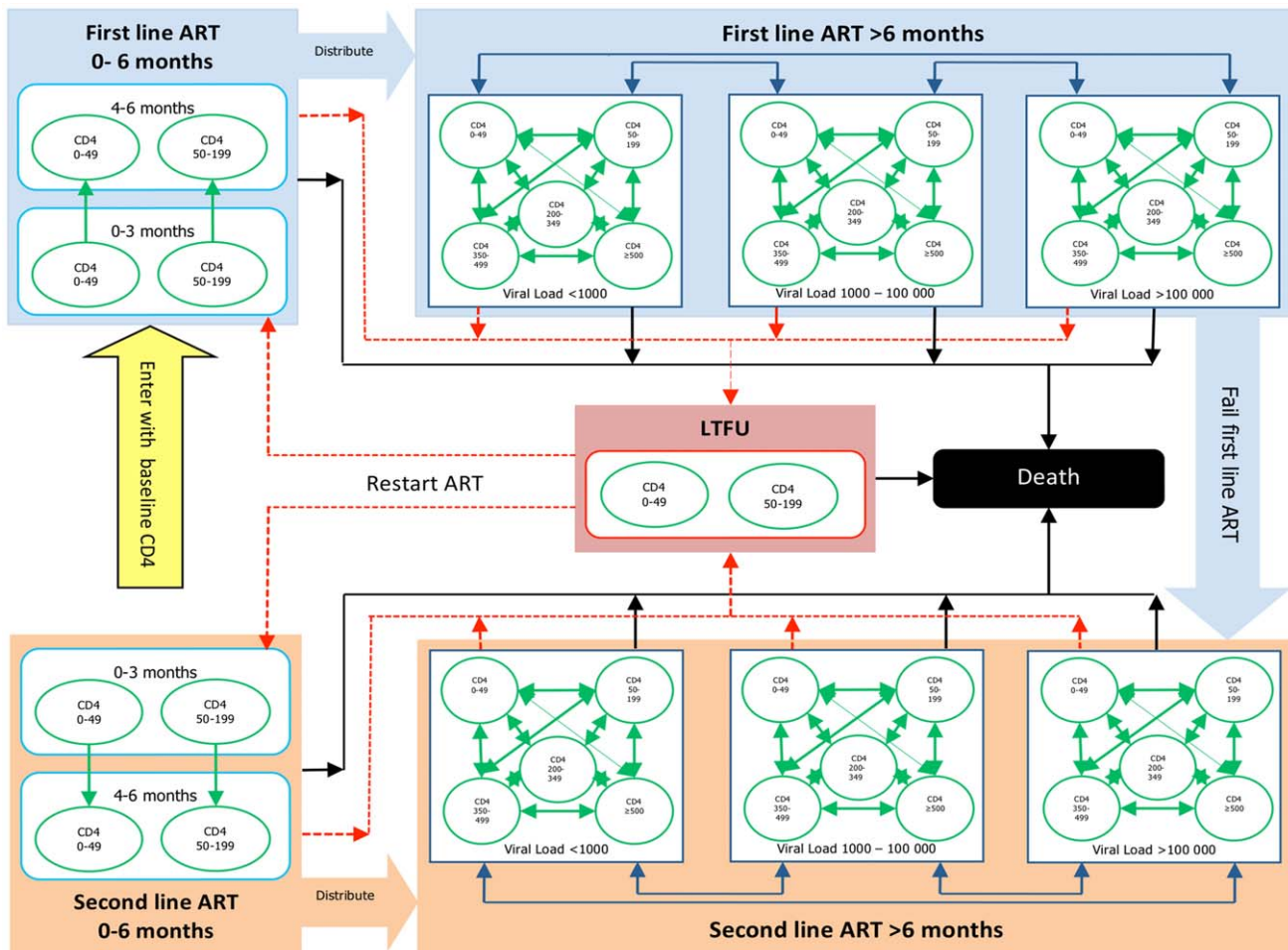


Figure 1. Markov model diagram.
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Scenario analysis

Clinic visit utilisation within the public-care program was intensive due to a policy decision by the program managers that all patients should be seen by a nurse or doctor every one to two months. In more recent years, the clinic visit utilisation has been substantially reduced to accommodate the growing number of patients. We therefore explored the impact of reduced clinic visit utilisation within the public-care program on the overall results.

Ethics statement

The study was approved by the Research Ethics Committee, University of Cape Town. All patients signed consent for their information to be entered into the central databases and analysed. Anonymity was ensured using generated identifiers and all personal data were deleted from the datasets.

Results

Cohorts

The characteristics and overall outcomes of the study cohorts are described in Table 1. We included 6372 and 963 patients from the public-care and private-care programs respectively. Median follow-up time on ART was shorter in the public-care cohort. No patients were transferred out to other facilities from the private-care program. The model fit diagnostics for both the private-care

and public-care programs are shown in figures S1 and S2 respectively. These include current CD4, current VL, line of therapy and status (current, LTFU or dead).

Health care utilization and unit costs in Markov states

Over the study period, 212,175 clinic visits in the public-care cohort and 10,477 GP visits in the private-care cohort were recorded. The contracted rate for a GP visit was 31.04 USD and the estimated cost of 24.53 USD for a clinic visit was derived by inflating the cost estimate from a previous publication [4]. The average monthly GP/clinic utilisation (with 95% confidence intervals) and the cost estimates are shown in table S1. Within both cohorts, utilisation was highest in patients restarting ART and, to a lesser extent, during the 0–6 months after starting ART, compared with the >6 months on ART phase. In this latter phase, monthly visit utilisation was lower in both cohorts. Importantly, the public-care cohort had approximately 2 to 4 times higher visit utilisation within the >6 months on ART phase compared with the private-care cohort.

The South African public sector guidelines were used for laboratory utilisation – the costs and utilisation are shown in table S2. CD4 and VL were taken 6 monthly, whilst other laboratory utilisation related to toxicity monitoring depended on the specific antiretroviral drugs and was higher in the first 6 months on ART.

Table 1. Cohort characteristics.

Characteristic	Khayelitsha	Broadreach
Numbers	6372	963
Age baseline (years)		
Median	33	34,9
IQR	(28,7 to 39,3)	(30,4 to 41,9)
Sex (%)		
Female	67,7	68,3
CD4 count (cells/ μ L) baseline		
Median	99	92
IQR	(44 to 161)	(44 to 146)
Unknown	435	3
Viral load (\log_{10}) baseline		
Median	5,1	5,1
IQR	(4,6 to 5,6)	(4,7 to 5,6)
Unknown	2941	241
Follow-up duration (months)		
Median	21,3	54,6
IQR	(11,7 to 33,4)	(29 to 57,8)
Status at end of study (%)		
Current	77,5	72,2
Transferred	6,3	0
LTFU	5,5	7,8
Deceased	10,6	20

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The utilisation of individual drugs within the first and second line ART regimens, the ART-related costs, and the hazard coefficients and transition probabilities for the model describing the transition between first and second line ART are shown in table S3 and figure S3. We assumed 100% utilisation of both ARV drugs and laboratory tests while within the ART model. The public-care cohort had higher zidovudine but lower efavirenz utilisation in the first line ART regimen. The public-care cohort had higher didanosine utilisation in the second line ART regimen. The transition probability of moving to second line ART was lowest in the 0–6 months after starting ART and highest in the 0–6 months after restarting ART. In the >6 month on ART phase, the transition probability of moving to second line ART decreased with lower VL and higher CD4 categories respectively, increased with time on ART and plateaued at about 3 years. The transition probabilities to second line ART were generally lower in the private-care cohort. The estimated distribution of time between first and second line ART was 61% and 39% in the public-care cohort versus 66% and 34% in the private-care cohort.

Effectiveness

The transition probabilities for the CD4 and VL models on ART are shown in table S4. The baseline CD4 category distribution for patients starting ART was similar in both cohorts: 30% in the 0–49 cells/ μ L category and 70% in the 50–199 cells/ μ L category. A lower baseline CD4 category was associated with a lower CD4 category distribution after 6 months on ART, but lower baseline CD4 category did not impact on the VL distribution. Public-care patients were more likely than private-care patients to have VL <1000 copies/ml (92% versus 87%) and

CD4 counts \geq 200 cells/ μ L (64% versus 42%) after the first 6 months on ART. This trend was similar for patients restarting ART, but the outcomes were worse: 61% and 43% had VL <1000 copies/ml, and 49% and 63% had CD4 counts <200 cells/ μ L for patients in the public-care and private-care cohorts respectively.

The transition probabilities and hazard coefficients for deaths on ART are shown in table 2. The transition probability to death was highest in the first 3 months on ART and in patients with a low pre-ART CD4 category. The transition probability to death was lowest for the first 6 months after restarting ART. For patients in the >6 months on ART phase, the transition probability to death decreased with lower VL category, higher CD4 category, and time on ART (using a Gompertz time function). The median of the Gompertz time function was 20 months in both cohorts, but the scaling constant was higher in the private-care cohort (1.19 versus 1.04). Thus there were more early deaths in the private-care cohort.

The hazard coefficients and transition probabilities related to the LTFU model are shown in table 3. The transition probability from ART to LTFU was lowest in the first 6 months after starting ART and highest in the first 6 months after restarting ART. Thereafter, the transition probability from ART to LTFU increased with higher VL category, lower CD4 category, and time on ART. We modeled the effect of time on ART by adapting the Gompertz function so that it plateaued. The median of the adapted Gompertz function was longer (12 months versus 8) and the scaling constant has higher (1.5 versus 0.5) in the public-care compared with the private-care cohort. We distributed patients entering the LTFU model as follows based on our analysis of the data: 30% to the 0–49 cells/ μ L and 70% to the 50–199 cells/ μ L CD4 categories. The transition probability from LTFU to restarting ART was higher in the private-care cohort (26% versus 13%) and independent of LTFU CD4 category.

The highest death rates were observed within the first year on ART for both cohorts, especially in the private-care cohort: 8% and 15% had died by 12 months and 32% and 39% had died by 120 months in the public-care and private-care cohorts respectively. The distribution of VL categories stabilized by 3 years to 90% and 85% of patients having a VL <1000 copies/ml within public and private-care cohorts respectively. The distribution of CD4 categories was more dynamic over time and the private -care cohort fared better with 50% versus 40% of patients having a CD4 \geq 500 cells/ μ L by 10 years. The percentage of patients who were alive and still on ART stabilized at approximately 80% for both cohorts, although the private-care cohort achieved this earlier due to generally higher transition probabilities to and from LTFU.

Ten-year and lifetime costs, outcomes, probabilistic sensitivity and scenario analysis

We ran Monte Carlo simulations for 10 years and until everyone had died to generate lifetime costs and outcomes together with their 95% confidence intervals, as shown in table 4. The conclusions we derived from the 10 year and lifetime estimates (with and without discounting) were congruent: the private-care program was approximately as effective, but was less costly than the public-care program. These reduced costs were predominantly driven by the lower level of utilisation in the private-care program. Given that the outcomes between the two programs were not significantly different, this finding suggests that reduced visit utilization has the potential to be cost saving (reducing costs without impacting on patient outcomes).

When we reduced the frequency of clinic visits in the >6 months on ART phase by two-thirds in the public-care program (in line with the changes introduced in late 2011 by the

Table 2. Transition probabilities and hazard coefficients for deaths on antiretroviral therapy.

Variables	Transition probabilities and hazard coefficients (95% CI) per 1 month cycle		
	Public-care	Private-care	
First 6 months after starting antiretroviral therapy			
Transition probability			
3 months CD4 0–49 cells/μL	0,035 (0,029 to 0,044)	0,040 (0,029 to 0,056)	
3 months CD4 50–199 cells/μL	0,010 (0,008 to 0,012)	0,017 (0,013 to 0,022)	
6 months CD4 0–49 cells/μL	0,011 (0,010 to 0,014)	0,027 (0,021 to 0,036)	
6 months CD4 50–199 cells/μL	0,003 (0,003 to 0,004)	0,011 (0,009 to 0,014)	
First 6 months after restarting antiretroviral therapy			
Transition probability: 0–6 months	0,008 (0,004 to 0,016)	0,004 (0,001 to 0,010)	
>6 months on antiretroviral therapy			
Hazard coefficient due to CD4 and VL			
CD4 0–49 cells/μL	VL <1,000 copies/ml	–5,01	–5,03
CD4 0–49 cells/μL	VL 1,000–100,000 copies/ml	–4,71	–4,69
CD4 0–49 cells/μL	VL >100,000 copies/ml	–3,83	–4,13
CD4 50–199 cells/μL	VL <1,000 copies/ml	–6,00	–6,5
CD4 50–199 cells/μL	VL 1,000–100,000 copies/ml	–5,69	–6,16
CD4 50–199 cells/μL	VL <1000 copies/ml	–4,82	–5,6
CD4 200–349 cells/μL	VL >100,000 copies/ml	–7,25	–7,48
CD4 200–349 cells/μL	VL 1,000–100,000 copies/ml	–6,94	–7,14
CD4 200–349 cells/μL	VL <1000 copies/ml	–6,07	–6,58
CD4 350–499 cells/μL	VL >100,000 copies/ml	–7,63	–8,53
CD4 350–499 cells/μL	VL 1,000–100,000 copies/ml	–7,32	–8,19
CD4 350–499 cells/μL	VL >100,000 copies/ml	–6,45	–7,63
CD4 ≥500 cells/μL	VL <1,000 copies/ml	–7,76	–8,16
CD4 ≥500 cells/μL	VL 1,000–100,000 copies/ml	–7,46	–7,82
CD4 ≥500 cells/μL	VL >100,000 copies/ml	–6,58	–7,26
Hazard coefficients for Gompertz function			
alpha	0,93 (0,52 to 1,34)	1,73 (1,17 to 2,28)	
beta – half-life (months)	20	20	

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program administrators), the estimated 10-year and lifetime costs within the public-care program approximated the levels observed in the private-care program. In other words, the programs were equivalent in terms of costs and outcomes.

Discussion

We determined that the private-care program had lower costs and similar outcomes to the public-care program at the time of the study using a novel Markov model. Key differences between the programs were less frequent visits and higher rates of returning to care after loss to follow-up in the private-care program, and lower early death rates on ART, but more deaths while LTFU in the public-care program. We estimated that the recent shifts towards less frequent visits in the public-care ART program would achieve large cost savings, making the costs of the two programs similar. These findings suggest that properly managed private-care programs can ease the burden of ART care in endemic countries by looking after public sector patients without increasing costs. Further, reducing clinic visits may be a viable strategy to save costs while maintaining outcomes in public sector programs.

Our Markov model included several significant improvements on previously published models [4,18–22]. First, we separated out the first six months on ART, as outcomes and costs in this period are driven by baseline CD4 count and program protocols (higher frequency of clinic visits and toxicity monitoring) [6]. Second, we developed a novel LTFU model, in which patients transitioned between ART and LTFU, changed baseline CD4 count within LTFU, and transitioned to death within LTFU. Third, we developed Markov models to account for CD4 and VL category changes within the ART and LTFU models. Fourth, we developed a more detailed model describing the transition between first line and second line ART, which is a major cost driver [23]. Fifth, the model included the impact of time on ART on the transition to LTFU, death, and second line ART. Finally, we assessed the external validity of the model by first developing the model using the public-care program data and then validating it using private-care program data. The fact that our novel Markov model was able to describe the data from two very different models of ART care suggests that its utility may be generalizable.

We are aware of one other study that compared costs and outcomes after 1 year in public-care and private-care programs for

Table 3. Transition probabilities and hazard coefficients related to loss to follow-up.

Variables	Transition probabilities and hazard coefficients (95%) per 1 month cycle		
	Public-care		Private-care
Transitions within ART model			
Transition probability to LTFU within 0–6 months on ART			
On starting ART	0,0085 (0,0080 to 0,0091)		0,0006 (0,0006 to 0,0006)
On restarting ART	0,0270 (0,0205 to 0,0356)		0,0251 (0,0251 to 0,0251)
Hazard coefficient to LTFU within >6 months on ART			
CD4 0–49 cells/μL	VL <1,000 copies/ml	–4,7	–5,13
CD4 0–49 cells/μL	VL 1,000–100,000 copies/ml	–3,79	–4,16
CD4 0–49 cells/μL	VL >100,000 copies/ml	–4,00	–4,37
CD4 50–199 cells/μL	VL <1,000 copies/ml	–5,31	–5,44
CD4 50–199 cells/μL	VL 1,000–100,000 copies/ml	–4,4	–4,47
CD4 50–199 cells/μL	VL <1000 copies/ml	–4,61	–4,68
CD4 200–349 cells/μL	VL >100,000 copies/ml	–5,73	–4,52
CD4 200–349 cells/μL	VL 1,000–100,000 copies/ml	–4,82	–3,56
CD4 200–349 cells/μL	VL <1000 copies/ml	–5,03	–3,76
CD4 350–499 cells/μL	VL >100,000 copies/ml	–5,73	–4,52
CD4 350–499 cells/μL	VL 1,000–100,000 copies/ml	–4,82	–3,56
CD4 350–499 cells/μL	VL >100,000 copies/ml	–5,03	–3,76
CD4 ≥500 cells/μL	VL <1,000 copies/ml	–5,73	–4,52
CD4 ≥500 cells/μL	VL 1,000–100,000 copies/ml	–4,82	–3,56
CD4 ≥500 cells/μL	VL >100,000 copies/ml	–5,03	–3,76
Hazard coefficients for Gompertz function			
alpha	1,5		0,5
beta – half-life (months)	12		8
Initial distribution within LTFU model			
CD4 0–49 cells/μL	0,278 (0,255 to 0,302)		0,243 (0,217 to 0,269)
CD4 50–199 cells/μL	0,722 (0,745 to 0,698)		0,757 (0,783 to 0,731)
Transitions within LTFU model			
Transition probability between CD4 category			
CD4 50–199 to CD4 0–49 cells/μL	0,005 (0,005 to 0,005)		0,006 (0,006 to 0,006)
Transition probability back to ART			
CD4 0–199 cells/μL	0,134 (0,128 to 0,141)		0,146 (0,139 to 0,154)
Transition probability to death			
CD4 0–49 cells/μL	0,006 (0,005 to 0,008)		0,006 (0,005 to 0,008)
CD4 50–199 cells/μL	0,001 (0,001 to 0,017)		0,001 (0,001 to 0,017)

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Table 4. 10 year and lifetime estimates of cost and outcomes of the private-care and public-care programs.

Treatment option	10 year estimates		Lifetime estimates	
	Costs (95% CI) in USD	Life years gained (95% CI)	Costs (95% CI) in USD	Life years gained (95% CI)
Undiscounted				
Public-care	8,825 (8,614 to 9,036)	7.6 (7.4 to 7.8)	18,734 (17,385 to 20,083)	14.1 (13.2 to 15.0)
Private-care	6,187 (5,997 to 6,377)	7.2 (7.0 to 7.4)	13,062 (12,077 to 14,047)	14.0 (13.1 to 14.8)
Discounted				
Public-care	7,688 (7,513 to 7,863)	6.7 (6.5 to 6.8)	13,305 (12,588 to 14,022)	10.4 (9.9 to 10.9)
Private-care	5,407 (5,250 to 5,564)	6.3 (6.2 to 6.5)	9,273 (8,704 to 9,842)	10.0 (9.4 to 10.5)

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public sector patients [24]. Their private-care program had significantly lower costs due to fewer GP visits and poorer patient retention than their public care program. The costs of providing ART care were similar, although patient retention was better in our programs. Lifetime analyses using Markov models populated with data from resource-limited settings predicted varying survival on ART (6 to 13 years) and varying discounted total costs (3,000 to 9,500 USD from the provider's perspective) [16,18,21–23,25,26]. Many of these models were developed using short term follow up data. Furthermore, retention within ART programs and cost of providing ART care in resource-limited settings varies dramatically [27,28]. We estimated that average survival on ART was longer than most resource-limited setting model estimates.

The patients included in this analysis were public-sector patients receiving ART care in accordance with WHO public sector ART program guidelines. Therefore the results from this analysis have important policy implications that are relevant to other resource-limited settings. The rapid expansion of access to ART in resource-limited settings is both needed [29] and challenging [30]. Our findings suggest that managed private-care for public sector patients could be used to increase access to ART, provided that the private practices follow national protocols and that loss to follow-up is managed – key components of the private-care program in our study. A similar model was implemented in Botswana to expand access to ART in areas where limited public-sector resources were available, by utilising doctors working in private practice to look after public sector patients [2]. Their findings suggested that ART care coverage was extended by 10% and public-sector programs were strengthened by the interaction [2]. We found that reduced utilisation of clinic visits, especially after the initial six months of care, would considerably lower costs of public-care programs. Finally, our model predicted that LTFU contributed significantly to deaths, utilisation of ART-related resources (on restarting ART), and attenuated CD4 recovery. This suggests that focusing on reducing LTFU could be a cost-saving strategy.

There were several limitations to our study. First, the findings in our study are based on a model that extrapolated the trends we observed over the first 3–5 years on ART predominantly. Second, we limited costs in this study to direct ART care costs, while the other components of care represent a significant portion of total costs [31]. Data on these other cost components were not available. Third, we did not account for the impact of adherence on the total cost of ART drugs, nor the changing composition of specific drugs within the therapy lines over time [31,32]. Fourth, given the limited data on actual laboratory utilisation, especially for toxicity monitoring, we set the laboratory utilisation to those recommended in national guidelines. Fifth, it is likely that the patients within the public-care program had better access to HIV clinic services than typical public-sector patients in South Africa, and this would have increased costs, and possibly enhanced patient retention and improved outcomes [33]. Sixth, the relative proportions of individual drugs within the lines of therapy differed between cohorts: *the average ART costs were marginally lower in the private-care program and the different regimens may have impacted the outcomes*. Seventh, given the different models of ART care and different settings in which the programs were based, these programs were not completely comparable and therefore the overall conclusions in terms of costs and outcomes cannot be regarded as definitive. Finally, our public sector clinic visit cost was based on secondary data, which may not capture recent programmatic changes in ART provision (including task shifting) and economies of scale and scope. However, it is difficult to predict

the extent to which this unit cost may under or overestimate costs. In moving towards universal access to ART, South Africa intends to offer ARVs from all primary care facilities, which will have implications for the efficiency of service provision and the resulting unit cost. Economies or diseconomies of scale can equally arise in small new facilities during start-up and in older large facilities with high patient volumes.

While analyses of provider costs and patient outcomes are crucial in guiding resource allocation for HIV care, it is equally important to consider barriers to patient access, particularly within the context of lifelong care [34]. Evidence suggests that the key barriers to ongoing ART care include the cost of transport to facilities as well as the opportunity cost associated with long waiting times in facilities [34,35]. Less frequent visits would mitigate these access barriers. One advantage of private care is that waiting times are usually shorter.

Conclusions

In conclusion, we have developed a novel Markov model that has the potential to improve the accuracy of estimations of future costs and outcomes of long-term ART care. We have used this model to evaluate two ART programs, and have shown that managed private-care ART programs have the potential to complement the public sector platform in resource poor settings, thereby enhancing and sustaining coverage of patients in need. Our findings suggest that cost savings could be achieved through reducing clinic utilization without compromising patient outcomes.

Supporting Information

Figure S1 Model calibration curves for the public-care ART program.

(TIF)

Figure S2 Model calibration curves for the private-care ART program.

(TIF)

Figure S3 Survival hazard coefficient for switching from first to second line therapy over time since starting antiretroviral therapy.

(TIF)

Table S1 General practitioner and clinic visit utilisation and costs on antiretroviral therapy within the private-care and public-care programs respectively.

(XLS)

Table S2 Laboratory costs and utilisation on antiretroviral therapy.

(XLS)

Table S3 The composition and costs of first line and second line antiretroviral regimens, and transition probabilities and coefficients for transitioning from first line to second line regimen.

(TIF)

Table S4 Transition probabilities and hazard coefficients of changes in CD4+ cell counts and viral load on antiretroviral therapy.

(XLS)

Author Contributions

Conceived and designed the experiments: RL GM MH JS ED SC. Performed the experiments: RL GM MH JS ED SC. Analyzed the data:

RL GM MH JS ED SC. Contributed reagents/materials/analysis tools:
 RL GM MH JS ED SC. Wrote the paper: RL GM MH JS ED SC.

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Chapter 9: Conclusion

9.1 Overview

In light of the 90-90-90 goals for 2020, it is crucial that LMICs address barriers to screening, ART initiation, adherence to ART, and retention in care if they are to eradicate the epidemic by 2030 [1]. In this thesis, we present a collection of studies focusing on the outcomes and cost-effectiveness of different models of ART delivery in South Africa. The focus on different models of ART delivery is relevant given that only 56% of the estimated 7.1 million PLWH in South Africa were accessing ART in 2016 [2] and yet many of the public sector clinics are already congested. This thesis presents novel approaches, including the possibility of home-refill by courier or using GPs to treat public sector patients, thereby reducing the burden faced by primary health care services while simultaneously improving patient outcomes. Such approaches are required both to reach the untreated and retain treated PLWH in resource-limited high-burden settings like South Africa [3].

The data for the studies presented in this thesis come from a variety of South African programmes, from which cohort data were extracted and prepared for analysis. This involved working closely with the programme administrators to extract and prepare the cohort dataset with an understanding of the various limitations and strengths of these data systems. The importance of real-world or observational data and their potential to inform policy decisions have been established [4, 5]. Working with these data, however, presents several challenges. For example, in the case of claims data from the AfA programme, this process was significant given the sheer volume of the data and the difficulty of assigning nearly 50,000 distinct items into sensible categories. A summary of these data and the methodologies is presented in Chapter 3, together with a cohort profile in chapter 4 of adults within the AfA programme. While the majority of patients receiving care through AfA were of black ethnicity and from South Africa, their socio-economic status would have been significantly better than that of most South Africans accessing HIV care through the public sector clinic system. The choice of antiretroviral drugs was also different. Therefore, given that the findings were based on observational data and included private sector programme data, their generalizability into public sector HIV programmes remains uncertain.

This thesis is presented as a series of studies, which together represent the typical journey followed within an economic evaluation, starting with source data, from which a cohort is established, then onto cost and outcome analyses and, finally, the development of a Markov model for the purpose of establishing the cost-effectiveness of a particular intervention for the purpose of informing policy at a national level.

In Chapter 5, a detailed cost analysis is presented, including the period leading up to ART initiation, which is not typically available for large numbers of patients in LMICs. The determinants of early and late costs are explored within the same chapter. In Chapter 6, an outcome analysis of a potential model of care for HIV patients is presented. In this analysis, we compare CD4 count, VL response, and survival on ART in home-refill by pharmacy and self-refill. In Chapter 7, an outcome analysis and cost analysis is presented, together with a literature review of Markov models from LMIC settings. The intention of this chapter is to provide a foundation for the establishment of a Markov model, the most common framework for evaluating cost-effectiveness. Finally, in Chapter 8, a novel Markov model is presented, where we compare the costs, outcomes, and cost-effectiveness of GPs versus standard of care (i.e., a primary HIV clinic in Cape Town) for public sector patients starting ART.

9.2 Key findings

In **Chapter 5**, we described the costs of HIV treatment and related care, taking into account the patients' CD4 and timing relative to starting ART (before, around, and long-term after starting ART). We found that variables associated with higher mean total costs changed considerably over time. Starting ART at higher CD4 counts or longer pre-ART care should reduce early costs. Monitoring ART adherence and implementing interventions to improve it should reduce later costs. Cost models of ART should take into account these time-dependent cost drivers and include costs before starting ART.

In **Chapter 6**, we compared home-refill by courier pharmacy with self-refill outcomes and found CD4 response, VL suppression rates, and adjusted survival (hazard ratio 0.90, 95% CI: 0.70–0.91) were improved in the home-refill group. Moreover, median CD4 count (390 versus 363 at 2 years and 483 versus 414 at 4 years) and viral suppression (81% versus 71% at 2

years and 82% versus 69% at 4 years) were significantly higher in those that switched from self-refill to home-refill.

In **Chapter 7**, the key variables associated with changes in mean monthly costs were: being on the second line regimen; receiving ART from 4 months prior to 4 months post-treatment initiation; having a recent or current CD4 count <50 cells/ μ L or 50-199 cells/ μ L; having mean ART adherence <75% as determined by monthly pharmacy refill data; and having a current or recent viral load >100,000 copies/mL. In terms of the likelihood of dying, the key variables were: baseline CD4 count <50 cells/ μ L (particularly during the first 4 months on treatment); current CD4 count <50 cells/ μ L and 50-199 cells/ μ L (particularly during later periods on treatment); and being on the second line regimen. The findings were informed by standard statistical approaches (i.e., GLM, survival model) but alternative approaches could include machine learning, which focuses more on data than hypotheses and is less vulnerable to missing priors.

In **Chapter 8**, we applied the lessons from Chapter 7 and built a Markov Model. Clinic visit utilization was higher, and death rates were lower in the first few years on ART in the public care compared with the private care programme. The model analysis found lifetime undiscounted survival estimates were 14.1 (95% CI 13.2–14.9) and (95% CI 12.7–14.5) years with costs of USD 18,734 (95% CI 12,588–14,022) and USD 13,062 (95% CI 12,077–14,047) in the private care and public care programmes respectively. When clinic visit utilization in the public care programme was reduced by two-thirds after the initial 6 months on ART, which is similar to current practice, the costs of the programmes were comparable.

9.3 Strengths and limitations of the studies

The focus of this thesis on models of ART delivery and the inclusion of under-represented or novel models, namely using private GPs to care for public sector patients and home-refill by courier pharmacy, respectively, are significant strengths of this thesis. There are few published studies on these approaches to patient care from which to inform policy, and the positive findings lend support to those wishing to undertake the necessary pilot studies to validate these associations. Improving patient outcomes and retention through differentiated models of care is key if we are to achieve the 90-90-90 UNAIDS goals, especially in LMICs where the burden of

disease as well as the impact of socioeconomic status on the ability to access care are significant. Moreover, the NHI plan for South Africa seeks to draw in the private sector and engaging with strategies such as those presented in this thesis (using private GPs to treat public sector patients and courier pharmacy companies to dispense chronic medications) approaches would seem to be positive for both patients and providers of health care in LMIC settings.

The major limitation of this body of work is that it is based on observational data and, therefore, the findings are subject to the limitations of selection bias and non-similarities in the cohorts and comparison groups. We were rigorous in the methodologies we applied but were constrained by confounder variables available for the analyses and the settings in which the studies were based. Marginal structural models offer a means of improving the robustness of the calculations and therefore could better inform policy and clinical trial decisions. The approach of using cohort data – in combination with rigorous methodologies – to inform policy is relevant given the contracting donor funding for research and operational systems in Africa. Furthermore, we were able to extract significantly more detailed and comprehensive cost data from the private sector cohort than is usually available in public sector settings. While the magnitude of the effects would be likely to differ in other settings, the variables influencing costs and survival in private settings are likely to be generalizable and therefore relevant to public sector programmes.

9.4 Policy recommendations

Our data have important clinical and public health implications for South Africa and other resource-limited settings. In spite of the limitations of the methodologies and datasets, these studies were able to influence policy decisions and shape the direction of future research because of the importance of research in ART delivery models and the limited availability of published research on the topic in LMIC settings.

An ART delivery model should be considered part of the emerging differentiated service delivery (DSD), a patient-centred approach that simplifies and adapts services across the HIV-cascade to reflect the preferences and expectations of different PLWH sub-populations while reducing unnecessary burdens on the health system [6]. Adherence to ART is complex and likely to be confounded; the burden that can be associated with self-ART refills is significant (travel to

a clinic for ART refills, long waiting time, loss of a day job, etc.) [7, 8], and therefore home delivery of ART represents a possible effective intervention to improve clinical outcomes while reducing patient burden in clinics in LMICs. An existing public-sector initiative within the Western Cape, South Africa, where a central pharmacy already prepares chronic medication “packs” to speed up existing clinic-based dispensing, could be adapted to include home-delivery for patients to alleviate clinic congestion and patient costs incurred in attending the clinic to collect ARVs [9]. With the aging of the HIV population and increasing incidence of non-communicable disease (NCD) co-morbidities [10], such home delivery models can include other chronic medication (e.g., hypertension, diabetes) [11].

A GP model for ART delivery for public sector patients has been successfully implemented in other resource-limited settings like Botswana [12]. Our findings suggest that such a model is cost-effective (saving costs and generating additional benefits) and should, therefore, be considered in South Africa. The findings are particularly relevant in view of the intention to incorporate private doctors, hospitals, administrators, and medical schemes into the NHI.

9.5 Recommendations for future research

1. Further research is needed to confirm the findings that home-refill by courier for the provision of ART in a public sector setting is indeed associated with improved outcomes. We are currently developing a marginal structural model (MSM) which will allow those who switched from home-refill by courier to self-refill to be included in the regression analysis. If the findings of an MSM analysis prove similar, we would recommend a pilot study be conducted to determine the impact in the public sector.
2. Further research is also needed to establish the cost-effectiveness of home-refill by courier for the provision of ART in a public sector setting in light of the positive findings in Chapter 6 and literature on adherence clubs. Ensuring adequate patient adherence to ART and retention in care through novel strategies is critical if we are to eliminate the HIV epidemic. Home-refill by courier would likely be associated with higher ART costs due to higher dispensing rates; given that less than 100% of medicine is collected in a self-refill setting, the outcome of the cost-effectiveness analysis will be uncertain.

3. Further research is needed on the impact and costs of centralized dispensing systems for public sector clinics (e.g., the Chronic Dispensing Unit in the Western Cape, South Africa, which simplifies dispensing for the pharmacist and shortens waiting times at public sector clinics in the Western Cape) [13].
4. Ongoing research is being conducted on a GP model for ART delivery in South Africa in anticipation of NHI implementation [14].
5. Further research is needed on the relationship between HIV and other chronic illness requiring ongoing medication as polypharmacy in itself creates further pill burden and, in some cases, additional visits. There is a renewed drive within government to launch the NHI in South Africa and independent GPs are key resources which have remained untapped in South Africa [15].

9.6 References

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Appendix 1:
Ethics approvals



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925

Telephone [021] 406 6492 • Facsimile [021] 406 6411

Email: nosi.tsama@uct.ac.za

Website: www.health.uct.ac.za/research/humanethics/forms

05 March 2015

REF NO: R007-2015

Prof G Maartens
Clinical Pharmacology
K-45
Old Main Building

Dear Prof Maartens

PROJECT TITLE: AID FOR AIDS AND MEDSCHEME COHORT, DIVISION OF CLINICAL PHARMACOLOGY, UCT

Thank you for submitting your Database to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for approval.

The HREC has **approved** the registration of your database.

The registration of this database is valid until 30 March 2018.

Please provide the HREC with an update if the registry continues beyond this period.

Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

Please provide the HREC with an update if the registry continues beyond this period.

Please quote the HREC REF in all your correspondence.

Yours sincerely

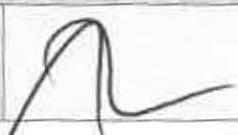
PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:R007-2015



FHS017: Annual Progress Report / Renewal

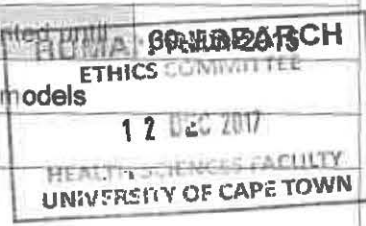
Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30/12/18
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC			Date Signed: 13/12/2017

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14 July 2017		
HREC REF Number	389/2008	Current Ethics Approval was granted until	30/12/2018
Protocol title	Development of African HIV economic and disease models		
Principal Investigator	Gary Maartens		
Department / Office Internal Mail Address	Division of Clinical Pharmacology K floor, OMB		
1.1 Does this protocol receive US Federal funding?			<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



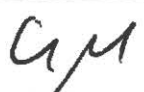
2. Protocol status (tick ✓)

<input type="checkbox"/>	Research-related activities are ongoing
<input checked="" type="checkbox"/>	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	
557/2013 - Survival of adults with HIV infection or Type 2 diabetes in the South African private sector	
074/2010 - Improving outcome ascertainment for retrospective cohort analyses of antiretroviral therapy programmes through linkages to South Africa vital Registration data	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	
Total number of records or specimens collected, reviewed or stored since last progress report	
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4. Signature

Signature of PI		Date	6 December 2017
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Appendix 2:

Aid for AIDS registration form submitted for database registration



Application Form Confidential

AfA does not dispense medication - Please fax this completed form to 0800 600 773 or email it to afa@afadm.co.za

This page needs to be completed by - **The Applicant** | Applications will be rejected unless signed by both Applicant and Doctor

Principal (Main) Member Details

First Name	<input type="text"/>	Surname	<input type="text"/>
Medical Scheme	<input type="text"/>	Gender	<input type="checkbox"/> MALE <input type="checkbox"/> FEMALE
Membership No.	<input type="text"/>	Option / Plan	<input type="text"/>

Patient Details

First Name	<input type="text"/>	Surname	<input type="text"/>
Dependant Code	<input type="text"/>	Gender	<input type="checkbox"/> MALE <input type="checkbox"/> FEMALE
ID Number	<input type="text"/>	Date of Birth	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

Treatment Support is a vital part of the AfA programme. Contact details must be supplied to enable us to provide you with this support.

Confidential Email	<input type="text"/>		
Postal Address for confidential mail	<input type="text"/>		
Postal Code	<input type="text"/>	Telephone(Home)	<input type="text"/>
Fax No.	<input type="text"/>	Telephone(Work)	<input type="text"/>
Preferred form of communication	<input type="checkbox"/> EMAIL <input type="checkbox"/> FAX <input type="checkbox"/> POST	Cellphone	<input type="text"/>
What time of day is the best time for AfA to contact you?	<input type="checkbox"/> MORNING <input type="checkbox"/> AFTERNOON	First Language	<input type="text"/>
		Second Language	<input type="text"/>

Next of kin or buddy who can be contacted if we cannot reach you (should know your HIV status)

First Name	<input type="text"/>	Telephone(Home)	<input type="text"/>
Surname	<input type="text"/>	Telephone(Work)	<input type="text"/>
		Cellphone	<input type="text"/>

I understand that all personal clinical information supplied to the Aid for AIDS (AfA) programme will be used to determine access to specific benefits for people with HIV infection. AfA will take all reasonable steps to maintain confidentiality. The programme's medical staff will review this information in order to make recommendations regarding the provision of these benefits. Your doctor, however, retains responsibility for your care, irrespective of the benefits so authorised.

I/we therefore, authorise any doctor, hospital, clinic, laboratory and/or medical facility in possession of any medical information regarding myself, the applicant or any dependant (also newly born baby), to provide the AfA programme with information that it may require. I warrant that the information in this application form is correct.

I acknowledge that completion of the application form does not automatically entitle me to any benefits and that acceptance to the programme is within the sole discretion of AfA. I acknowledge that I am familiar with the conditions and benefits of the programme, notwithstanding representation by any other party; and agree to abide by and undertake to familiarize myself with the rules of the programme as amended from time to time. I acknowledge that benefits authorised by the AfA programme are subject to scheme rules and that non adherence to the programme could result in my benefits from this programme being cancelled. I acknowledge that I will be responsible for any co-payments as per scheme rules or payment for any medication and/or investigations not authorized by AfA.

I understand that acceptance onto Aid for AIDS means that an AfA treatment support counsellor will contact me.

I herewith authorize AfA and its agents/medical staff to disclose the medical information relevant to my HIV infection to third parties for the purpose of scientific, epidemiological and/or financial analysis without disclosure of my identity.

Patient's Signature

Date

Medical Aid No:	Dep Code:	Patient Name:	Page 1 of 4
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Application Form Confidential

AfA does not dispense medication - Please fax this completed form to 0800 600 773 or email it to afa@afadm.co.za

This page needs to be completed by - **The Doctor**

Doctor Details

Surname & Initials	<input type="text"/>	Practice No.	<input type="text"/>
Email Address	<input type="text"/>		
Postal Address	<input type="text"/>		
Postal Code	<input type="text"/>	Telephone	<input type="text"/>
Preferred form of communication	EMAIL	FAX	POST
	Cellphone <input type="text"/>		
	Fax <input type="text"/>		

Clinical History

When was HIV infection first diagnosed? (Please attach reports)

Type of screening test	<input type="text"/>	Test date	D D M M Y Y Y Y
Type of confirmatory test	<input type="text"/>	Test date	D D M M Y Y Y Y
Is the patient currently being treated for tuberculosis?	YES NO	If YES, specify start date	D D M M Y Y Y Y

Has the patient previously been exposed to antiretrovirals? YES - MTCT prophylaxis YES - Other NO

If YES, please provide details - Note: If the application is for a baby please list mom's previous ART history.

Drugs	Start Date	End Date	Duration (Months)	Reason for discontinuation

Current combination patient is taking Start Date D D M M Y Y Y Y

Please list all other medication the patient is taking, including prophylaxis

Is the patient allergic to any medication? Sulphonamides YES NO Other allergies? YES NO If YES, specify

Information required to prevent adverse side-effects of certain drugs

Current heavy alcohol intake? (i.e. more than 4 drinks per day for a long period of time)	YES NO
Current recreational drug use? (Cannabis, Cocaine, Ecstasy, LSD etc.)	YES NO
Current depression or psychiatric illness?	YES NO
If YES, specify treatment	<input style="width: 200px;" type="text"/>
Current use of traditional or herbal remedies?	YES NO

AfA does not dispense medication - Please fax this completed form to **0800 600 773** or email it to **afa@afadm.co.za**

This page needs to be completed by - **The Doctor**

Clinical Examination

Weight kg

Height cm

WHO Clinical Staging

1	2	3	4
---	---	---	---

Please tick disease below if Stage 3 or 4

Pregnant

YES	NO
-----	----

If YES, specify:

Expected date of delivery

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Expected mode of delivery

NVD	C/S
-----	-----

Expected date of C/S

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Clinical Stage 3 - Adult / Adolescent

Unexplained severe weight loss (>10% of body weight)	
Unexplained chronic diarrhoea > one month	
Unexplained persistent fever > one month	
Persistent oral candidiasis	
Oral hairy leukoplakia	
Pulmonary tuberculosis	
Severe bacterial infections (e.g pneumonia)	
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	
Unexplained anaemia, neutropaenia, chronic thrombocytopenia	

Clinical Stage 3 - Paediatric

Unexplained moderate malnutrition	
Unexplained persistent diarrhoea (14 days or more)	
Unexplained persistent fever > one month	
Persistent oral candidiasis (after first 6 weeks of life)	
Oral hairy leukoplakia	
Acute necrotizing ulcerative gingivitis / periodontitis	
Lymph node TB	
Pulmonary TB	
Severe recurrent bacterial pneumonia	
Symptomatic lymphoid interstitial pneumonitis	
Chronic HIV-associated lung disease including bronchiectasis	
Unexplained anaemia, neutropaenia, chronic thrombocytopenia	

Clinical Stage 4 - Adult / Adolescent / Paediatric

HIV wasting syndrome (See Clinical Guidelines for definitions)	
Pneumocystis pneumonia	
Recurrent severe bacterial pneumonia	
Chronic herpes simplex infection	
Oesophageal candidiasis	
Extrapulmonary tuberculosis	
Kaposi's sarcoma	
Cytomegalovirus infection (retinitis or infection of other organs)	
Central nervous system toxoplasmosis	
HIV encephalopathy	
Extrapulmonary cryptococcosis including meningitis	
Disseminated non-tuberculous mycobacterial infection	
Progressive multifocal leukoencephalopathy	
Chronic cryptosporidiosis	
Chronic isosporiasis	
Disseminated mycosis	
Recurrent septicaemia (including non-typhoidal Salmonella)	
Lymphoma (cerebral or B-cell non-Hodgkin)	
Invasive cervical carcinoma	
Atypical disseminated leishmaniasis	
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy	

Is there any degree of peripheral neuropathy?

YES	NO
-----	----

If YES, please specify

MILD	MODERATE	SEVERE
------	----------	--------

Is there any other significant clinical finding?

YES	NO
-----	----

If YES, please specify

AfA does not dispense medication - Please fax this completed form to 0800 600 773 or email it to afa@afadm.co.za

This page needs to be completed by - **The Doctor**

Special Investigation Results (Please provide copies of reports. Supply as many results as possible, including baseline results)			
Date Test Performed (DD/MM/YYYY)	CD4 count (cells / mm)	CD4% (must be provided for children)	Viral Load (copies / ml)

Additional Investigations

Test Done? If yes, specify results

Test Date

Blood count(s) (Essential prior to approval of Zidovudine)

YES	NO		D	D	M	M	Y	Y	Y	Y
-----	----	--	---	---	---	---	---	---	---	---

Baseline ALT (Essential prior to approval of Nevirapine)

YES	NO		D	D	M	M	Y	Y	Y	Y
-----	----	--	---	---	---	---	---	---	---	---

Serum creatinine/eGFR (Essential for patients with renal failure or prior to approval of Tenofovir)

YES	NO		D	D	M	M	Y	Y	Y	Y
-----	----	--	---	---	---	---	---	---	---	---

Medication (Generic equivalents and fixed dose combination tablets will be authorised unless otherwise stated)				
Antiretroviral Therapy	Strength (e.g. 10mg)	Directions (e.g. 1 tds)	Period in use (months)	Period required (months)

Other Medication Required (Associated with the management of HIV)					
Diagnosis	Medicines	Strength (e.g. 10mg)	Directions (e.g. 1 tds)	Period in use (months)	Period required (months)

Acknowledgement by Examining Doctor

Please Note:

- Tariff code 0199 will only be paid for the first time completion of the application form. The form must be completed in full and signed by both the patient and the doctor.
- Approval for ongoing antiretroviral therapy will only be considered if the result and date of a recent CD4 count and viral load is supplied. Only medication recommended in the Aid for AIDS Clinical Guidelines will be considered for reimbursement. Please refer to these guidelines or contact Aid for AIDS on 0800 22 7700, or at afa@afadm.co.za for further information. Motivations will however always be considered. Please contact AfA for assistance if required.

I certify that the above particulars are – to the best of my knowledge and belief – true and accurate, having conducted a personal examination and procured the tests and/or other diagnostic investigations referred to. I confirm that I have counselled the patient on the importance of adhering to medication and monitoring test regimens. I acknowledge that the Aid for AIDS programme will rely on such particulars when making any recommendations regarding payment for treatment to the relevant medical scheme. I acknowledge that telephonic discussions will be taped for medico-legal purposes.

Doctor's Signature

Date

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---