THE IMPACT OF A LARGE SCALE TREATMENT PROGRAM ON HIV TREATMENT DELIVERY IN A RESOURCE LIMITED SETTING

- A Case Study of Urban Treatment in Johannesburg, South Africa –

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A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfillment of the requirements for the degree of Doctor of Philosophy

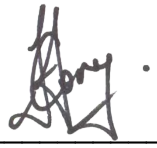
Johannesburg, 2016

Declaration

I, Lawrence Camdon Long, declare that the work contained in this thesis is my own work, except to the extent indicated in the acknowledgement sections.

This thesis is being submitted for the degree of Doctor of Philosophy, at the University of Witwatersrand, Johannesburg, South Africa.

This work has not been submitted for any other degree or examination in this or any other university.



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LAWRENCE CAMDON LONG (PHD Candidate)

7 November, 2016

Publications

The following peer reviewed publications are included as part of this thesis (order of publication):

1. Long L, Brennan A, Fox MP, Ndibongo B, Jaffray I, Sanne I, Rosen S. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med. 2011;8(7):e1001055.

2. Long LC, Fox MP, Sauls C, Evans D, Sanne I, Rosen SB. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. PLoS One. 2016;11(2):e0148546.

3. Long LC, Rosen SB, Brennan A, Moyo F, Sauls C, Evans D, Modi SL, Sanne I, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Submitted to PLoS One. Under review.*

4. Long LC, Evans DH, Rosen SB, Sauls C, Brennan A, Sanne IM, Fox M. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. *Submitted to JIAS. Under review.*

Formatting and language

As prescribed by the Faculty of Health Sciences style guide the references are presented using the Vancouver format and are numbered in ascending order in the text, and are listed in that order in the references. The references are referred to in the text by a number in square parenthesis (i.e. [2]). The references are listed at the end of every chapter and a complete list in Appendix K.

The results chapters (i.e. Chapters 7 – 10) are the published articles and are presented as they were on acceptance / submission. The text and reference formatting has been adapted to match that of thesis, but the structure is that prescribed by the journal.

The journal articles were submitted in American English and for consistency this is carried through the thesis.

Permission to publish

There were four journal articles included in the thesis. Two of the journal articles are currently published in open access journals with Creative Commons Attribution license and do not require additional permission to be reused or included in this thesis. The two remaining journal articles are currently under review and permission will be sought once they are accepted if required.

Abstract

Introduction

This thesis investigates the impact of a large-scale HIV treatment program on the outcomes and costs associated with HIV treatment delivery, using urban South Africa as a case study. In order to investigate HIV treatment delivery it is broken down into two major components; 1) the chronic outpatient treatment of HIV and 2) the acute inpatient treatment of HIV related conditions.

Outpatient HIV treatment

Through task shifting the South African outpatient HIV treatment program evolved over time to scale up in an environment of limited resources. There is no economic evaluation of task shifting in a routine environment in South Africa. Papers 1 and 2 focus on understanding the outcomes, costs, and cost effectiveness of partial and full task shifting. The results of this work provided evidence to support the shift to nurse initiation and management of antiretroviral treatment (NIMART). It also highlighted the fact that within the NIMART program there may be a need to triage patients between primary health clinics and hospital based outpatient clinics to better utilize scarce resources.

Inpatient HIV treatment

Prior to antiretroviral treatment (ART) inpatient care of acute HIV related conditions was common, but with the rollout of antiretrovirals in 2004 it was anticipated that this would reduce. Since 2004 there has been no economic evaluation, which speaks specifically to the shifting HIV burden on inpatient facilities. Papers 3 and 4 focus on understanding the HIV burden on inpatient facilities by examining the outcomes (mortality) and costs associated with HIV positive admissions. The results show that almost half (45%) of inpatient medical admissions were confirmed HIV positive, not on ART and accounted for the majority of the costs. In addition to that, the majority of medical inpatients (58%) who died were HIV positive, which lends support to other evidence that suggests that national HIV mortality is seriously under reported in South Africa.

Conclusion

Large-scale ART continues to move outpatient HIV treatment further along the task-shifting continuum, while maintaining outcomes with some potential reductions in cost. However, large-scale ART has not had the expected impact of substantially reducing the HIV burden on inpatient facilities.

Word count: 350 (Max 350)

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Acknowledgements

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To Greg for sacrificing so much to walk this path with me. Your practical approach to life made things happen when I was convinced they could not. This body of work would not have been possible without your love and support.

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List of abbreviations

3TC	lamivudine
AIDS	acquired immune deficiency syndrome
ART	antiretroviral treatment
ARV	antiretroviral
ASSA	Actuarial Society of South Africa
CCMT	comprehensive care, management and treatment site
CD4	cluster of differentiation 4 (measure of immune system)
CEA	cost effectiveness analysis
CI	confidence interval
CIPRA	Comprehensive International Program of Research on AIDS
CVD	cardio vascular disease
EFV	efavirenz
HAART	highly active antiretroviral treatment
HIV	human immunodeficiency syndrome
HSRC	Human Sciences Research Council
IC	in care and responding
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
LTFU	lost to follow-up
MSF	Médecins Sans Frontières
NACM	National ART Cost Model
NGO	non-governmental organizations
NIC	no longer in care
NIMART	nurse initiated and managed antiretroviral treatment
NR	not responding
NVP	nevirapine
OI	opportunistic infection

PDE	patient day equivalent
PHC	primary health clinic
PHCN	primary health care nurse
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission of HIV
PYO	patient days per 100 patient years observed
RN	registered nurse
RR	relative risk
SANAC	South African National AIDS Council
SSA	sub-Saharan Africa
StatsSA	Statistics South Africa
STD	sexually transmitted disease
STI	sexually transmitted infection
STRETCH	streamlining tasks and roles to expand treatment and care for HIV
TB	tuberculosis
TDF	tenofovir
TLC	Themba Lethu Clinic
UNAIDS	Joint United Nations Programme on HIV/AIDS
USD	United States Dollars
UTT	universal test and treat
WHO	World Health Organization
YO	years old
ZAR	South African Rand

CHAPTER 1 - Introduction and overview

1.1 Introduction

This thesis was designed to investigate the impact of a large-scale treatment program on HIV treatment delivery in a resource limited setting. Impact for the purposes of the thesis is defined using the broad health economics approach of a full economic evaluation, which must include both costs and effectiveness to evaluate impact [1]. I therefore determine the impact of changes in the HIV treatment delivery model (i.e. change of provider from doctor to nurse; change of location from secondary to primary health facilities) brought on by increases in program scale by examining the change in both costs and outcomes ('full economic evaluation'). From a clinical perspective there are some generally agreed best practices for the treatment of HIV outlined by the World Health Organization (WHO) [2, 3], but routine implementation often requires adaptation. Large increases in the scale of a treatment program also require adaptation of the treatment guidelines and delivery model. For the purposes of this thesis a treatment delivery model is the approach used to provide the recommended clinical treatment (i.e. the combination of service provider, service location, and population being served). The adaptations are reflected in the varied and changing HIV treatment guidelines and delivery models found across countries, including South Africa [4-6]. While increased treatment coverage is an important national objective [7] it is equally important to understand the effect that expansion has on the costs and associated outcomes of patients as treatment delivery models are adapted. To address this aim there were four objectives:

Objective 1: Evaluate the treatment outcomes and cost-effectiveness of shifting the management of stable ART patients to nurses at a primary health care facility in South Africa.

Objective 2: Evaluate the cost and cost effectiveness of nurse initiated and managed antiretroviral therapy (NIMART) at a primary health care facility with NIMART at a secondary health facility in South Africa.

Objective 3: Determine the disease and cost burden of HIV on an inpatient facility in South Africa.

Objective 4: Estimate the changes in the mortality profile of an inpatient facility in South Africa since the large scale roll out of Highly Active Antiretroviral Therapy (HAART).

The rationale for these objectives is outlined in Chapter 6 based on the literature review. Four publications were produced to meet these objectives and they are presented in this thesis. The thesis is divided in four sections each outlined in Section 1.2.

1.2 Overview

Section 1 – Literature review

Section 1 includes a review of the relevant literature regarding impact of treatment program scale on HIV treatment delivery in South Africa. The literature review is divided into five chapters, which focus on:

(1) the scale of the HIV epidemic in South Africa (Chapter 2),

(2) the history of the HIV treatment delivery model (outpatient and inpatient) (Chapter 3),

(3) costs and outcomes of HIV outpatient treatment (Chapter 4),

(4) the costs and outcomes of HIV inpatient treatment (Chapter 5) and

(5) the rationale, aim and objectives for this thesis in the context of the literature (Chapter 6).

Section 2 – HIV outpatient treatment

The aim of Section 2 is to determine the impact (costs and outcomes) of various levels of task shifting and decentralization as the treatment model was adapted in response to increasing scale. To examine these issues two studies were conducted: (1) The cost and outcomes associated with partial task shifting and decentralization of HIV outpatient services (Chapter 7) and (2) the cost and outcomes associated with full task shifting and decentralization of HIV outpatient services (Chapter 8).

Section 3 – HIV inpatient treatment

The aim of Section 3 is to determine the impact (costs and outcomes) of widely available antiretroviral outpatient treatment on HIV related inpatient treatment. To examine these issues two studies were conducted: (1) the burden (resource usage / cost) of medical inpatient admissions by HIV status and reason for admission (Chapter 9) and (2) the mortality profile of medical inpatient admissions by HIV status (Chapter 10).

Section 4 – Discussion

The aim of Section 4 (Chapters 11 and 12) is to combine and summarize the findings from each of the studies presented in this thesis and outline how they achieved the research aim and objectives of the thesis in order to contribute to an improved understanding of the impact of changing treatment delivery models as scale is increased. The significant programmatic and policy implications of the research are highlighted. Finally, the limitations of the research are discussed, and areas for further research are identified.

1.3 References

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SECTION 1 – LITERATURE REVIEW

Section 1 Aims

- To describe
  - the scale of both the HIV epidemic and the antiretroviral therapy treatment program in South Africa
  - the development and changes in the HIV treatment delivery model in South Africa
  - and evaluate the literature examining the costs and outcomes of HIV related inpatient treatment in South Africa
  - and evaluate literature examining the costs and outcomes of task shifting and decentralization in HIV outpatient treatment in South Africa
- To present the rationale, aims and objectives for this thesis in the context of the literature

This section is divided into five chapters. Chapter 2 describes the scale of the South African HIV epidemic historically and how the HIV treatment program grew to be the largest program in the world. Chapter 3 describes the development of the South African HIV treatment delivery model in the context of a growing epidemic and rapidly growing treatment program. Chapter 4 reviews research evaluating the costs and outcomes of HIV related *inpatient* treatment in South Africa. Chapter 5 reviews the research that has reported on the costs and outcomes of HIV *outpatient* treatment in South Africa. In particular, Chapters 4 and 5 evaluate the current research highlighting gaps in the literature that require additional investigation. Finally Chapter 6 provides the rationale, aim and objectives for the thesis, in the context of the reviewed literature.

CHAPTER 2 – Scale of HIV in South Africa

2.1 Introduction

The research topic is set in the context of a large-scale HIV treatment program. As scale is relative and there are a number of different measures which can be used to determine scale, this chapter reviews the major measures of scale in order to show that the South African treatment program can be considered 'large-scale'.

2.2 Review method and data

This chapter reviews the scale of the HIV epidemic and treatment program in South Africa as described by various sources including government statistics, global reports and modeled estimates. Often I found large variance in reported statistics depending on the source. For consistency government statistics were reported whenever available. The sections below synthesize the data on the following three themes: (1) scale of the HIV epidemic, (2) scale of the HIV treatment program and (3) other measures of treatment program scale.

2.3 HIV epidemic in South Africa

A major determinant of the scale of any public health program is the scale (size) of the underlying condition. In 1982 the first HIV infection was reported in South Africa [8]. By 1990 it was estimated that there were already 50,000 people living with the disease in South Africa [9]. Public health specialists began to realize the possible implications of a generalized epidemic in South Africa and the spread of the virus was monitored through annual anonymous antenatal surveillance sites. Karim and colleagues found that the epidemic took off in the 1990's with antenatal HIV prevalence rising from 0.76% in 1990 to 22.4% in 2000 [8]. While antenatal surveys overestimate HIV in the general

population, HIV prevalence in the general population was estimated to be increasing from 0.37% [10] in 1990 to 13.1% in 2000 [9]. Both of these estimates demonstrated the devastating spread of HIV in South Africa – in 10 years more than 10% of all adults (15-49 years old) were HIV positive and 3.1 million South Africans were living with HIV [9].

By 2000 the South African public health community was aware of the size of the epidemic and the speed at which it was growing. Numerous models and primary data reports each year described the increasing size and impact of the epidemic. Table 2-1 shows the scale of the epidemic from 2001-2015. As there is no single consistent data source that reports on all these variables over this time period, various sources are used. In order to maintain some consistency, data sources were selected in the following order: 1) Most recent official government report (i.e. Statistics SA), 2) most recent local organization report (i.e. HSRC, ASSA) and finally in the absence of a local source 3) the most recent international report (i.e. UNAIDS, WHO). Even though this approach of data collation ensured that most of the data points were obtained from the same sources, which used similar methods, there were still some inconsistencies in the trends. For example, HIV prevalence estimates between 2001 and 2003 show a decline in 2002, which is likely an artifact of the data and methods used to calculate prevalence in that year.

Table 2-1. Size of the HIV epidemic in South Africa*.

Year	Total Population	PLHIV	Prevalence	New Infections	AIDS Deaths
2001	44,561,000	4,100,000	9.40%	565,000	198,030
2002	45,454,000	4,020,000	8.80%	555,000	271,419
2003	46,429,823	4,140,000	9.00%	549,000	306,365
2004	46,586,607	4,250,000	9.10%	546,000	334,281
2005	46,888,200	4,350,000	9.20%	541,000	345,607
2006	47,390,900	4,510,000	9.40%	530,000	289,321
2007	47,850,700	4,710,000	9.70%	520,000	228,384
2008	48,687,000	4,930,000	10.00%	500,000	195,835
2009	49,320,500	5,130,000	10.20%	470,000	179,461
2010	49,991,300	5,320,000	10.40%	410,000	183,465
2011	50,586,757	5,480,000	10.60%	408,000	200,654
2012	52,341,695	5,650,000	10.70%	390,000	197,090
2013	52,982,000	5,830,000	10.90%	350,000	177,624
2014	54,002,000	6,020,000	11.10%	340,000	151,040
2015	54,956,900	6,190,000	11.20%	n/a	162,445

*The following references were used to compile this table using the methodology described above: [9-24]; PLHIV: People Living with HIV; Public treatment started in 2004 (Highlighted in red)

Table 2-1 shows a number of measures of the scale of the epidemic in South Africa. The absolute number of people living with HIV (PLHIV) has steadily increased since 2001 making South Africa the country with the largest absolute HIV burden in the world [22]. Since 2001 the number of new infections has reduced consistently over time while AIDS deaths peaked just after the start of the public sector program in 2004 (highlighted in red in Table 1). Table 2-1 reports prevalence for the whole population and not select sub populations (i.e. women at ante natal clinics or adults), which may be at higher risk and as a result have a higher prevalence. Prevalence has also increased since 2001, although at a declining rate. This likely reflects the reduction in new infections and the fact that the treatment program allows PLHIV to live longer. It may also partly reflect changes in data collection and prevalence estimation methods over the years. In 2015 South Africa reported the fourth highest HIV prevalence in the world amongst 15-49 year olds at 18.9%, after Swaziland (27.7%), Botswana (25.2%) and Lesotho (23.4%) [25].

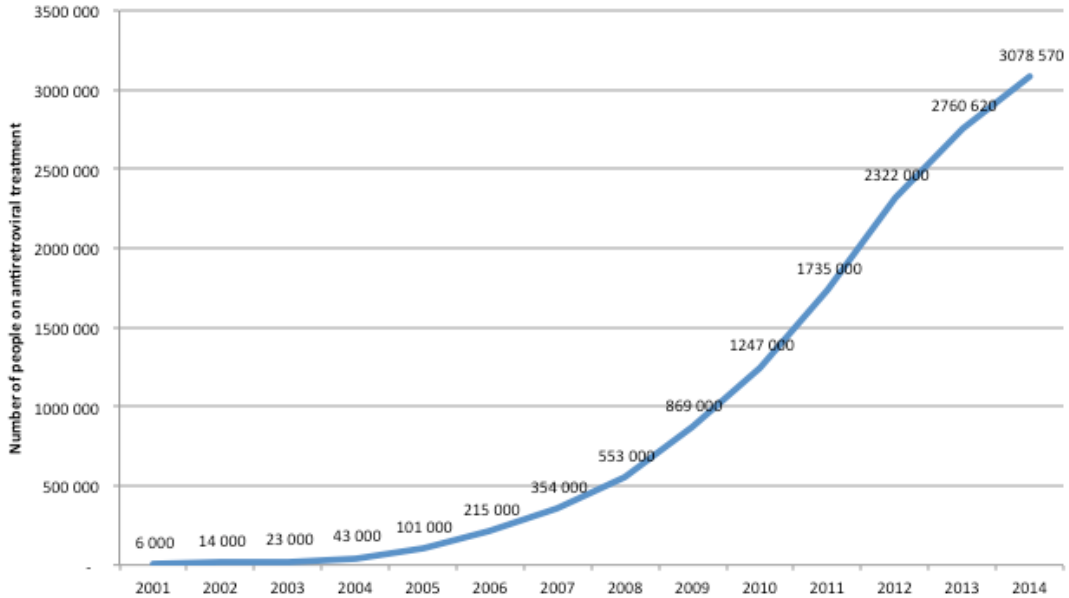
These data show that South Africa has the largest generalized epidemic in the world and the high HIV prevalence makes it a public health priority for the South African National Department of Health. The scale of the South African

epidemic would in turn drive the scale of the treatment program in South Africa. This is discussed in the next section.

2.4 Treatment population and coverage in South Africa

In order to address the growing epidemic and its associated mortality, the South African government began the roll out of a public sector HIV treatment program in 2004. There are a number of statistics that can be used to summarize the size or scale of the HIV treatment program in South Africa including the number of patients enrolled in care, the number ever initiated onto treatment and the number of patients currently on treatment. While each has benefits and drawbacks in terms of describing impact, the number of patients currently on treatment best reflects that scale of the treatment program, as it does not overstate coverage by including patients who have left the treatment program. Figure 2-1 shows the sharp increase in the number of people on life-long antiretroviral treatment from 2001 to 2014.

Figure 2-1. Number of people on antiretroviral treatment*.



*This figure includes data from Johnson (2014) [10] and UNAIDS (2016) [26].

With the rollout of the national treatment program in 2004 the number of patients on antiretroviral treatment has grown substantially over the last 10 years. (See Figure 2-1.) Prior to 2004 very few patients could access treatment in the public sector, most of which was restricted to clinical trials. In 2014 South Africa reports a total number of patients on treatment of 3,078,570 [26]. In 2014 this was the largest single country treatment population in the world, with the next largest country program that of India with 830,707 people receiving antiretroviral treatment [26].

While South Africa clearly has the largest treatment program in the world, program size alone does not allow us to fully evaluate the program scale and its potential for further growth. Treatment coverage, defined as the total number of people on treatment divided by the total number in need of treatment, provides a measure of program scale relative to the need for treatment. In 2010 UNAIDS reported treatment coverage in South Africa was 55% based on the eligibility criteria from the WHO 2010 treatment guidelines [27]. However this dropped to 42% in 2013 when WHO redefined treatment eligibility to include all those with a CD4 count ≤ 350 cells/mm^3 [22]. This drop in coverage occurred because the denominator includes more people who are considered eligible for treatment based on the prevailing country guidelines. Therefore as countries change treatment eligibility criteria to include more patients, treatment coverage will change even if progress is being made in increasing access. For this reason it is less useful to look at treatment coverage as a measure of scale over a long period where eligibility criteria are shifting. However, if the government of a country indicates ‘target’ treatment coverage levels (i.e. aspirational policy goals) then when compared to actual treatment coverage this may be used as an indicator of likely increase in program scale. For example if universal coverage is defined as providing treatment to 80% of all patients eligible for treatment and government sets this as their public health target, then any treatment coverage level below 80% indicates that the government would be likely to increase the scale of their treatment program in order to reach the target. The South African government does have a target of universal coverage, which means that there

is still likely to be significant growth in the scale of the treatment program if the target is to be reached.

While measuring program scale at the level of the patient is the most common approach used, alternatives exist, as discussed in the next section.

2.5 Other measures of treatment program scale

In addition to measuring scale at the patient level, scale of the program can also be measured at the level of the facilities or health care worker. These are both resources (costs) required to provide treatment and their lack or availability, which determine and shape the treatment model chosen, which in turn affects the outcomes.

In order to provide health services to as many people as possible, South Africa has a tiered facility approach with many primary health care facilities offering basic services going up to a few tertiary health care facilities offering specialized services. In 2012 it was reported that South Africa had 3,880 public health facilities [28]. In South Africa HIV treatment in the public sector was initially limited to specialist outpatient facilities that had stringent requirements for accreditation and required, by law, doctors to initiate therapy. This meant that by 2008, four years after roll out started, only 362 (9%) facilities were offering antiretroviral treatment [29]. In 2010 government announced that all public health facilities would offer antiretroviral therapy and in order to facilitate this they relaxed the facility accreditation criteria. From then onwards the number of facilities offering antiretroviral treatment increased rapidly from 1,015 facilities [30] in 2010 to 2,300 facilities in 2012 [28] to 3,450 facilities in 2013 [31]. With approximately 88% (3,450/3,880) of the public health facilities in South Africa offering antiretroviral treatment this measure also indicates the large-scale of the HIV treatment program.

The rapid increase in facilities offering treatment at all levels of the public health system meant that the type and number of staff members able to treat

HIV also needed to change. Since the roll out of the national treatment program in 2004 there have been very few reports of the scale of the treatment program in terms of actual human resource usage or expected human resource requirements. An early study indicated that if antiretroviral treatment were offered at primary health facilities it would require 20% of the existing professional nurses' effort to manage HIV patients, suggesting that new staff would need to be hired to offer this service [32]. The original doctor-led HIV treatment operational plan indicated that between 2004 and March 2008 an additional 4,393 (879 per year) nurses and 628 doctors [33] would be required. As of 2006 this would mean approximately one fifth (20%) of all newly trained nurses would need to be allocated to HIV treatment.
As treatment access was expanded in South Africa the treatment model evolved to become more nurse centric as doctor led care slowed expansion. In 2010 nurses were empowered to initiate and manage the majority of patients on antiretroviral treatment [5], yet at the time there were only 250 nurses qualified to carry out this role as a primary care giver [31]. Despite this, in response to the scale up, government and public sector partners trained approximately 23,000 nurses by 2013 [31]. This again indicates the large scale of the HIV treatment program in terms of human resource requirements.

2.6 Summary

South Africa has the largest absolute burden of people living with HIV in the world and its treatment program has grown rapidly to provide access for this population. By any measurement (i.e. number on treatment, number of facilities offering treatment, number of health care workers providing treatment) the current treatment program can be considered large scale.

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CHAPTER 3 - HIV treatment delivery in South Africa

3.1 Introduction

The thesis aims to examine the impact of changes in the HIV treatment delivery model in South Africa. The South African HIV treatment delivery model mandated by the National Department of Health for the public sector has evolved a number of times as the treatment program has grown. This chapter reviews the evolution of the HIV treatment delivery model in South Africa to place the models evaluated in the thesis in the context of a change continuum. By looking at the past changes it allows trends to be identified and provides some insight into likely changes to treatment delivery in the future.

3.2 Review method and data

This chapter reviews the history of the HIV treatment delivery model in South Africa. South Africa has a wealth of information regarding HIV and its treatment from a number of different sources (i.e. government, private sector, non-governmental organizations (NGO), donors), but for the purposes of this review only the official, published national HIV treatment guidelines for South Africa were used. To provide international context we compare the South African guidelines with the WHO treatment guidelines for resource limited settings. The first sub-section below provides a general overview of the treatment model and the subsequent sub-sections review its evolution over time to date.

3.3 Overview of treatment model

There is no one globally accepted gold standard for HIV treatment delivery. Most countries have dynamic models that have changed over time as a result of external factors and South Africa is no different. Duncombe and colleagues suggest that there are four 'levers' (characteristics) of tiered care and it is the adjustment of these 'levers' (characteristics) that will result in different models of care [34]. The 'levers' (characteristics) that they put forward are: service location, health worker cadre, service frequency and service intensity [34]. In order to describe the evolution of the HIV treatment delivery model in South Africa we borrow from this approach and use service location, health worker cadre and patient population (i.e. eligibility criteria) to classify the treatment models. This is summarized in Table 3-1 below and described in each of the subsequent sections by time period.

Table 3-1. Evolution of the South African ART treatment model.

Time Period	Location / Level	Health Care Worker	Adult life long ART eligibility	Guidelines / Reference
1988 - 2003	Primary health care facilities with movement upward as disease progressed	Basic, initial opportunistic infection treatment managed by nurses, but complex cases managed by doctors	No ART - All symptomatic HIV positive patients received palliative care	HIV and AIDS / STD Strategic Plan for South Africa 2000-2005 (2000) Recommendations for the prevention and treatment of opportunistic and HIV related diseases in adults (2000)
2004 - 2009	Accredited health care facilities, which because of the requirements are often specialist clinics at secondary and tertiary facilities	Doctors are the primary clinicians and required for initiation and management of patients on antiretroviral treatment	All patients who have a CD4 cell count ≤ 200 cells / mm^3 or WHO Stage IV AIDS defining illness	Operational plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa (2003) National Antiretroviral Treatment Guidelines (2004)
2010	Primary health clinics are allowed to initiate, manage, monitor and refer HIV patients	Nurses are the primary clinician and initiate and manage the antiretroviral treatment of HIV patients	All pregnant women and TB/HIV co-infected patients who have a CD4 cell count ≤ 350 cells / mm^3 or patients who have a CD4 cell count ≤ 200 cells / mm^3 or WHO Stage IV AIDS defining illness	Clinical guidelines for the management of HIV & AIDS in adults and adolescents (2010) South African Antiretroviral Treatment Guidelines 2010 (2010)
2011 - 2013	Primary health clinics are allowed to initiate, manage, monitor and refer HIV patients	Nurses are the primary clinician and initiate and manage the antiretroviral treatment of HIV patients	All patients who have a CD4 cell count ≤ 350 cells / mm^3 or WHO Stage III or IV AIDS defining illness	Statement on the meeting of SANAC (2011) The South African Antiretroviral Treatment Guidelines 2013 (2013)
2014	Primary health clinics are allowed to initiate, manage, monitor and refer HIV patients	Nurses are the primary clinician and initiate and manage the antiretroviral treatment of HIV patients	All patients who have a CD4 count ≤ 500 cells / mm^3 or are pregnant or WHO Stage III or IV AIDS defining illness	National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults (2014)
2016	Primary health clinics are allowed to initiate, manage, monitor and refer HIV patients; stable patients are offered differentiated models of care in the community	Nurses are the primary clinician and initiate and manage the antiretroviral treatment of HIV patients; stable patients can be monitored in the community using community health workers	All patients, irrespective of CD4 count	Government Memo - Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients (2016)

3.4 Pre-2004: HIV treatment in South Africa

Many years passed between the first reported South African HIV deaths in 1982 until the public health community and the government began a vigorous response to the HIV epidemic. This may have been because the epidemic started as a concentrated epidemic (1982-1987) [35]. The concentrated epidemic was reported to be amongst homosexual men, hemophiliacs and foreign African mine workers [36, 37]. Given the small scale of the epidemic and the thought that it was limited to populations whom the Apartheid government considered low priority very little attention was given to the epidemic over the next decade.

The generalized epidemic only really became evident in later years (1988-1994) [35]. It was estimated that in 1989 between 44,763 – 63,076 South Africans were HIV positive and by the end of 1991 it would have increased to between 316,725 – 446,300 [38]. The first ante natal survey conducted in 1990 found 0.8% of pregnant women to be infected [36]. The growing HIV epidemic was raised at the Fourth International Conference on Health in southern Africa held in Maputo (Mozambique) in 1990. Based on consensus reached at this conference amongst multiple stakeholders a policy document known as the 'Maputo Statement on HIV/AIDS' was released [39]. It outlined the approach that should be taken in developing HIV/AIDS policies for the growing HIV epidemic in South Africa. In 1991 civil society created a national advisory group known as NACOSA (Networking HIV/AIDS Community of South Africa) whose aim was to inform government policy around HIV and AIDS [40]. In South Africa 1994 brought with it democracy and a new ruling political party and the management of HIV was not high on the new governments priority list. Despite this NACOSA managed to lobby for a draft National AIDS Plan and this was accepted by the new government in 1994 [41]. This plan focused purely on prevention interventions thought at the time to be effective, but history would should that it was unsuccessful in slowing the epidemic.

Once the virus expanded to the general population the epidemic grew exponentially (1995 onwards) [35] and during Mandela's presidency HIV prevalence rose from 4% in 1994 to 22% in 1998 [42]. In 1997 the Inter-ministerial Committee on AIDS (IMC) was created with Deputy President Thabo Mbeki as the chair [42]. At the end of 1998 the Treatment Action Campaign (TAC), a civil society group advocating for treatment, was created with Zachie Achmat, an HIV positive activist, as the leader [40]. The next ten years in South Africa (1998-2008) saw increasing AIDS denialism by the ruling party, in particular the sitting president, Thabo Mbeki [43, 44]. The Treatment Action Campaign and other civil society groups led the call for HIV treatment in South Africa during this difficult time.

It was only after 2000 when national mortality started to increase that the government began to realize the possible impact [35]. Bradshaw and colleagues concluded that between 1997 and 2003 adult mortality had a real increase of 40% and that given the age groups in which it was increasing it could largely be attributable to HIV/AIDS [45]. Karim and colleagues described this period as the "AIDS mortality phase" because of the rapid increase in AIDS related deaths [35]. Up until this point there were no official guidelines for the treatment of AIDS and patients were treated symptomatically and only for opportunistic infections.

It was only in the "AIDS mortality phase" that the South African government began to issue official guidelines for the management of HIV in the public sector. In January 2000 the South African National AIDS Council (SANAC) was formed, replacing the inter-ministerial committee. Then in February of that year SANAC and government released their first national strategic plan (2000-2005) for the management of HIV [42]. This document called for clear guidelines for the care and treatment of HIV positive people in the public health sector, but it did not specifically call for or address the need for antiretroviral treatment. In response to this call guidelines were released in October that year for the management of HIV positive people presenting with associated opportunistic infections and conditions [46] as well as the palliative

treatment for patients with AIDS. The treatment model, such as it was, was limited to the early treatment of opportunistic infections at primary health clinics with a movement to specialist facilities after the inevitable failure of drugs at the primary health clinic. While this treatment for HIV related conditions and opportunistic infections was offered to patients who presented for treatment there were no official HIV treatment or care programs in which patients could be enrolled and monitored. Patients were treated on an ad-hoc basis as they presented.

The release of the national strategic plan and the palliative guidelines for HIV positive patients in 2000 seemed to signal that the South African government was responding to the growing epidemic, but at the same time President Thabo Mbeki started to question the link between HIV and AIDS [44]. Amidst the growing discord between scientists, clinicians and government President Mbeki established the Presidential AIDS Advisory Panel which included amongst others, scientists that supported his claim that HIV did not cause AIDS [47]. Concurrently international clinical trials were showing the effectiveness of using antiretrovirals to prevent the spread of HIV from an infected mother to her unborn child – prevention of mother to child transmission (PMTCT) [48]. The government was however not willing to implement this policy nationally and civil society took the government to court. In July 2002 the constitutional court ruled in favor of providing treatment for all HIV positive pregnant women [37, 40, 49]. This breakthrough judgement marks a major turning point in the government sentiment towards antiretroviral treatment and subsequently cabinet released a statement saying that the cornerstone of their HIV/AIDS response was that “HIV caused AIDS” [50]. In April 2002 a Joint Health and Treasury Task Team was established to propose options for the HIV treatment response beyond PMTCT and based on their final report government gave the Department of Health permission to develop an operational plan for a national antiretroviral treatment program. In November 2003 the ‘Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa’ was presented and approved by cabinet [33]. Through the support of civil society organizations (e.g. Treatment Action Campaign) and international agencies (e.g. Clinton

Foundation, US President's Emergency Plan for AIDS Relief - PEPFAR) the development and subsequent implementation of the operational plan was significantly faster than it otherwise would have been [37]. Unfortunately President Mbeki maintained his stance on HIV and this meant that during his presidency the HIV response was not as fast as it could have been – it is estimated that the ten years of AIDS denialism in South Africa cost 330,000 people their lives [51].

3.5 2004 – 2010: HIV treatment in South Africa

In early 2004 the first national public sector HIV treatment program was launched based on two critical documents: an operational plan and national antiretroviral treatment guidelines [4, 33]. The treatment delivery model outlined in these documents called for doctor-led antiretroviral treatment in specialized, accredited HIV treatment facilities. As stringent requirements for accreditation of treatment facilities was put in place that typically could not be met in primary health facilities, most of the initial ART programs were established in secondary and tertiary level facilities known as Comprehensive HIV and AIDS Care, Management and Treatment sites (CCMT). While these programs were part of the public health system they only offered HIV services and were not well integrated into other parts of the public health system.

Since 2004, eligibility criteria for antiretroviral treatment have been evolving in relation to the WHO guidelines. Under the initial ART program guidelines, patients who had a WHO stage IV AIDS defining illness or a CD4 count ≤ 200 cells/mm^3 were eligible for treatment. This differed slightly from the World Health Organization (WHO) 2003 guidelines which in addition recommended initiation of patients who had a WHO Stage III condition and a CD4 count ≤ 350 cells/mm^3 [52]. In 2009 the WHO recommended that all HIV infected patients should initiate as soon as their CD4 count ≤ 350 cells/mm^3 or if they had a Stage III or IV condition [53].

In 2010 the South African government issued new guidelines for the management of HIV [5, 54], which altered the treatment delivery model in a number of ways. For the first time the government officially endorsed and provided a legal framework for the use of nurses as the primary clinician for the initiation and management of antiretroviral treatment. This change was in recognition of the shortage of health care workers to run the current treatment model and that the program had to increase the number of people able to prescribe ART if the scale of the program was going to be increased in the short term [55]. In addition the new guidelines specifically stated that all primary health clinics would become antiretroviral treatment sites. This effectively shifted the bulk of the outpatient treatment to the lowest tier of the public health system. At the same time, the ART eligibility criteria did not increase to the WHO recommended threshold of 350 cells/mm^3 which meant that South Africa was still not in line with the WHO recommendations for when to start antiretroviral treatment [53, 56].

3.6 2011 – Current: HIV treatment in South Africa

The evolution of the South African HIV treatment model has taken place in the presence of a strong move towards universal health coverage, but the exact relationship between this disease centric program and the broader public health approach are unclear. The South African constitution provides the right to health care [57] and this was used to advocate for HIV treatment as well as the development of the National Health Insurance (NHI) program, which is South Africa's tool for achieving universal health coverage [58, 59]. The latest global development goals call for the end of AIDS as well as universal health coverage by 2030 [60] with no clear indication of priorities in situations where resources are limited. The primary health care system is the main conduit for universal health coverage under the proposed NHI model and it could be argued that the rapid development of the HIV treatment model in South Africa and its devolvement to the primary health clinics with additional resources has strengthened South Africa's move to universal health coverage [61]. There are also concerns being raised that the push for universal health coverage in

resource limited settings may come at the expense of HIV programs and the gains they have made [62]. As the global push for universal health coverage becomes stronger South Africa will need evidence to support the prioritization of disease centric programs like HIV or take the chance of prioritizing universal health coverage over a particular disease.

Despite the increased pressure for limited resources the HIV treatment model in South Africa has continued to keep pace with international guidelines, reflecting the current priorities of government. In 2011 an official statement released after a meeting of the South African National AIDS Council (SANAC) confirmed that South Africa would now initiate all HIV positive patients with a CD4 count ≤ 350 cells/mm^3 or a Stage III or IV condition [63] bringing South Africa in line with the 2010 WHO recommendations [56]. South Africa released a revised version of their treatment guidelines in 2013 which reflected this change in eligibility and also introduced the use of fixed dose combinations (i.e. multiple drugs combined into a single tablet to simplify pill burden) for use in the first line regimen [6]. In the same year WHO released new guidelines recommending the initiation of antiretroviral treatment with a CD4 count ≤ 500 cells/mm^3 [64]. The following year, 2014, when South Africa released its consolidated treatment guidelines they updated the treatment initiation threshold to make anyone who was pregnant or had a CD4 count ≤ 500 cells/mm^3, or a Stage III or IV condition eligible for treatment initiation [65]. This again brought South Africa in line with the internationally accepted standard of practice as recommended by the WHO. The World Health Organization has subsequently released updated eligibility criteria in 2015 which state that a HIV positive person is eligible to initiate irrespective of CD4 count [3]. This approach, commonly known as “universal test and treat” (UTT), was endorsed by the South African government in August 2016 and made part of the guidelines, effective from 1 September 2016 [66]..

The current UTT guidelines in South Africa have effectively removed the eligibility criteria for antiretroviral treatment initiation. In their current format however they do not allow for treatment initiation on the same day as testing HIV positive. This is not possible as baseline bloods are still required prior to

initiation and these tests are not currently point of care [65]. As a result UTT in South Africa will not eliminate loss to initiation after testing. In the future we may see the government adjusting the guidelines to allow same day treatment initiation to improve the uptake of treatment after testing. Similarly, we may see the initiation of patients ultimately moving to the community so that the many patients tested in the community can be started immediately. Over time these changes may effectively reduce the current issue of loss to initiation.

All of these changes in eligibility criteria effectively increase the HIV positive population eligible for antiretroviral treatment. This increase in need and eventually demand, places pressure on the antiretroviral treatment delivery model, which in turn results in changes in the treatment delivery model and / or treatment outputs. This thesis examines these changes in the context of costs and outcomes.

3.7 Summary of the treatment model in South Africa

Prior to the roll out of treatment in South Africa, treatment of HIV related conditions were split between outpatient and inpatient facilities. Outpatient treatment facilities were used for the less complex treatment of opportunistic infections. As the disease advanced the use of inpatient treatment was more prevalent, in particular for terminal, end of life care. In other words the earlier treatment model explicitly incorporated both treatment locations and utilized health care workers at various levels. It was clear that the disease was affecting all levels of the public health system.

With the advent of antiretroviral treatment in South Africa the guidelines no longer speak specifically to the inpatient treatment of HIV positive patients for HIV related conditions. At best the guidelines may suggest the referral of complex patients from the outpatient facility to an inpatient facility but there is no guidance on how this might be done and how this fits within the new

treatment model. This may be because it is assumed that a successful HIV outpatient antiretroviral treatment program will no longer require acute HIV related inpatient treatment. Badri and colleagues note that in industrialized countries the roll out of antiretroviral treatment was associated with a shift from inpatient treatment to outpatient treatment [67]. While in theory this may be true (due to reduced opportunistic infections) it is also possible the introduction of antiretroviral therapy would lead to more HIV positive patients presenting for inpatient care with antiretroviral toxicities or side effects. Without evidence to support the assumption that inpatient treatment is not an important component of the HIV treatment model, it is essential to include HIV related inpatient treatment when considering the impact of a large scale HIV treatment program.

For this reason I consider the HIV treatment model in South Africa to consist of two main components: 1) inpatient treatment for the management of acute HIV related conditions; and 2) outpatient treatment, for the chronic management of HIV with antiretroviral treatment. The impact (costs and outcomes) of changes in the treatment delivery model is reviewed in the following two chapters.

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CHAPTER 4 - HIV inpatient treatment

4.1 Introduction

This thesis was designed to investigate the impact of a large-scale treatment program on HIV treatment delivery in a resource limited setting. As noted in Chapter 3 the HIV treatment delivery model includes both inpatient and outpatient treatment components. This chapter focuses on reviewing the literature related to HIV related *inpatient* treatment.

Inpatient treatment cannot be broken down into distinct models of treatment as described in section 3.3 where outpatient treatment models were defined using the characteristics provided by Duncombe [34]. Inpatient treatment is by definition relatively homogenous in terms of service location (i.e. all secondary or tertiary facilities), health worker cadre (i.e. all doctor led), intensity (i.e. length of stay dependent on reason for admission not model) and frequency (i.e. there are not multiple visits per admission). The biggest changes that can occur to the inpatient component relate specifically to the population accessing this treatment. The population can vary in absolute size (burden) and by reason for admission (disease / condition), which determines the distribution of these patients within wards of an inpatient facility. This is covered in section 4.3. The associated outcomes and costs of this component are covered in section 4.4 and 4.5 respectively.

4.2 Review method and data

This chapter reviews the literature on HIV related inpatient treatment. I defined HIV related inpatient treatment as the acute treatment of a condition related to HIV in a facility requiring admission. Whether or not treatment is directly related to a patient's HIV status is often not stated in the literature. For the purposes of the

review, all publications that cover inpatient treatment of HIV positive patients were considered, irrespective of whether their reason for admission was included.

As this thesis focuses on HIV related inpatient treatment in South Africa the following search terms were used in PubMed to produce an initial list of publications: "South Africa" and "Inpatient" or "Hospital" and "HIV". This was done initially at the start of the thesis and subsequently updated and revised based on a final search conducted on 16 January 2016.

The updated search yielded 3,171 unique records. The thesis is particularly focused on the impact of the public sector antiretroviral treatment program, which only started in 2004 in South Africa. Therefore the search was further limited to the four years preceding the start of the rollout in order to describe the inpatient model preceding the availability of wide spread public sector treatment. Therefore the 702 publications, which were published prior to 2000, were excluded.

Then the titles of the remaining 2,469 publications were reviewed initially by title, which excluded 2,397, and then by abstract for the 72 that remained. Publications were excluded if they:

- Reported on countries other than South Africa,
- Modeled results instead of using primary data,
- Focused on a specific disease rather than all HIV admissions,
- Did not report on the burden (cost or prevalence) of or outcomes for HIV inpatients.

An exception was made for publications that focused on tuberculosis (TB) because of the known high rates of comorbidity between HIV and TB. There remained a total of 44 unique publications, which required full review.

As each publication was reviewed the relevant references were cross-checked and in this way additional publications and grey literature were added to the publications finally reviewed and included. A total of 38 publications were finally included and are tabulated and summarized in Appendix I (Supplementary Table 8). The sub-sections below review these publications within three main themes:

(1) burden of HIV on inpatient facilities; (2) outcomes of HIV positive inpatients and (3) resource usage and/or costs of HIV related inpatient treatment.

4.3 Burden being placed on inpatient facilities

Inpatient treatment for HIV related conditions in the absence of antiretroviral treatment was predominantly palliative and in some instances end of life care. The HIV related admissions were a burden that the health care system had not dealt with before. HIV disease has three distinct phases: 1) acute infection, which typically does not require any treatment (2-4 weeks), 2) clinical latency (chronic HIV infection) which has no symptoms (approximately 10 years) and 3) AIDS, which is symptomatic and typically requires treatment (between 1 and 3 years). The long period between infection and the possible need for inpatient treatment meant that by the time the burden became evident at healthcare facilities the epidemic was already well developed. In the absence of a successful outpatient treatment program for HIV patients the estimated burden on the public hospitals in Africa was considered unsustainable and there was concern that AIDS patients might crowd out non HIV positive patients trying to access inpatient care [68, 69]. More than a decade since the roll out of the national HIV treatment program in 2004 there is little known about its impact on HIV related hospitalizations [70].

One of the reasons that the burden of HIV on inpatient facilities in South Africa is not very well understood is that routine inpatient statistics do not provide sufficient information to disaggregate admissions by HIV status. This issue was raised by Nojilana and colleagues who found that the underreporting of deaths due to AIDS was 53% in a South African academic hospital because routine statistics could not reliably be disaggregated by HIV status [71]. In some instances the lack of reported HIV status in inpatient statistics reflects the fact that patients are admitted not knowing their HIV status and either refuse the offer of a HIV test or are not offered an HIV test. A recent study reported that in 2013 one sixth of HIV positive inpatients learned of their status for the first time in hospital [70]. This means that in the absence of consistent HIV testing and record keeping routine inpatient

statistics may not be accurate and proxies for HIV inpatient burden should be used.

Disease profile as a proxy of burden

In the absence of routine inpatient statistics which record HIV status accurately the strong association between HIV and certain opportunistic infections / conditions mean that changes in inpatient disease profiles can be indicative of HIV related inpatient burden. For this reason it is important to understand the disease profile of HIV positive inpatients in order to use this as a proxy for shifts in the HIV burden. In South Africa all of the studies which reported reason for inpatient admission over time showed increases in the percentage of admissions attributable to tuberculosis [72, 73] or pneumonia and other infectious diseases [73, 74] during the time period when HIV prevalence was increasing. A few of these also reported increases in the absolute number of admissions over the study period [72, 73]. Not all of the earlier studies reported HIV status and so in some studies it was not clear what was driving the change in admission disease profile. In studies which reported reasons for admission by HIV status, tuberculosis accounted for 15% to 63% of HIV positive admissions [70, 72, 75-78]. This variation could be attributable to different study time periods, locations or hospital types, but tuberculosis was consistently the leading cause of admission amongst HIV positive admissions. A study which tested for HIV amongst tuberculosis related inpatient admissions found that the majority (70%) of these patients were HIV positive [73]. These studies strongly suggest that increased inpatient admissions for tuberculosis or other infectious diseases in South Africa are associated with increases in HIV prevalence amongst admissions. Even in the absence of confirmed HIV status we can then conclude that HIV related inpatient admissions have and continue to place an increased burden on hospitals.

Understanding the variation in burden by facility

The research reported above suggests that the HIV inpatient burden is not spread equally among and within facilities and understanding the potential reasons for variation are important as the inpatient facility type (i.e. tertiary, district, specialist, medical ward, surgical ward) influences the type of patient admitted (i.e. a TB hospital only admits TB patients, a tertiary hospital admits patients with more

complex conditions than a district hospital, a surgical ward admits surgical patients) which in turn may explain why some facilities are likely to experience a higher inpatient burden due to HIV than others.

Specialist facilities

As there are very few specialist inpatient facilities in South Africa the majority of the HIV inpatient burden is carried by non-specialist hospitals, but depending on the specialty, certain specialist inpatient facilities can have a high HIV prevalence. As noted above, the large number of inpatients that present with HIV and tuberculosis as co-morbid diseases suggest that tuberculosis hospitals or wards are likely to have a high HIV prevalence. This is supported by the literature, which reports that the majority of tuberculosis drug sensitive patients at a tuberculosis hospital are HIV positive [79, 80]. Non-specialist hospitals that offer specialist clinics (i.e. tuberculosis) for conditions closely linked with HIV are also impacted. The patients that present at these clinics are more complex with more advanced disease [80]. This results in more patients being admitted and referred to higher care facilities. This suggests that specialist inpatient facilities, which focus on conditions associated with HIV infection, are likely to experience a higher burden and more complex patients.

General facility – medical wards

Even within a facility it is likely that the HIV burden is not uniform across all wards. Inpatient facilities assign patients to a ward based on their original reason for admission. Typically inpatient facilities have medical wards (non-surgical), surgical wards and specialist wards (i.e. maternity). Patients with advanced HIV disease have weakened immune systems and the majority of the conditions that they present with are medical (non-surgical). It is expected therefore that the medical wards would have more HIV related admissions than surgical wards. In the period around the public sector rollout of antiretroviral therapy in South Africa in 2004, hospitals were reporting a HIV prevalence amongst medical admissions of between 32% and 54% [81-83]. Given the timing of these studies the benefits of the national treatment program would not have been reflected in the results. A study five years after the national rollout in 2009 showed similar results with an HIV prevalence of 31% amongst medical admissions [84]. The most recent report

of medical admissions in 2013 reports that nearly two thirds (60%) of their medical admissions are HIV positive, with only 45% of those on antiretroviral treatment at the time of admission (35.7% naïve, 19.3% interrupted treatment) [70]. This is a startling result given that effective treatment had been available for almost a decade at this point, yet it appears that the burden on medical wards is still high and may have increased. This was however for a site in the Western Cape province in South Africa and the conclusion may not be generalizable to the rest of the country.

General facility – surgical and specialist wards

Non-medical inpatient wards account for a much smaller percentage of the total inpatient beds, but can still experience relatively high HIV prevalence depending on the ward. HIV related complications do not often necessitate surgery and as a result the prevalence in the surgical wards prior to the rollout of antiretroviral therapy was closer to that of the general population (12%-33%) [85, 86]. On the other hand specialties such as obstetrics and gynecology experienced a higher HIV prevalence prior to the rollout of antiretroviral therapy (40%-45%) because the populations they served traditionally had a higher HIV prevalence than the general population [87, 88]. Given that medical wards have the largest number of beds and a higher prevalence than other wards, focusing on medical wards for the inpatient component of the thesis would address the bulk of HIV related inpatient burden.

Pediatric population

Although pediatric HIV patients when compared with adult HIV patients were a smaller population in South Africa they still placed additional burden on the inpatient facilities. Prior to the roll out of antiretroviral treatment in South Africa the HIV prevalence of pediatric inpatients ranged from 4-33% [89-92]. This suggests a lower or equal prevalence to that of the adult inpatient population during a similar time period. Unlike the adult inpatient population the reported pediatric HIV prevalence (8-19%) in the period after the rollout of antiretroviral treatment in South Africa appeared to be lower [93, 94]. This improvement has been attributed to the effectiveness of antiretrovirals and the prevention of mother to child transmission (PMTCT) program [94]. Given that the pediatric HIV population in

South Africa is much smaller compared to the adult HIV population and that the treatment program appears to be successfully reducing the burden of HIV related pediatric inpatient care, the thesis focuses on the adult HIV related inpatient burden in South Africa.

Link between burden and treatment

The clinical effectiveness of antiretrovirals has been proven and patients on treatment show increases in their CD4 counts (immune system reconstitution) and reductions in their viral load [95]. Improvements in the patients' immune system should translate into lower medical admissions. Recent research provides some evidence of this by showing that current CD4 count increases are associated with a lower rate of hospitalization [76]. A cohort study tracked inpatient days around the time of antiretroviral treatment initiation and found a dramatic reduction after treatment initiation; 2,549 inpatient days per 100 patient years observed (PYO) prior to initiation, to 476 inpatient days per 100 PYO in the first 48 weeks on treatment and 73 inpatient days per 100 PYO thereafter [96]. This literature suggests that an increasing public sector treatment program should be associated with more patients on antiretroviral treatment and as a result a reduction in the HIV related inpatient admissions. It is this relationship between increasing treatment availability and HIV related inpatient burden that will be examined in the thesis.

4.4 Outcomes

In order to determine the success of the HIV treatment program (inpatient and outpatient) it is necessary to be able to measure changes in outcomes of HIV patients over time. This thesis focuses on the individual level effects (i.e. vital status, retention, immune status, viral suppression) of HIV treatment programs rather than population effects (i.e. prevention effects, household / family impact, workforce effect). HIV related inpatient treatment is the admission for the treatment or management of a HIV related condition. Since in most instances it is not admission for the initiation of antiretroviral treatment the typical measures of HIV treatment outcomes (i.e. viral load suppression, CD4 count improvement) are not appropriate for the inpatient component of HIV treatment. As the reasons for

HIV related admissions vary widely there is no universal clinical outcome that can be used for all admissions with the exception of mortality. Typically, publications might report in-hospital mortality, transfer to another facility, or discharge. In a few cohort studies outcomes after discharge such as initiation on treatment, viral suppression or 12-month mortality may also be reported. The various outcome measures for HIV related inpatient admissions are reviewed below.

Pediatric mortality

As inpatient facilities traditionally separate adults and children, pediatric inpatient mortality is often reported separately from adults. In the years before the roll out of the national antiretroviral treatment program hospitals reported increasing pediatric inpatient mortality associated with HIV [74, 92, 97], with one study reporting that HIV was the most prevalent specific cause of pediatric inpatient death at the hospital [97]. This trend was also noticed in the specialist pediatric intensive care units, which reported significantly lower survival rates amongst HIV positive pediatric inpatients [91]. Since the large-scale roll out of antiretroviral treatment programs, one study has reported a reduction in HIV related mortality amongst pediatric patients, which they attributed to antiretrovirals and the prevention of mother to child transmission program [94]. This mortality data reflects the reduced pediatric HIV inpatient burden since the roll out of antiretroviral treatment in South Africa and the success of the treatment program.

Mortality by ward / hospital type

Untreated HIV brings with it an increased risk of death and so it follows that the higher the burden (prevalence) on a particular ward the higher the HIV related mortality is expected to be. The literature supports this showing that high prevalence specialist wards such as maternity and tuberculosis showed a rapid rise in associated mortality prior to the national roll out of antiretroviral treatment. In the period prior to the roll out of antiretroviral treatment maternal mortality was reported to grow between two to three fold [88, 98] and inpatient mortality in a tuberculosis hospital almost doubled [99]. Interestingly adult surgical wards do not appear to share this phenomenon of increased mortality associated with HIV prevalence [100] – this may be attributed to the fact that the reason for surgery is

often not HIV related. This suggests that when HIV is related to the reason for admission there is an increased risk of death.

Mortality around treatment initiation

It has been noted that there is high HIV associated mortality around the time of ART initiation [101]. In order to be eligible for treatment initiation under the original treatment guidelines patients had to present with a compromised immune system (CD4 cell count ≤ 200 cells/mm^3) or an AIDS defining illness. This meant that at the time patients initiated treatment they were also likely to be highly immune compromised and as a result at high risk for death. Research has shown that starting patients earlier (i.e. with a higher baseline CD count) may reduce HIV related morbidity including inpatient admissions – essentially shifting inpatient treatment to outpatient treatment [102].

Mortality and co-infection with tuberculosis

Tuberculosis has been noted as a major reason for HIV related admission [69] and research into HIV related inpatient mortality in South Africa clearly implicates tuberculosis as a major contributing factor. In the period around the rollout of public antiretroviral treatment in South Africa inpatient mortality was shown to be increasing with HIV-TB co-infection strongly correlated with and one of the leading causes of death [73, 103, 104]. The impact of tuberculosis on HIV related inpatient admissions is not unique to South Africa. A recently published systematic review found that tuberculosis is the leading cause of admission and inpatient mortality amongst HIV positive adults and children worldwide [105]. It is for these reasons that public health specialists and policy makers have recommended that TB and HIV programs should be integrated in terms of diagnosis and treatment [102]. The strong overlap between HIV and TB related inpatient admissions will be key to understanding the success or failure of the antiretroviral program in reducing the burden of HIV related inpatient care on the public health system.

Cause of death verification

Most research on HIV associated inpatient mortality relies on retrospective record review to determine cause of death and comorbid conditions. Post mortem

verification of cause of death via autopsy is rare. The few studies that did perform post mortem verification confirmed that tuberculosis was the major contributing factor to HIV related inpatient mortality. A rural hospital that performed systematic autopsies of select HIV positive patients who died between 2000 and 2008 found that 38% had some form of tuberculosis [106]. In 2009 a postmortem review of HIV positive mortality at a tertiary hospital in Gauteng province showed that 64% of the deaths could be attributed to tuberculosis [101]. These publications confirm and provide additional evidence of the inpatient burden from TB and HIV co-infected patients on the public health system.

Post discharge mortality

While mortality is one of the most commonly reported outcomes for studies examining HIV related inpatient admissions, the mortality reported is generally only mortality that occurs in the facility. Post discharge mortality amongst HIV positive inpatients can be high. A district hospital in KwaZulu-Natal in 2007 reported a 5% inpatient mortality rate amongst HIV patients, but this went up to 25% by 24 weeks post discharge [77]. However this was not seen in a tertiary hospital in the Western Cape province, which in 2009 reported that 12 month mortality after admission was not associated with HIV status at admission [84]. A more recent study in the Western Cape reported that a 2013 cohort of HIV positive inpatients had an in-hospital mortality of 5%, 13% at 90 days and 18% at 180 days post discharge, respectively [70]. The main clinical diagnosis amongst those who had died by 180 days was tuberculosis (39%) and other AIDS defining illnesses (21%) [70]. These publications suggest that in-hospital mortality during the initial admission may underestimate true mortality related to this admission.

Treatment and mortality outcomes

With the roll out and rapid scale up of the public sector antiretroviral treatment program in South Africa, reasons for inpatient admission and mortality outcomes may change. Effective early treatment should reduce the number of inpatients presenting with opportunistic infections related to HIV. As the number of patients on antiretrovirals increases one might expect an increase in hospital admissions related to adverse drug reactions (ADR) to the antiretroviral medication. Soon after the rollout of public antiretroviral treatment in South Africa a study reported

that ADRs were a more common reason for admission amongst patients that were on HIV treatment compared to those not on HIV treatment [102]. Another study during the same time period also reported that the majority of ADR related inpatient admissions were amongst HIV positive patients, but that most of these patients were not on antiretrovirals and the ADR was related to the treatment of other conditions (i.e. tuberculosis) [83]. Both of these studies occurred soon after the national roll out and it may have been too early to see a marked increase in antiretroviral ADRs at hospitals. A more recent study in the Western Cape found that 9% of all inpatient deaths were HIV-positive adverse drug reactions and the majority of these patients were on antiretrovirals and / or tuberculosis medication [107]. The combination of more tolerable HIV treatment regimens and earlier initiation appears to have kept the HIV related ADR inpatient morbidity and mortality relatively low – although higher than the general population.

Treatment initiation as an outcome

While survival until discharge is the desired outcome for an inpatient, a patient who is not on antiretroviral treatment, but is admitted for an HIV related complication needs to initiate ART rapidly, to reduce the risk of death and readmission. Very few studies report rates of antiretroviral treatment initiation during admission or afterwards. In 2005 a study in Gauteng reported that the majority of patients who were admitted for tuberculosis and subsequently died were HIV positive (94%) and of those 87% had a CD4 count ≤ 200 cells/mm^3 making them eligible for treatment – yet none of these patients were on ART [103]. This was in the early years of the public treatment program and low treatment coverage was to be expected. More recently (2007) however, it was reported that in a hospital in KwaZulu-Natal less than half (45%) of the HIV positive treatment naïve patients admitted for tuberculosis or another opportunistic infection (therefore treatment eligible) had initiated antiretroviral treatment within six months of discharge[108]. A third (31%) died before they could initiate treatment [108]. The scale up of treatment has improved treatment initiation and this is reflected in a 2013 cohort that showed only 63% of HIV positive inpatients with CD4 counts ≤ 200 cells/mm^3 initiated treatment – yet the majority of these (55%) were still not on treatment (36% naïve and 19% interrupted) [70]. Only 25% of these patients were taking their medication and were virologically suppressed [70]. This provides

evidence that while adherent patients on treatment are less likely to be hospitalized, large-scale antiretroviral treatment availability is not sufficient to reduce the HIV related inpatient burden. Understanding the reasons for HIV related admissions in the era of large-scale antiretroviral treatment access is one of the key research questions of this thesis.

4.5 Resource usage and costs

In the absence of treatment, HIV/AIDS inpatients have been reported to use more resources than the average inpatient [68] Only using the number of HIV related admissions as a measure of burden does not take into account the fact that each admission is unique in terms of the resources it uses (burden). These resources can be measured using various approaches and in some cases can have financial costs assigned to them to allow comparison against other admissions.

Length of stay

Not all publications that go beyond the number of HIV related admissions to measure burden will measure individual patient resource usage directly. Many publications use length of stay as a proxy for measuring resource usage. This approach assumes that each day spent in the hospital is identical in terms of resources used (i.e. clinician time, drugs dispensed, diagnostics performed, ward type). While this is not always true it provides more information than looking at the number of admissions alone. Depending on the study design, inpatient days can either be reported as the total number of inpatient days per patient over some time period (i.e. could be multiple admissions) or they can be reported as length of stay per admission. The former is often used in cohort studies when there is longitudinal follow up and the latter is often used when studies focus on admission events rather than a time period.

Length of stay - medical wards

The literature shows a clear relationship between HIV status and length of stay as well as antiretroviral treatment status and length of stay. In the period prior to the public roll out of antiretroviral treatment (pre-2004) the literature showed that both

adult [87] and pediatric [91, 92] HIV positive admissions had on average longer lengths of stay when compared to their HIV negative counterparts. In 2000 an antiretroviral treatment clinical trial in South Africa reported a decrease in the length of stay amongst those on antiretroviral treatment and that the use of inpatient services increased with the severity of the HIV infection (AIDS vs. non-AIDS) [67]. Two studies, which took place after the public roll out of treatment in South Africa, reported apparently contradictory results with patients on antiretroviral treatment having longer lengths of stay and associated costs [76, 82]. Both publications suggested that this counter intuitive result could have been driven by immune reconstitution inflammatory syndrome (IRIS), which occurs soon after antiretroviral treatment initiation and can result in hospital admissions [76, 82]. These studies may not have captured the end of life, palliative inpatient care required for patients not on antiretroviral treatment. This reasoning was supported by a longitudinal study in the private sector that reported high hospitalization rates around the time of treatment initiation and a significant reduction thereafter [109]. The literature clearly supports the fact that prior to the availability of antiretroviral treatment HIV positive admissions had on average longer admissions. The comparison of average inpatient usage for HIV positive patients on and off treatment is not as clearly defined, but suggests that there could be high inpatient usage around the time of treatment initiation.

Length of stay – Other wards / facilities

Previous publications have focused on admissions to medical wards, although in some publications the type of ward is not always clear. In contrast to the medical wards, a surgical ward in KwaZulu-Natal province reported that there was no difference in length of stay by HIV status, but that surgical interventions were more common amongst HIV positive patients [100]. This might suggest that the intensity (resource usage including length of stay) of medical admissions is correlated with HIV status, while the intensity of surgical admission might not be or the correlation is weaker. Generally inpatient care for HIV is acute and limited in length, but tuberculosis, an HIV related condition, can require extended hospital admissions. In 2011 a specialist TB hospital in the Western Cape province reported an average admission length of 99 days amongst HIV positive

tuberculosis patients [79]. The burden of HIV on such specialist hospitals is overwhelming.

Costs of inpatient admissions

Using length of stay is a sufficient measure of resource usage for an admission if the average resource usage per day is constant, however resource usage per admission can have a great deal of variability. In order to capture this resource usage in a manner that allows for comparison, unit costs should be applied to the resources used and then the total costs per admission can be compared. Inpatient costs are presented in a number of ways in the literature depending on the underlying study design.

Measuring inpatient costs in a cohort

Often when the study design includes a cohort with longitudinal follow up then inpatient costs are presented as part of overall cost (outpatient plus inpatient costs) [67, 109-113]. In these studies costs are presented as total cost of inpatient treatment over time (100 patient years, 12 months, patients lifetime etc.), but do not provide a breakdown of cost by reason for admission, nor do they comment on the overall admission profile and burden on the respective inpatient facilities.

It is likely that results using this approach are skewed towards patients in care and treatment, who ultimately may use less inpatient resources than those who are not part of a HIV care and treatment program and may not even know their status. The literature notes that inpatient costs are higher around the time of ART initiation, particularly prior to initiation, but then decrease once on treatment [109, 110]. This supports the notion that trying to determine HIV related inpatient costs by following cohorts, which are more likely to be treated, can lead to an underestimation in both overall cost and cost per admission. If the intention of the study is to understand the cost and burden of HIV on inpatient facilities then the best approach would be to examine the population being admitted to a hospital rather than starting from the patient and following them waiting for an admission. This thesis aims to examine the burden of HIV on inpatient facilities and follows this approach.

Cost as a function of health

Intuitively one would expect 'sicker' patients to incur greater inpatient costs than less sick patients and this is supported by literature around HIV related inpatient admissions HIV infected adults have higher costs than those not infected – driven mostly by longer lengths of stay, but also more drug and diagnostic usage [82]. Amongst HIV positive inpatients lower baseline CD4 counts and higher viral loads are associated with increased mean inpatient costs predominantly between four months before and eight months after starting antiretroviral treatment [109]. Not surprisingly then, other research shows that starting patients on antiretroviral treatment earlier with higher CD4 counts reduces hospital admission rates and the associated costs [76].

Cost drivers

If inpatient costs are determined based on patient level resource usage (i.e. micro costing), it not only provides a more accurate cost estimate but also provides an opportunity to look at the main cost drivers. Interestingly, although antiretroviral medication was always considered very expensive, particularly in the years around the national roll out, medication costs comprised a small proportion of total patient specific costs [69]. There are two possible reasons for this. Firstly, many patients were neither on ART when admitted nor were they ever initiated while admitted and secondly, for those patients on treatment, most were supplied ART from outpatient ART programs and therefore this was not considered an inpatient cost [69]. In adult [102] and pediatric [114] populations it is reported that the bulk of inpatient costs are non-curative. The majority of non-curative costs consist of costs associated with length of stay (often referred to as 'hotel' costs), which means that the difference in inpatient costs by HIV status is being driven by a longer stay rather than more intensive resource usage per day.

4.6 Summary of HIV inpatient treatment in South Africa

Prior the availability of antiretroviral treatment in the public sector end of life, palliative inpatient treatment was the bulk of the government public health response to the HIV epidemic. With the roll out of public antiretroviral treatment

the treatment model shifted to outpatient treatment with the expectation that inpatient facilities would see a subsequent reduction in burden. There is limited literature showing any change in the HIV burden being placed on inpatient facilities in South Africa in the context of large-scale antiretroviral access and the literature that is available does not identify the major drivers for this burden and the associated costs and outcomes. This critical gap in the literature is addressed by this thesis.

4.7 References

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CHAPTER 5 - HIV outpatient treatment

5.1 Introduction

This thesis was designed to investigate the impact of a large-scale treatment program on HIV treatment delivery in a resource limited setting. As noted in Chapter 3 the HIV treatment delivery model includes both inpatient and outpatient treatment components. This chapter focuses on reviewing the literature related to HIV related *outpatient* treatment.

In contrast to inpatient treatment, outpatient treatment can be broken down into distinct models of treatment as described in section 3.3. using the characteristics provided by Duncombe [34]. In order to increase the scale of the HIV public treatment program in South Africa the two major characteristics, which changed, were location (i.e. decentralization) and health worker cadre (i.e. task shifting). The other characteristics of intensity and frequency were altered only slightly over time. Section 5.3 describes the models of decentralization and task shifting that have been used in South Africa and sections 5.4 and 5.5 review the associated outcomes and resource usage (costs), respectively.

5.2 Review method and data

This section reviews the academic literature on HIV related outpatient treatment. I defined HIV related outpatient treatment as the chronic treatment of HIV (not HIV related conditions) in a facility where patients were treated on an outpatient basis (i.e. not resident or admitted). Some publications examine both the inpatient and outpatient treatment of HIV positive patients. For the purpose of the review, all publications that covered the outpatient treatment of HIV positive patients were considered irrespective of whether or not they included inpatient treatment as well.

Outpatient treatment in South Africa has evolved substantially since it was first rolled out in 2004. There have been numerous studies that focus on the original outpatient model implemented in 2004 and described in Chapter 3. This model is not the focus of this body of work. As a result of the increased need, demand and government mandate for antiretroviral treatment, the outpatient model was changed in 2010 to nurse initiated and managed antiretroviral treatment (NIMART). The NIMART model utilized task shifting, which included decentralization, to improve access to treatment. This literature review focuses on the impact of this model and any other alternative models of task shifting and / or decentralization proposed for South Africa.

The primary literature search was to identify publications that reported on the impact of the current outpatient treatment model, NIMART, in South Africa. The following search terms were used in PubMed to produce the initial list of publications: “South Africa” and “Outpatient” and “HIV” limited to publications including and after 2010, when NIMART became part of the guidelines. This was done initially at the start of the PhD and subsequently updated and revised based on a final search conducted on 29 January 2016.

The updated search yielded 87 unique records. These publications were then reviewed initially by title and then by abstract (38) for those that remained. Publications were excluded if they:

- Reported on countries other than South Africa,
- Reported on outpatient treatment models prior to 2010,
- Focused on a disease other than HIV,
- Did not report on the cost and / or outcomes for HIV outpatients.

There remained a total of 29 unique publications, which required full review.

A secondary search was done to capture papers specifically evaluating alternative treatment models using task shifting and / or decentralization. The following search terms were used in PubMed to produce the initial list of publications: “South Africa” and “HIV” and “decentralization” or “task shifting” with no limitation on year of publication. This was done initially at the start of the PhD and

subsequently updated and revised based on a final search conducted on 29 January 2016.

The updated search yielded 335 unique records. As this thesis is particularly focused on the impact of the public sector antiretroviral treatment program, which only started in 2004 in South Africa, 162 publications published prior to 2004 were excluded.

The titles of the remaining 173 publications were reviewed initially by title and then by abstract (89) for those that remained. Publications were excluded if they:

- Reported on countries other than South Africa,
- Focused on a disease other than HIV,
- Did not describe an outpatient model of treatment,
- Did not incorporate task shifting or decentralization.

There remained a total of 69 unique publications, which required full review.

The results of the primary (29) and secondary (69) search were combined and the unique articles were reviewed. In order to be included the articles had to include the current NIMART program in South Africa or speak to other models or examples of task shifting and / or decentralization in South Africa. As each publication was reviewed the relevant references were cross-checked and in this way additional publications and grey literature were added to the publications finally reviewed and included. A total of 18 publications were included and are summarized and tabulated in Appendix I (Supplementary Table 9). The sub-sections below pull together information from these publications into three main themes: (1) models of task shifting and decentralization; (2) outcomes of HIV positive inpatients and (3) resource usage and/or costs of HIV outpatient treatment.

5.3 Models of task shifting and decentralization

Task shifting and decentralization definition

The increasing scale of the HIV epidemic in resource-limited settings often puts pressure on the health care worker / health care facility centric approach to HIV treatment delivery. In 2008 the WHO released one of the first global guidelines recommending that countries incorporate task shifting into their national strategy for organizing the health workforce [115]. There are many definitions of task shifting and decentralization in the literature, but in order to maintain consistency for this review we will use the broad definitions from the World Health Organization. According to the WHO task shifting is the "rational redistribution of tasks among health workforce teams" [115]. Typically task shifting would be the movement of the provision of certain health services from one cadre (i.e. doctors) to another less trained cadre (i.e. nurses). Decentralization is often a component of task shifting, but may not always occur. Decentralization is the movement of the provision of services from one facility (i.e. hospital) to another less specialized facility (i.e. primary health clinic). For the purposes of this review we consider decentralization to be a component of task shifting.

Public health environment conducive to task shifting

In 2006 the first cost effectiveness analysis of antiretroviral treatment in South Africa using local, primary cost data was published [111]. This analysis noted that universal coverage (i.e. every person in need being able to access treatment) of antiretroviral treatment would place an unprecedented burden on developing country resources (i.e. finances, infrastructure and health care workers) and recommended that less resource intensive delivery models for ART be explored even if they were less effective [111]. In scaling up HIV treatment access using the initial doctor-led treatment model the limiting resource for South Africa was health care workers. When compared with many other sub-Saharan African countries South Africa is relatively well resourced. However when compared with developed countries, sub-Saharan Africa (SSA) has a shortage of health care workers as indicated by a much lower ratio of health care worker to population across all levels of health care workers [116]. This problem is exacerbated by the fact that within these countries, including South Africa, there is a high burden of

infectious disease, high emigration of trained health care workers and low motivation for those that remain [116]. South Africa may be worse off than others as it suffers from a quadruple burden of disease: communicable, non communicable, peri-natal and maternal, and injury related [117]. In addition to that the success of the HIV treatment program has increased life expectancy, which is likely to contribute to the growing non-communicable disease burden while at the same increasing the burden on facilities for managing HIV patients on treatment [117].

In South Africa it has been noted that limited human resources in the health care sector are a major barrier to achieving universal antiretroviral treatment coverage [118]. HIV prevalence amongst doctors and nurses was reported to be similar to that of the general population, which means that the epidemic is eroding the very human resources needed to curb the spread of the disease [119]. It is has been put forward that this human resources shortage could be addressed in part or fully by task shifting, but on its own task shifting probably cannot be a permanent solution to health worker shortage [120-123]. Task shifting does not reduce the number of staff, but rather reduces the reliance on certain cadres. For task shifting to be a permanent solution the current cadre accepting new responsibilities would have to have spare capacity (i.e. otherwise other services would be compromised) or a new cadre that has never been part of the health care workforce would have to be created. Task shifting does however provide an option, which in the short- to medium-term increases access to treatment and may be cost effective.

Taxonomy of task shifting models

Task shifting with or without decentralization can occur at any level within the public health system and in some extreme instances it can even move certain tasks outside of the traditional public health system (i.e. movement of treatment to a community center administered by non-clinicians). It can also shift some or all of the steps associated with treatment (i.e. management only or initiation and management). The various combinations of task shifting and decentralization can be classified according to the cadre to whom (i.e. non-physician clinician, nurse, people living with AIDS) and the facility to where (i.e. hospital, clinic, community

center) the task is being shifted to [116, 124] as well as the degree (i.e. partial or full) of task shifting [125] or decentralization [126]. Using a combination of the classifications above I discuss task shifting according to the following classifications below: 1) the original treatment delivery model in South Africa, 2) partial task shifting within the health system, 3) full task shifting within the health system, and finally 4) task shifting outside of the traditional health system.

Original treatment delivery model

The South African national antiretroviral treatment delivery model launched in 2004 was based on national treatment guidelines. These guidelines stipulated the minimum staffing levels and the facility characteristics necessary for accreditation as a treatment site.

The treatment model was doctor led, an approach which was more typical of less resource-constrained settings. Doctor led care was initially chosen because of legislation restricting the prescription of antiretroviral treatment to doctors. As a result treatment sites were largely hospital based as this is where many of the doctors in the public sector were located [122]. In theory the starting point for patients was the primary health clinics where nurses would screen and diagnose patients with HIV. Once patients were eligible for treatment they would be referred to antiretroviral treatment clinics for treatment initiated and managed by doctors [119]. Antiretroviral treatment clinics were single service facilities (i.e. not integrated) and generally associated with or located within a secondary or tertiary facility. The treatment program in South Africa was centralized and vertical and these characteristics constrained the planning and deployment of the antiretroviral treatment program [127]. As the treatment delivery model was prescribed and required accreditation there was little room for innovation, which meant that provinces, districts and facilities were not able to adapt the model to suit their situation, needs and constraints [127].

The human resource requirements of this model and the rapid scale up of the program resulted in the development of new cadres of health care workers (i.e. lay counselors, peer educators) to support its implementation [119]. Even with the support of these new cadres there were not enough health care workers to initiate

and manage the expected patient volumes if doctors remained the primary clinician for HIV treatment. The increasing scale of the program and the limits of the doctor led treatment model led to calls for task shifting of treatment roles [55, 128].

Partial task shifting within the health system

The scale up of the national HIV treatment program in South Africa resulted in a number of changes to the antiretroviral treatment delivery model, one of which was the role of nurses in HIV care and treatment including task shifting [119]. In the early stages of the national roll out of antiretroviral treatment in South Africa there was a regulatory barrier to full treatment task shifting from a doctor to a nurse. The nurses scope of practice as defined by governmental and regulatory policies did not allow them to initiate and manage patients on antiretroviral treatment preventing full treatment task shifting [119]. As a result there were a number of attempts to partially shift treatment to a lower cadre and / or facility in ways that were still considered appropriate for the regulations at that time.

A number of these attempts are described in the literature and often referred to as "down referral". One of the earliest reported attempts of partial task shifting and partial decentralization occurred in the Free State and was described by Janse van Rensburg and colleagues in 2008 [32]. This model differed from the original treatment delivery model by using doctor-led hospital sites to initiate patients and then directing or referring patients to nurse-led primary health clinics to monitor patients on treatment. Patients then returned to doctor-led initiation sites for repeat prescriptions and more advanced diagnostic monitoring (i.e. viral loads) [32]. The partial task shifting approach of doctor initiation and management shifting to doctor initiation and nurse management within the same facility (i.e. no decentralization) was first evaluated in a randomized clinical trial setting (CIPRA) in South Africa by Sanne and colleagues in 2010 [129]. In the same year Searle and colleagues reported a similar approach to that of Sanne, except in a more routine setting and involving decentralization. In this instance patients were down referred from a doctor initiation site once stable to a primary health clinic for monitoring by a nurse and then up referred if the patients were no longer deemed stable [130]. Medication was dispensed at the initiation facility and transported to the primary

health clinic for distribution to patients to comply with the regulations at the time regarding dispensing and site accreditation. In 2011 we conducted the first full evaluation (i.e. outcomes and costs) of a similar model, which used partial task shifting and decentralization in Gauteng, South Africa. This publication is Paper 1 (CHAPTER 7) of this thesis [131, 132]. The most recent model of partial task shifting and decentralization was reported by Grimsrud and colleagues in 2014 and referred to a program in the Western Cape, South Africa [133]. This model was similar to those described above in that it down referred stable patients already initiated to nurse managed care, with the difference being that the patients were referred to a nurse run facility on the same premises, so there was no true decentralization [133].

Overall the partial models of task shifting in South African always included some component of handing over parts of the treatment function from a doctor to a nurse. Decentralization was often part of this process, but not always. The next step would be the shift of the full treatment function to a lower cadre when regulations (i.e. prescription and dispensing regulations) allowed.

Full task shifting within the health system

Prior to 2010 in South Africa the scope of practice of nurses did not allow them to initiate and manage patients on antiretroviral therapy [119] as they were not able to prescribe antiretroviral drugs. In addition, accreditation to become a comprehensive care, management and treatment site (CCMT) excluded most primary health clinics, which effectively stopped decentralization.

Despite these regulatory constraints Médecins Sans Frontières (MSF) piloted a program of full task shifting and decentralization with government agreement, starting in 2004 as the national treatment program rolled out in South Africa. The model was known as the Lusikisiki model and comprised decentralization of services to a primary health clinic, task shifting of all treatment responsibilities from a doctor to a nurse and community support for the patients [55]. This model was managed directly by MSF, so while it did use public health facilities, it could not be called routine implementation. In hindsight the MSF team was far ahead of the government and other partners with this treatment delivery model. It took the

government six years (2004-2010) to adjust the treatment guidelines and regulations to allow nurse initiation and management of patients (NIMART) and decentralization to primary health clinics. This long delay in part reflects the government's unclear priorities during a period when the President and the Minister of Health were supporting scientists that denied the link between HIV and AIDS [44]. In addition to that South Africa had chosen a model of treatment based on resource rich countries where doctor centric models of treatment were possible. The shift to NIMART required health professionals to change their mindset around the complexity of HIV care and treatment in addition to change the regulations to make nurse treatment at a primary health level possible [119].

In those six years the only other significant report that evaluated or reported on full task shifting and decentralization in South Africa was a pragmatic, parallel, cluster-randomized trial run in the Free State province by Fairall and colleagues [134]. It was known as the STRETCH model (Streamlining Tasks and Roles to Expand Treatment and Care for HIV) and involved training nurses to be the primary clinician and shifted treatment to primary health care facilities [134]. The implementers noted that STRETCH was complex to implement and the pragmatic nature of the trial meant that very few (26% of patients in the intervention arm) patients were actually initiated onto treatment by nurses [123, 134]. The STRETCH model also fell short of routine implementation because of the nature of the trial and the additional support offered.

In 2010, with launch of the new national treatment guidelines, the South African government officially endorsed a full treatment task shifting approach from doctors to nurses and decentralization from specialized facilities (i.e. CCMT sites) to primary health clinics [54]. Regulatory obstacles were overcome with short intensive training qualifying nurses to initiate and manage patients on ART. Today most of the historic CCMT sites still exist and remain doctor led, within specialist treatment facilities (i.e. not integrated with other services), but the majority of new patients are initiated by nurses at primary health clinics. A 2012 survey of African health professionals across 15 countries found that NIMART is practiced widely, but regulations and pre-service training are often insufficient to support this model. They recommend additional investment to make NIMART sustainable and

effective [135]. There is no full (costs and outcomes) comparative evaluation of the routine implementation of the NIMART program in South Africa. This gap is addressed in this thesis.

Task shifting outside of the traditional health system

Task shifting and / or decentralization still traditionally stay within the public health system (i.e. task shifting is to another medical professional and decentralization is to another health facility). Given South Africa's serious human resource constraints it has become clear to policy makers that additional approaches are needed (e.g. moving patients from health care facilities into the community for management by community members). South African public health professionals recognized early on, that task shifting was essential, but also that it must extend beyond the level of the medical professional to volunteers and the community [136, 137]. In 2013 Davies and colleagues reported that 40% of nurse posts in South Africa lie vacant and up to 50% of their work time is consumed with administrative tasks [138]. This suggests that overdependence on nurse-based task shifting is unlikely to solve the limitation of the health care system and we should be considering options outside of the traditional health system.

One option is to identify small components of treatment provision that might be appropriate for task shifting to a person not medically trained. Mitchell and colleagues present one example of this type of task shifting by triaging patients on treatment to non-physician counselors using an electronic screening protocol [139]. The screening protocol is used to determine which patients require a full medical exam with a clinician (doctor or nurse). It has been estimated that the tool might lower the clinician burden by nearly 30% [139].

A 2013 systematic review of antiretroviral treatment task shifting and decentralization beyond the health system (i.e. into the community) in sub Saharan Africa (SSA) found only three countries that had evaluated such approaches and South Africa was not one [140]. Most of the models were some variation on home-based antiretroviral treatment delivery, but one was patient-led antiretroviral treatment dispensing in peer groups [140].

Subsequent to the systematic review, in 2015, Grimsrud and colleagues report on a model of managing stable ART patients outside of the traditional health care system called community-based adherence clubs [141]. This involves the full decentralization of treatment services to a community venue where all treatment related services including clinical visits and monitoring bloods are performed. Partial task shifting occurs from the nurses to community health workers who monitor patients and dispense prepackaged drugs, but nurses still conduct clinical checkups and monitoring bloods. Apart from reducing the use of limited resources, task shifting to the community may have the added benefit of reducing the visit burden on the patient and in so doing improve retention [142].

South Africa does not have clear guidelines on the use of volunteer non-medical personnel in the treatment of antiretroviral treatment, although many facilities make use of the cadre. Task shifting to volunteers does occur (i.e. for patient education or counseling), but Campbell and colleagues note that it is not a sustainable approach because stipends are not always offered and when they are they are usually low and paid irregularly [136]. In order for task shifting and decentralization beyond the health system to be sustainable and effective there needs to a strategy for recognizing the volunteers as part of the official medical community and remunerating them accordingly.

Task shifting in specific populations

Almost without exception, the HIV treatment task shifting literature focuses on the general adult population with no information on specific sub populations that may respond differently to task shifting and / or decentralization. The most obvious population not covered is the pediatric population. There have been no publications that report specifically on the task shifting and decentralization of pediatric HIV treatment in South Africa despite the fact that nurses in primary health clinics are treating pediatric patients. Fayorsey and colleagues report on the decentralization of pediatric treatment in five sub Saharan African (SSA) countries, none of which are South Africa [143]. A subsequent systematic review in 2014 by Penzzato and colleagues identified eight cohort studies that looked specifically at this [144]. Only one of these cohorts was in South Africa, but in the pre-NIMART era and only the maintenance of pediatric patients had been moved to nurses

[145]. To date there has not been a proper evaluation of routine task shifting for the management of pediatric patients in South Africa.

As a result of the high rate of several opportunistic infections associated with HIV, in particular tuberculosis, there have also been programs of decentralization and task shifting of tuberculosis treatment for co-infected patients. Jacobson and colleagues examined this in a rural setting in Kwazulu-Natal [146] where they explore down referral of select stable TB patients on tuberculosis treatment to primary health clinics from the district hospital. These patients were also HIV infected and on antiretroviral treatment. Task shifting is thus also being used for more complex HIV positive patients (i.e. those with co morbidities). Given the high prevalence of co-morbidities amongst HIV infected patients this means that a much larger percentage of HIV patients could be managed with the task shifting approach.

Task shifting of non-treatment functions

The majority of task shifting in the antiretroviral treatment delivery model has focused specifically on clinical treatment, but there are some supportive roles that have also benefited from task shifting.

In 2010, not only did the South African government officially endorse NIMART, but they also amended the National Health Act (Act No. 61 of 2003) to allow non-health care workers to draw blood specifically for HIV screening [147]. The Act was then updated again in 2011 to allow the collection of buccal samples as well as blood (i.e. for oral swab and blood HIV testing) [148]. Nurses, who had to conduct any procedure that involved blood or tissues samples, previously held this role. The change in regulation allowed task shifting from nurses to minimally trained lay counselors for HIV testing. This change has been fully adopted by the public health community such that in 2015 Mwisongo and colleagues conclude that the majority of HIV counseling and testing is performed by lay counselors and testers [149]. As with volunteers, the recognition of this cadre as part of the formal health system is essential if it is going to be improved and supported [149].

These supportive roles (i.e. lay counselors, lay testers) have also facilitated the scale up of antiretroviral treatment in South Africa. There is very little literature that describes these models of task shifting and none that conduct full evaluations (i.e. costs and outcomes) of them in routine settings.

Another area where task shifting could be beneficial is around dispensing medication. A pharmacist in a medical facility traditionally does the dispensing of antiretroviral medication. If it were possible to prepackage drugs for stable patients and have them delivered, this task could be shifted to lay people outside of facilities in convenient community locations (e.g. church halls) [142]. Such an approach would also free up pharmacist's time and decongest clinics. This approach might also have benefits to the patient in terms of time and money saving because of the proximity of the pickup point to where they live.

5.4 Outcomes

In order to determine the success of the HIV treatment program (inpatient and outpatient treatment) it is necessary to be able to measure changes in the outcomes of HIV patients over time. HIV outpatient treatment is defined as the provision of antiretroviral treatment in an outpatient setting (i.e. without admission). Depending on the perspective taken by the evaluator there are a number of ways in which the outcomes of the outpatient treatment delivery model could be evaluated. From the health care provider perspective treatment outcomes might be considered the most critical outcome, yet from a patient perspective quality of care or access may also be relevant. The outcomes of the various treatment models according to these perspectives are presented below. For the treatment outcomes I use the general treatment model classifications identified in section 5.3.

Treatment outcomes – Partial task shifting within the health system

As noted above, partial task shifting was often referred to as 'down referral' and normally included just the shift of the management of patients already on treatment, to nurses. In 2006 a down referral program of stable patients on

treatment showed that the majority of patients reached the down referral facility (78%), of those only 13% became lost to follow-up and almost all patients with 6- and 12-month viral loads were suppressed (90% and 97% respectively) [130]. There was however no comparison arm so the outcomes of the down referral program could not be compared with those of the standard of care. Subsequent to this, the results of multiple comparative studies (randomized clinical trial, pragmatic clinical trial and evaluation of routine implementation) showed that nurse management of patients after treatment initiation is no worse than doctor managed care in terms of retention, viral load suppression and adherence [129, 131-134, 150, 151]. Paper 1 of this thesis was part of this body of evidence and showed for the first time that partial task shifting was effective in a routine setting [131, 132]. Two systematic reviews confirmed the findings of these studies concluding that there is likely no difference in treatment outcomes between doctor and nurse managed care for adults [125] and pediatric patients [144]. One study tracked the retention of patients through the down referral process and identified that the biggest loss was prior to reaching the down referral facility (59%) or after their first visit (10%) and only a third (31%) were lost after more than one visit [151]. These results provided strong evidence for the benefits of partial task shifting in South Africa and supported the investigation of full task shifting.

Treatment outcomes – Full task shifting within the health system

There is very limited data on the outcomes of full task shifting in South Africa. The first report of full task shifting and decentralization in South Africa (2006) (Lusikisiki Model) showed that the nurse-led primary health clinic site achieved good, equivalent outcomes compared to the standard of care at the time, doctor-led care [55]. The only other report is that related to the STRETCH trial, which found no difference in mortality between doctor initiated and managed care compared to nurse initiated and managed care, but this lack of effect may have been driven by the large difference in loss to follow-up between arms (2% primary health clinics vs. 19% hospitals) [134]. The results of this trial are also difficult to interpret as the hospital, doctor initiated arm had patients with more advanced disease and the majority of patients in the primary health clinic, nurse initiated arm were actually initiated by doctors [134].

Several papers reviewed the global literature for examples of full task shifting, but there are still very few publications that report on this. A systematic review of sub Saharan Africa reports that full task shifting reduces loss to follow up and increases retention [152]. Interestingly, this benefit is attributed to the decentralization, which is often associated with task shifting [152]. A meta-analysis published in 2013 examining treatment outcomes of full task shifting showed that mortality, CD4 count increase and viral load failure were similar across groups, but that lost to follow-up was lower amongst the non-physicians (i.e. nurses) [153]. This improvement in lost to follow-up may again be linked to the decentralization associated with the non-physician arm. This was supported by a systematic review of full task shifting which found high quality evidence to support no additional mortality risk at 12 months and moderate quality evidence to support decreased lost to follow-up in the non-physician arm at 12 months [125].

Treatment outcomes – Decentralization

There is a small body of literature that speaks specifically to decentralization (i.e. the movement from one level facility to another facility at a lower level or to outside the traditional health system), as opposed to task shifting with decentralization as one component. A meta-analysis of decentralization has shown that when compared with standard of care, partial decentralization (i.e. only movement of some of the treatment function) led to less attrition after 12 months in care, but that full decentralization showed no difference in mortality or loss to follow-up [126]. When decentralization moved treatment outside of the traditional health system (i.e. to the community from a health facility) there was no difference in mortality or loss to follow-up when compared with the standard of care [126]. A review of pediatric treatment decentralization in sub Saharan Africa (SSA) (five countries not including South Africa) showed that compared to secondary or tertiary health facilities, primary health facilities show a reduction in loss to follow-up and mortality [143]. This body of literature suggests that some of the benefits to reducing attrition may be related to the decentralization component of task shifting – that is, making the treatment more accessible for the patient.

Treatment outcomes – Task shifting outside of the traditional health system

Only two systematic reviews have reported on the outcomes of task shifting outside of the traditional health system – neither of them included any South African studies [125, 140]. The first review concluded that there was moderate quality evidence showing no difference in mortality or loss to follow-up at 12 months [125]. The second review included studies with very different patient populations, but all of those that were comparative studies reported outcomes that were similar between facility based and community based programs [140]. The only publication to report outcomes of task shifting to locations outside of the traditional health system in South Africa was by Grimsrud and colleagues who report on the treatment outcomes from a community-based adherence club. At 12 months community-based adherence clubs were associated with low rates of mortality, lost to follow-up and viral load rebound (0.4%, 6.2% and 1.7% respectively) when compared with standard of care and when compared with facility based adherence clubs had similar results [141].

Patient outcomes

From a patient perspective there may be a number of benefits or drawbacks to task shifting and / or decentralization treatment models. Using task shifting to increase access does mean that patients will be treated by a lower cadre of health care worker and / or in a lower level health care facility. This may be accompanied by some perceived or real differences in quality of care from the patients' perspective. Generally patients were accepting of management by nurses, and were satisfied with the service because they felt more respected, perceived less stigmatization and had longer, more holistic consultations when compared with doctor led care [150] [151, 153]. Despite these expressed benefits some patients still preferred seeing a doctor over a nurse as their primary health care provider [150]. Patients in two other studies showed slightly differing perspectives stating that nurse initiation and management did not reduce the time to treatment initiation [123], they preferred their existing relationship with the centralized facility, perceived less stigmatization at the centralized facility and thought that this facility offered more ancillary services [118].

Overall the literature suggests that task shifting, including decentralization, would reduce the costs experienced by the patient in accessing treatment. This would

occur due to reduced transportation and meal costs, reduced waiting and travel times, and the reduced visit frequency in some instances [118, 133, 150]. That said, because many down-referred patients preferred to be treated by doctors, it was reported that some incurred higher costs to visit private physicians and practice self-care [150].

Task shifting (partial and full) within and outside the health system appears to, at least maintain treatment outcomes and potentially provide some non-treatment benefits to patients. The impact of large-scale full task shifting of HIV treatment from doctors to nurses in South Africa as routine practice has not been answered in the literature and this is one of the research questions addressed in this thesis.

5.5 Resource usage and costs

In resource constrained settings achieving desirable outcomes needs to be balanced against the resources used to obtain those outcomes and their associated cost. Resource usage for outpatients can refer to any input used to treat patients in an outpatient setting. This would include, but is not limited to, drugs, diagnostic testing and visits to a health care worker. Resource usage can be converted to financial costs, which can also incorporate less tangible resource usage like utilities or space.

There are generally two primary approaches to costing; 1) micro costing based on actual patient resource usage with unit costs assigned; and 2) modeled costing which uses assumptions regarding resource usage and / or costs based on expected usage (i.e. treatment guidelines) or other relevant literature. Given that HIV treatment is intended for the life of the patient, micro costing is often done over a discrete time period (i.e. 6 or 12 months after initiation), whereas modeled costs are easier to extrapolate for the life of the patient. The perspective for these resource usage and / or costing exercises is generally that of the health care provider (i.e. what costs does the health care provider incur providing outpatient treatment to a particular patient?) rather than that of the patient.

There is a dearth of resource usage and cost data for comparative studies of task shifting and / or decentralization for HIV treatment in South Africa. Comparative studies that use the same costing methods and outcome measures allow a direct comparison between alternative treatment models that deliver the same outcome. These evaluations are critical for evidence based policy decisions as they balance effectiveness against available resources and cost. Only two papers were identified that reported micro costing of outpatient treatment and one of those papers is Paper 1 of this PhD.

Modeled Costs

South Africa has over the years had a number studies which have modeled the costs and outcomes of HIV treatment [111, 154-159]. There was no consistent model or method used across these studies, but the majority estimated costs from the providers perspective and used Markov states. Many of them investigated proposed interventions (i.e. changes in treatment guidelines, changes in treatment eligibility), yet none of them reported on the costs or outcomes associated with the task shifting of treatment. A South Africa centric Markov cost model, the National ART Cost Model (NACM), was used in preparation for the change in guidelines to incorporate task shifting and decentralization. This was a budget modeling exercise and was done by Meyer-Rath and colleagues for the period 2010-2017 [160]. It included not only task shifting from doctors to nurses, but also from pharmacists to pharmacy assistants as well as decentralization to primary health clinics [160]. The inputs (i.e. costs and effectiveness) for this model were generated from the literature, as at the time there were no studies to estimate these costs accurately. The model indicated that national treatment guidelines could be improved without increased budget, partially through task shifting which reduced costs [160]. Models are essential for the determining projected costs and outcomes into the future, which in turn provides evidence for policy change. Their usefulness and accuracy is directly linked to quality and relevance of the data used to populate them. Evaluations reporting the effectiveness and unit costs associated with various proposed or actual changes in the guidelines are critical in supporting these models and evidence based policy change.

Visits and staffing costs

Even if task shifting does not reduce the number of patient visits required, it might reduce the cost of each visit as it would be conducted by a health care worker of a lower cadre. In 2009 Zachariah and colleagues confirmed this and report that the cost and remuneration of medical assistants and clinical officers is lower than that of doctors with comparable performance in certain situations [116]. More recently Hontelez and colleagues used a time in motion study to determine the requirements for staffing under various scenarios in South Africa [161]. They found that nurse-initiated treatment could reduce the overall salary costs by 7% compared to the doctor centric model [161].

Of course if the visits required by the patient increase with task shifting the cost benefit of task shifting may be diminished. Paper 1 (CHAPTER 7) showed that for the management of stable patients the biggest difference in resource utilization was related to the number of patient visits – there were more at the primary health clinic run by nurses compared to those at the hospital clinic run by doctors. The primary health clinic visits however were at a much lower cost per visit which meant that there was not much difference in the overall visit costs [131]. These findings were reported in Paper 1 of the thesis. The STRETCH trial of nurse initiated antiretroviral treatment showed similar results in that the total number of visits (both doctor and nurse) in the nurse initiation arm was higher when compared to the control arm [134]. In the STRETCH trial it was also noted by the nurses that there was an increase in administrative burden, but the authors suggest that this was as result of the increase in the number of patients rather than the fact that nurse led care has a higher administrative burden per patient [123].

In Johannesburg hospitals it was reported that in the 12 months after the introduction of NIMART there was a 39% reduction (389 to 238 patients per month) in the number of patients that initiated at the hospital facilities (i.e. original CCMT sites), while at the same time a 26% increase in the monthly ART patients initiated in the region (580 to 732) [162]. This suggests a shift in initiations from the hospital facilities to the primary health clinic (decentralization) for initiation by a nurse (task shifting), potentially attributable to better access. The reduction in

visits at the hospital clinic freed up resources, which allowed for more complicated cases to be managed at the hospital clinic [162].

The only study examining extending antiretroviral treatment into the community reported that patients could be kept out of the health care facility completely (zero visits at the facility) and that management in the community required less frequent monitoring and fewer clinic visits [141].

Even when there was not necessarily decentralization, task shifting was reported to increase nurse workloads and decrease doctors' routine workload, suggesting that task shifting was relieving the scarcest resource [123]. Task shifting does not necessarily reduce the number of visits, but rather shifts it to a lower cadre. If the lower cadre is already fully utilized and there is no increase in the staffing at this level then task shifting can result in the crowding out of existing services [32]. For this reason the true impact of task shifting on staffing may not be fully realized if we just examine HIV treatment, but rather need to incorporate all the services at a facility or within the public sector.

Patient costs

When task shifting and decentralization are applied, from the patient perspective the costs are expected to be lower when compared with doctor led care at centralized facilities. The lower patient cost can be attributed to easier access (i.e. closer facilities) and reduced travel costs [116]. A meta-analysis of the effect of task shifting found only three studies that included patient costs and confirmed that there was indeed a reduction in patient travel costs [125].

Total costs

A systematic review of task shifting from doctor-led to nurse-led care for HIV treatment concluded that there was conflicting evidence regarding the cost to the health care system and that the implementation costs of nurse led care might be higher than doctor led care [125]. There were two studies undertaken in South Africa on the cost of providing nurse-led compared to doctor-led care and they also reported conflicting results. In Paper 1 of this thesis we found a slightly lower cost (11% reduction) for the management of stable ART patients by a nurse at a

primary health clinic compared to doctor management at a hospital clinic [131]. This was in contrast to the STRETCH trial, which reported higher costs for nurse initiation and management of patients compared to doctor initiation and management [163]. A large proportion (45%) of the difference in cost between the two arms in the STRETCH trial was explained by the difference in the number of nurse and doctor visits between arms [163].

There is even less cost data for task shifting that moves treatment out of the traditional health system into the community. A systematic review of community based antiretroviral treatment suggests that costs of the community model may be similar to that of the facility model [140]. This was only based on a few studies and none of which were in South Africa [140].

5.6 Summary of HIV outpatient treatment in South Africa

The original South African outpatient HIV treatment model focused on doctor-led care in specialist clinics. In order to rapidly expand HIV outpatient treatment in South Africa it was necessary to adjust the model to allow nurse led care. There was very little in country evidence to support this change, both in terms of effectiveness and cost. Although the majority of HIV outpatient treatment in South Africa is now nurse-led there is still no full evaluation (i.e. effectiveness and costs) of this approach in a routine setting.

This lack of research to support evidence-based policy around HIV treatment delivery models is not unique to South Africa. A recent systematic review of HIV treatment delivery models in sub Saharan Africa (SSA) highlighted the dearth of comparative studies providing evidence for implementation strategies [124]. This thesis aims to provide evidence to support the policy decisions around the implementation of task shifting for the management of HIV outpatient treatment.

5.7 References

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CHAPTER 6 - Aims and objectives

6.1 Rationale for the studies contributing to this thesis

6.1.1 Overview

The intention of the thesis is to make a meaningful contribution to the public health literature of HIV treatment models for countries with large, generalized epidemics, in particular how the treatment models might evolve in order to reach scale. In order to do this a number of studies were conducted, the results of which are synthesized in this thesis.

South Africa was considered a suitable country to conduct this research as it has both a large, generalized HIV epidemic (Chapter 2.3) and one of the largest treatment programs in the world (Chapter 2.4). The intensive nature of the data collection required to conduct the research limited the number of study sites. I decided on study sites within Johannesburg, as Johannesburg was a clear example of an urban population with both relatively high HIV prevalence and good treatment coverage [164].

While this section focuses on only the most recent and relevant literature, it clearly highlights that South Africa has a relatively extensive body of public health research on HIV and its associated treatment models. In order to make the research presented in this thesis relevant I focused on topics which were both under researched and had clear policy implications. Very few studies have used primary, patient-level data to present both the costs and associated outcomes of public HIV treatment models. Using primary, patient level data is time consuming and resource intensive, but produces detailed, reliable results. Including both costs and outcomes is required for a full evaluation; in particular if the research is to be used to inform policy in a resource limited setting like South Africa. For this

reason all of the research presented here incorporates a methodology, which covers both costs and outcomes, based on primary, patient level data.

The work presented in this thesis is the product of three independent study protocols, each of which received its own site and ethics approval. This was necessary because the study populations, study designs and objectives were different and could not be incorporated into a single study protocol. The treatment model consists of two major components; chronic outpatient treatment and acute inpatient treatment. Two studies deal specifically with the outpatient component (Chapters 7 and 8, Papers 1 and 2 respectively) and one study deals with the inpatient component (Chapters 9 and 10, Papers 3 and 4 respectively). The rationale for each individual study is provided in the sub-sections below.

6.1.2 Study 1: Management of stable patients by nurses at a primary health clinic

As outlined in section 3.4 the initial outpatient treatment model for HIV in South Africa used stand-alone specialist clinics (vertical), led by doctors. Vertical health programs require time to setup and are often relatively expensive as they stand outside existing programs rather than leveraging off existing infrastructure. The use of doctors as the primary care treatment provider in the HIV program also limited the scale of the program as South Africa has insufficient health care professionals, in particular doctors.

Once it was clear that highly active antiretroviral treatment (HAART) was effective in the treatment of HIV and it was integrated into the public health system in South Africa it became imperative to scale up the program rapidly to try and meet the need and demand for services. The initial vertical, doctor led program was quickly overwhelmed and given the speed and scale at which the response was needed it became clear that this approach would be both slow and resource intensive to scale up. At this point alternative treatment delivery models were sought in order to alleviate the issues with the original approach.

South Africa had an extensive nurse-led, primary health clinic network and one option for rapid scale up was to make use of this network. Fear that the complexity of the treatment regimen was inappropriate for a primary health care worker and the fact that regulation in South Africa hindered complete roll out to primary health clinics, including preventing nurses from prescribing ARVs, meant that full decentralization and task shifting did not happen immediately. In the interim non-governmental organization treatment partners began to test alternative treatment delivery models that worked within the constraints of the public health system at the time.

One of these alternatives was the partial decentralization and task shifting of treatment to primary health clinics and nurses. This involved the down referral of a stable patient already initiated onto treatment to a primary health clinic for management by nurses. This model had been shown to be effective in a clinical trial setting but this pilot would be the first time it was attempted in a routine public health setting in South Africa. A study protocol was designed to investigate the cost effectiveness of such an approach compared to the standard of care at the time, doctor-initiated and managed care at a specialized HIV facility.

This study provided the data to produce CHAPTER 7 (Paper 1).

6.1.3 Study 2: Retrospective cost-effectiveness analysis of nurse- initiated and managed antiretroviral treatment for HIV/AIDS in South Africa

Partial decentralization and task shifting, while cost effective, was still too slow for the rapid scale up needed to effectively deal with the large generalized epidemic in South Africa and to meet the South African government's mandate for universal treatment access. The rate-limiting factor was that initiation could not be performed at the primary health clinics by nurses and so while the partial approach could handle more patients on treatment it would still be slow to scale up using the specialized doctor-led facilities.

Although there was no formal research to support full decentralization and task shifting in a routine South African setting, the government used evidence from clinical trials, Chapter 2 (Paper 1) and similar research as well as research from other countries to adopt a treatment delivery model where nurses could initiate and manage patients on antiretrovirals. This program was known as nurse initiation and management of antiretroviral treatment (NIMART) in South Africa.

NIMART was the government mandated treatment delivery model which meant that for the first time primary health clinics led by nurses would be initiating and managing HIV patients on antiretroviral treatment. It also meant that the original specialized HIV, doctor-led treatment facilities based predominantly at secondary and tertiary public health facilities would shift to a NIMART approach. However these facilities for the most part remained single service, HIV treatment facilities with a higher ratio of doctors and nurses to patients than might be found in a typical primary health care facility. Although nurses often do provide both initiation and management of ART at these facilities, the involvement of doctors is often higher because of their availability. In addition to this the facilities are often more advanced with access to further specialized services.

Since the routine implementation of NIMART as the national treatment delivery model of HIV treatment in South Africa there has not been any study that has costed these services in routine implementation and the associated outcomes using primary, patient level data. Accurate costs are critical for budgeting purposes and the outcomes while often reported on, are rarely reported on as cohort data from direct patient record review.

As NIMART has become policy and will remain for the foreseeable future because of the scale of the services required, comparing NIMART against a purely doctor-led program is neither useful nor possible in the public sector. I compare NIMART at a primary health clinic with NIMART at a secondary, specialized HIV facility. The assumption was that the specialized HIV facility may be more costly because of a higher cadre of staff to patient ratio as well as the infrastructure, but that outcomes were equivalent for similar patients. A study protocol was designed to

investigate the costs and outcomes associated with the routine implementation of NIMART at two types of health facilities, namely primary and secondary.

This study provided the data to produce CHAPTER 8 (Paper 2).

6.1.4 Study 3: Analysis of the cost of HIV-related inpatient care using unlinked, retrospective data

All public health care facilities in South Africa, from primary to tertiary, are under serious strain because of limited resources. Inpatient facilities in the public sector struggle to meet the demand for services and are routinely at capacity. There is limited data available and reported on of the HIV related burden placed on public health inpatient facilities in South Africa. These data were reported more frequently prior to the roll out public HIV treatment in South Africa, but since then no studies have tried to measure this. This is probably because in the presence of a large-scale HIV treatment program the burden of HIV related admissions should be low and most research has focused on outpatient treatment models.

While the stigma of HIV and AIDS appears to have reduced to some degree a recent survey reported that 36% of HIV positive patients reported some external stigma, some of which may have been from health care providers [165]. As a result there is still resistance from health care providers to record HIV as a reason for admission to hospital or as a reason for death. As result these routinely reported statistics can rarely be stratified by HIV status and many public health professionals think that they routinely under represent the HIV burden. The HIV burden on inpatient facilities is important as an indicator of the success of the outpatient treatment program. Estimating the cost associated with these admissions is critical in understanding the impact of the burden and whether HIV related admissions routinely use more resources than similar patients on treatment or those who are HIV negative. Mortality data allow comparison with local and national statistics to determine whether or not the mortality profile has changed since the introduction of large-scale access to HIV care and treatment.

Given the capacity constraints of these facilities it is critical to understand whether the outpatient treatment program is positively impacting the HIV related burden being placed on inpatient facilities in South Africa. A study was designed to investigate the reason for and costs and outcomes associated with medical admissions stratified by HIV status. This study further investigated mortality stratified by HIV status to provide evidence to support the mortality statistics in South Africa related to HIV.

This study provided the data to produce CHAPTER 9 and CHAPTER 10 (Paper 3 and 4, respectively).

6.2 Aim and objectives of thesis

The overall aim of this thesis is to examine how the costs and outcomes of the current HIV treatment model in South Africa have changed in the context of a large scale, national treatment program.

The South African HIV treatment model comprises two major components, namely outpatient treatment for the chronic care and treatment of HIV positive patients and inpatient treatment for acute conditions related to HIV either prior to the initiation of antiretroviral treatment or while on antiretroviral treatment. The thesis comprises four objectives, which cover both of these components. The research addressing each objective is presented as independent manuscripts forming chapters 7 to 9 in this thesis.

6.2.1 Objectives addressing the outpatient treatment of HIV positive patients

As outlined in Chapter 2 the scale of the outpatient HIV care and treatment program required a shift in the South African treatment model, namely decentralization of treatment from specialized HIV clinics to primary health clinics and task shifting from doctors to nurses. Objective 1 and 2 address this issue by examining the costs and outcomes of a partial approach, where only stable

patients were sent to primary health clinics for nurse management, and a full approach, where both the initiation and management of patients occurred at primary health clinics by nurses.

Objective 1: Evaluate the treatment outcomes and cost-effectiveness of shifting the management of stable ART patients to nurses at a primary health care facility in South Africa.

Objective 2: Evaluate the cost and cost effectiveness of nurse initiated and managed antiretroviral therapy (NIMART) at a primary health care facility with NIMART at a secondary health facility in South Africa.

6.2.2 Objectives addressing the inpatient treatment of HIV positive patients

As outlined in Chapter 3 in the absence of publically available, effective treatment for HIV, patients would eventually become ill and die, many of them receiving palliative, end of life care in secondary and tertiary inpatient facilities. A consequence of introducing effective, widely accessible antiretroviral treatment should be a reduction in acute HIV related inpatient treatment and its associated mortality. Objective 3 and 4 address this issue by examining a cohort of medical inpatients and reporting their reason for morbidity and / or mortality and its associated cost, by HIV status.

Objective 3: Determine the disease and cost burden of HIV on an inpatient facility in South Africa.

Objective 4: Estimate the changes in the mortality profile of an inpatient facility in South Africa since the large scale roll out of Highly Active Antiretroviral Therapy (HAART).

6.3 References

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SECTION 2 – HIV OUTPATIENT TREATMENT

Section 2 Aims

- To examine the impact (costs and outcomes) of various levels of task shifting and decentralization of outpatient HIV care and treatment, by
  - Determining the costs and outcomes of partial task shifting and decentralization, and
  - Determining the costs and outcomes of full task shifting and decentralization.

This section is divided in to two chapters (Chapters 7 and 8), which focus on the cost and outcomes of partial and full task shifting and decentralization of HIV related outpatient care and treatment, respectively. Chapter 7 determines the impact of partial task shifting by examining the cost effectiveness off shifting stable HIV patients to less specialized facilities and staff. Chapter 8 determines the impact of full task shifting by examining the costs and outcomes of routine nurse initiated and managed antiretroviral treatment at two levels of the public health care system, primary and secondary.

CHAPTER 7 – Paper 1:

Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort

At the time of this thesis submission, Paper 1 was published in PLoS Medicine. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university. See Appendix A for a PDF version of the published article.

Reference: LONG L, BRENNAN A, FOX MP, NDIBONGO B, JAFFRAY I, SANNE I, ROSEN S. 2011. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. *PLoS Med,* 8, e1001055. http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001055

7.1 Abstract

Background: To address human resource and infrastructure shortages, resource-constrained countries are being encouraged to shift HIV care to lesser trained care providers and lower level health care facilities. This study evaluated the cost-effectiveness of down-referring stable antiretroviral therapy (ART) patients from a doctor-managed, hospital-based ART clinic to a nurse-managed primary health care facility in Johannesburg, South Africa.

Methods and Findings: Criteria for down-referral were stable ART (≥11 mo), undetectable viral load within the previous 10 mo, CD4>200 cells/mm^3 , <5% weight loss over the last three visits, and no opportunistic infections. All patients down-referred from the treatment-initiation site to the down-referral site between 1 February 2008 and 1 January 2009 were compared to a matched sample of patients eligible for down-referral but not down-referred. Outcomes were assigned based on vital and health status 12 mo after down-referral eligibility and the average cost per outcome estimated from patient medical record data. The down-referral site (n = 712) experienced less death and loss to follow up than the treatment-initiation site (n = 2,136) (1.7% versus 6.2%, relative risk = 0.27, 95% CI 0.15–0.49). The average cost per patientyear for those in care and responding at 12 mo was US$492 for down-referred patients and US$551 for patients remaining at the treatment-initiation site (p<0.0001), a savings of 11%. Down-referral was the cost-effective strategy for eligible patients.

Conclusions: Twelve-month outcomes of stable ART patients who are down-referred to a primary health clinic are as good as, or better than, the outcomes of similar patients who are maintained at a hospital-based ART clinic. The cost of treatment with down-referral is lower across all outcomes and would save 11% for patients who remain in care and respond to treatment. These results suggest that this strategy would increase treatment capacity and conserve resources without compromising patient outcomes.

7.2 Introduction

The rapid expansion of large-scale provision of care and treatment for HIV/AIDS in sub-Saharan Africa has placed tremendous pressure on the region's human resources. As a result, the World Health Organization, other international agencies, and national governments are actively encouraging the shifting of clinical care responsibilities to lesser trained, less expensive, and generally less scarce cadres of the clinical workforce [115].

In South Africa, a major component of this ''task shifting'' strategy is to reduce the role of doctors in managing patients on antiretroviral therapy (ART), in favor of primary health care nurses (PHCNs). Unlike in many countries in the region, South Africa's national treatment program has been largely managed by doctors. Nurses have not been authorized to dispense antiretroviral drugs (ARVs), initiate patients on treatment, or conduct medical examinations in lieu of doctors. The number of accredited sites authorized to provide ART has thus been limited by the availability of doctors. Since most primary health care facilities are staffed entirely by nurses, most accredited ART sites have been located at hospitals rather than primary care clinics.

There is a small but expanding body of evidence from sub- Saharan Africa demonstrating that nurses managing ART patients at primary health care facilities can achieve very good outcomes. A recent systematic review of task-shifting in Africa identified seven cohort studies of nurse-initiated and/or nurse-managed adult treatment [122]. Those that reported outcomes generally showed nurses achieved comparable or superior results to doctor-led treatment in the same general setting, but only one undertook a direct comparison of doctor-managed versus nurse-managed treatment of similar patient populations [55]. Primary health care facilities achieved better outcomes than hospitals in a recent study from South Africa, but patients were treated by doctors at both levels [166]. A prospective controlled evaluation in Swaziland found equally good outcomes amongst stable HIV patients managed by nurses in a primary care facility compared to those receiving routine hospital care [167]. Malawi has shown similar success in decentralizing care and allowing non-physician clinicians to initiate ART

[168]. In Kenya a clinical trial evaluated whether the ART management could be partially shifted from health care workers to persons living with HIV/AIDS who would monitor patients within the community [169]. This showed similar clinical outcomes but with fewer clinic visits. No studies have estimated the cost differences between the two approaches using primary data.

In 2010, the South African government revised its HIV treatment guidelines for the first time since the program launched in 2004. Among a host of changes to drug regimens, eligibility criteria, and monitoring protocols, the revised guidelines included the following two objectives: to ‘‘enable nurses to initiate ARVs for treatment and prevention’’ and to ‘‘enable primary health care facilities to initiate, manage, monitor, and refer patients.’’ Justification for this change included a recently published randomized trial set in South Africa demonstrating that, under the carefully regulated conditions of a clinical trial, patients initiated on ART by doctors, but monitored by nurses, at primary health care clinics achieved similar treatment outcomes as those managed solely by doctors [129].

Prior to the 2010 guideline revision, a number of interventions to shift treatment delivery to lower level facilities and from doctors to nurses had already been piloted in routine care settings. Among these was a strategy of ‘‘down referring’’ stable, adult ART patients from a central hospital to nearby primary clinics—the same strategy tested by the randomized clinical trial in South Africa, but in a routine care setting—pioneered by the Gauteng Province Department of Health and Right to Care, a South African nongovernmental organization supported primarily by the United States President’s Emergency Plan for AIDS Relief. To evaluate the implications of this down-referral strategy for treatment outcomes and costs, we conducted a cost-effectiveness analysis of the treatment program at the Themba Lethu Clinic in Johannesburg and a nearby primary health clinic serving as a down-referral site.

7.3 Methods

7.3.1 Ethics statement

The University of the Witwatersrand and Boston University provided ethical approval of the study. In order to protect the anonymity of the patients, the study was conducted as an unlinked, retrospective analysis of a patient data set that did not contain any individual identifiers.

7.3.2 Down-referral procedures

Under the down-referral strategy evaluated in this study, all patients receive pre-ART care and initiate ART at an accredited, hospital-based HIV/AIDS clinic, which we will refer to as the treatment-initiation site. For patients who are eligible for and accept down-referral, management of their care is moved to a down-referral site, which is a primary health clinic (PHC). PHCs typically provide reproductive, maternal, and child health care, TB treatment, HIV testing, and other basic services but are not typically accredited to provide ART.

To be eligible for down-referral, patients must have been on ART for at least 11 mo; they must have no opportunistic infections, a CD4 cell count >200 cells/mm^3, and a stable weight as reflected by <5% weight loss between the last three visits; and their latest HIV viral load within the last 10 mo must be undetectable (<400 copies/ml). The treatment-initiation site involved in this study performs the first routine viral load test after 4 mo on treatment, and the second at 10 mo, establishing the time intervals used in the down-referral criteria. Treatment-initiation site patients who meet these criteria are invited (but not required) to transfer to a down-referral site. For those who accept down-referral, the treatment-initiation site doctor then writes a prescription for 6 mo of ARVs. Down-referred patients are dispensed a 2-mo supply of ARVs at the treatment-initiation site and make an appointment at the down-referral site for 2 mo later. All subsequent ARV pickups occur at the down-referral site. At both the treatment-initiation and down-

referral sites, stable patients are scheduled for medication pickups every 2 mo. Treatment follows South African national guidelines, which during the study period called for a first-line regimen of stavudine, lamivudine, and nevirapine or efavirenz and routine CD4 counts and viral load tests every 6 mo.

The main difference between the routine monitoring conducted at the down-referral site and the treatment-initiation site is the cadre of clinical staff involved. While the treatment-initiation site relies on medical consultations with doctors, patients at the down- referral site see only PHCNs, professional nurses with a qualification in primary health care. Down-referred patients have a nurse consultation at every routine visit (every 2 mo), while patients at the treatment-initiation site have a doctor consultation only every 6 mo. At each visit, the PHCN asks whether the patient has had any unexplained weight loss, experienced symptoms related to hyperlactatemia, and/or visited any other medical facility since the last appointment. If none of these events has occurred, the patient collects a 2-mo supply of medications and is scheduled for an appointment 2 mo later. Otherwise, if any of these events has occurred, the PHCN conducts a full consultation. The PHCN may prescribe or change non-ARV medications and renew existing ARV prescriptions but cannot alter the patient's original ARV prescription. After a full consultation, the PHCN can continue the patient on the standard drug collection and visit schedule (i.e., every 2 mo), treat the patient and request a follow- up visit before the next scheduled visit, or up-refer (return) the patient to the treatment-initiation site. The PHCN also does a routine blood draw 4 mo into each 6-mo prescription cycle, with samples processed for viral load, CD4 count, full blood count, alanine aminotransferase, aspartate aminotransferase, and, de- pending on drug regimen, cholesterol, triglycerides, creatinine, and/or lactates. Based on the results of these tests, the PHCN can renew the patient's ARV prescription for another 6 mo, change any concomitant non-ARV medications, draw blood again to confirm the laboratory findings, and/or up-refer the patient immediately. Both sites performed the same routine monitoring tests every 6 mo, but doctors at the treatment-initiation site were allowed to order additional laboratory tests if required, whereas nurses at the down-referral site had a restricted list of laboratory tests available and had to up-refer a patient if non-routine tests were indicated.

Patients who are up-referred to the treatment-initiation site remain under treatment-initiation site care until a treatment- initiation site doctor recommends (re-)down-referral. At both sites, a patient who is more than 3 mo late for the next scheduled visit is classified as lost to follow up.

7.3.3 Study sites

The treatment-initiation site in this study is the Themba Lethu Clinic (TLC) of Helen Joseph Hospital in Johannesburg, a large public sector ART clinic at a secondary hospital. The site, which has been described in detail elsewhere [170], started providing ART in April 2004 and has since initiated more than 18,500 patients on treatment. Treatment is initiated and managed by doctors, as required by the treatment guidelines in place in South Africa until 2010. The clinic is sponsored by the Gauteng Province Department of Health, with additional support from the United States President's Emergency Plan for AIDS Relief.

Due to increasing patient numbers and shortages of human, financial, and infrastructural resources, TLC began down- referring to PHCs within its patient catchment area in 2008. Its first down-referral site was Crosby Clinic, a PHC of the City of Johannesburg roughly 3 km from TLC. Crosby Clinic established a down-referral wing that has its own ART waiting area, consultation rooms, and pharmacy and operates independently of other PHC departments. It can therefore be closely integrated with the treatment-initiation site and avoid the long patient waiting times that are characteristic of many PHC facilities. Because it is located near the treatment-initiation site, patient transport costs are similar between the two facilities.

The treatment-initiation and down-referral sites make use of the same electronic patient management and data system, Therapy Edge-HIV. The system transfers patient records between the treatment-initiation and down-referral sites when a patient is down- or up-referred, alerts the provider if up-referral is required, and automatically transfers files and schedules appointments as needed.

7.3.4 Sample selection and matching

We conducted a secondary analysis of routinely collected data from a cohort of patients followed in a routine care setting. As the intervention had already been implemented, we were unable to randomize to limit confounding. Instead, we used a quasi- experimental design in which we matched down-referred patients (down-referral group) to non-down-referred patients (treatment- initiation group) to attempt to create similar populations at the time of eligibility for down-referral. We included all ART patients down-referred from TLC to Crosby Clinic between 1 February 2008 and 1 January 2009. Down-referred patients were matched to not down-referred patients 1:3 based on gender, age (18–24.99, 25–29.99, 30–39.99, 40–49.99, and $50 y), time on ART (in 6-mo intervals), ARV regimen at study eligibility, and CD4 count at study eligibility (0–99, 100–199, 200–349, and ≥350 cells/mm^3). Matching was accomplished though propensity scores [171, 172]. We allowed treatment-initiation site patients to be used as a match more than once, but not within the same 6-mo time interval. Patients were excluded from both groups if they were (1) down- referred to a site other than Crosby Clinic, (2) had <12 mo of potential follow up after down-referral or down-referral eligibility, (3) initiated treatment outside TLC, (4) had a non-standard treatment regimen; or (5) had missing or erroneous medical record data. In the remainder of this paper, ‘‘study eligibility’’ refers to eligibility for either group.

7.3.5 Data collection

Methods for data collection and costing have been described previously [173]. Taking the provider’s perspective, each study participant’s electronic medical record was reviewed, and resource usage data for the 12-mo period following down-referral eligibility were collected. For down-referred patients who returned to the treatment-initiation site during the study period (i.e., were up- referred), resource utilization included resources provided by the treatment-initiation site. Resources captured included ARVs, non- ARV medications, laboratory tests, outpatient visits, infrastructure, equipment and furnishings, data capture, and

program management. An outpatient visit at the treatment-initiation site included consultations with both a nurse and a doctor; if a patient also collected medications, an additional pharmacy cost was added to the total visit cost. An outpatient visit at the down-referral site was limited to a consultation with the PHCN, who also dispensed medications. Utilization of fixed resources (e.g., infrastructure and administrative staff) for participants who died or were lost to follow up was prorated based on the number of months the patient remained in care. Unit costs were estimated in 2009 South African rand from service provider price lists and financial information provided by the sites. Costs were converted to US dollars at a rate of R8.40 to US$1.00.

7.3.6 Data analysis

Each study participant at both sites was assigned to a single outcome category on the basis of patient status 12 mo after down- referral eligibility. Criteria for assigning outcomes were adapted from previous work in South Africa assessing patient outcomes 12 mo after treatment initiation [173]. To cope with inconsistent timing of clinic visits and laboratory tests, medical record information within a 3-mo window on either side of 12 mo (i.e., 9–15 mo after down-referral eligibility) was used in determining outcomes, as shown in Table 7-1.

Table 7-1. Criteria for assigning HIV treatment outcomes.

Outcome	Criteria for assigning outcome	Comments
Excluded from study	Started treatment prior to public rollout	Patient initiated ART prior to the South African national treatment plan launched in April 2004
	Outside of study period	Down-referred / eligible for down-referral before February 2008 or after January 2009
	Less than 12 months of potential follow up	Started ART < 12 months prior to data collection or transferred formally to a different site; informal transfers without medical record notation are recognized as loss to follow up
	Non standard ARV regimen	Patient on a regimen which was not part of the national treatment guidelines during the study
	Missing matching data / erroneous data	Includes patients who do not have a viral load, CD4 count, regimen, weight, age or gender
No longer in care (NIC)	Died	Only reported deaths included; deaths never reported to the site are recognized as loss to follow up.
	Lost to follow up	≥3 months late for last scheduled consultation or medication pickup
In care but not responding (NR)	Detectable viral load (virologic failure);	Viral load > 400 copies/ml in month 9-15
	If no viral load available, insufficient CD4 change (immunologic failure).	CD4 decrease of ≥30% from peak or ≤ baseline in month 9-15
In care and responding (IC)	Undetectable viral load	Viral load ≤ 400 copies/ml in month 9-15
	If no viral load available, sufficient CD4 change	CD4 within 30% of peak and > baseline in month 9-15
	If no viral load or CD4 count available, still in care.	Default outcome for patients remaining alive and in care but without laboratory results

Using these criteria, outcome assignments were made hierarchically, as illustrated in Figure 7-1. Up-referral—return of a down- referred patient to the treatment-initiation site for monitoring and care—was not considered a discrete outcome. Outcomes for up-referred patients were assigned using the same criteria as for all other patients, as defined in Table 7-1 and costs incurred at the treatment-initiation site following up-referral are included in the cost per down-referred patient.

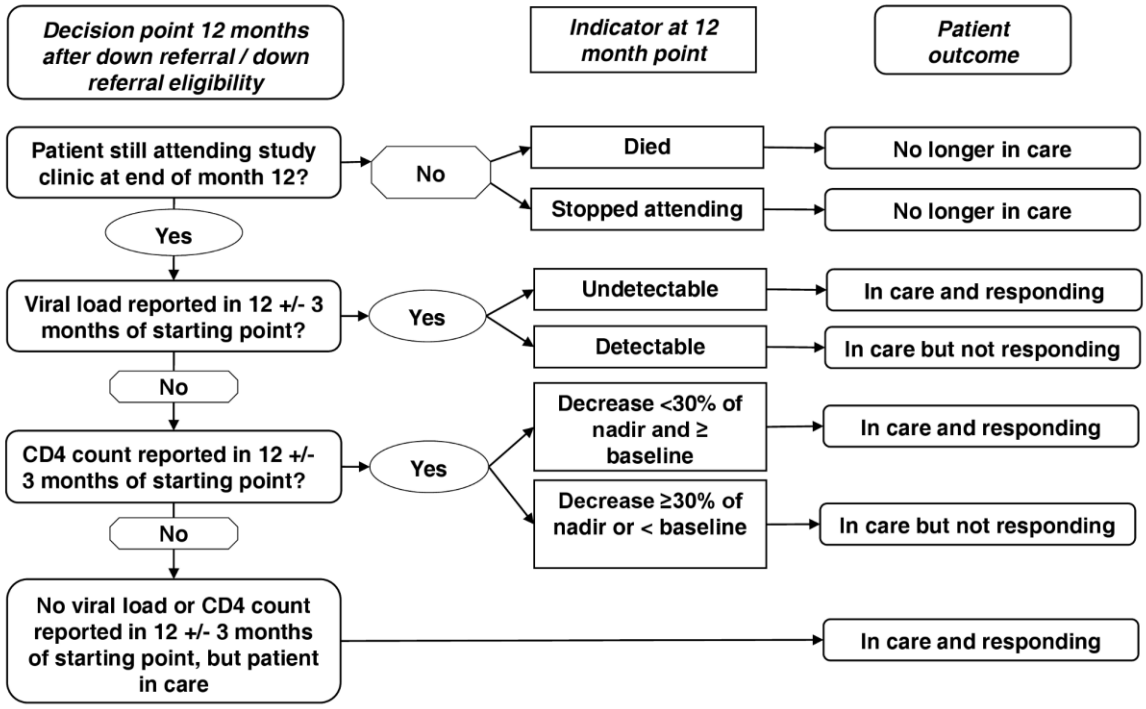

Figure 7-1. Decision process for assigning HIV treatment outcomes.

Patients were placed in a mutually exclusive patient outcome category 12 mo after study enrolment – no longer in care, in care and responding or in care and not responding. Patient outcomes were defined based on the patient's vital status, presence in the clinic, viral load or CD4 count at 12 mo after study enrolment. For those patients alive and in treatment, viral load was the preferred outcome indicator, but in the absence of viral load CD4 count was used and if neither were available then it was assumed the patient was in care and responding based on their presence in the clinic. The diagnostic result closest to 12 mo, but within 3 mo (9–15 mo) was used.

Once an outcome was assigned, we estimated a total cost for each patient based on all resources utilized during the 12-mo study period. We estimated an average cost per patient-year in care for each outcome category by site. The cost-effectiveness of the two sites was compared on the basis of average cost per patient remaining in care and responding at the 12-mo point. We created 95% confidence intervals (CIs) around these estimates using bootstrapping with 10,000 replicates [174].

7.4 Results

7.4.1 Sample selection and cohort characteristics

Selection of patients from each site is illustrated in Figure 7-2, and study participants are described in Table 7-2. We enrolled 712 study participants from

the down-referral site and 2,136 patients from the treatment-initiation site. There was little difference between the groups in the characteristics on which they were matched. Down-referred patients excluded because of missing data were similar to patients in the down-referral group in terms of age, time on ART, CD4 count, and treatment regimen.

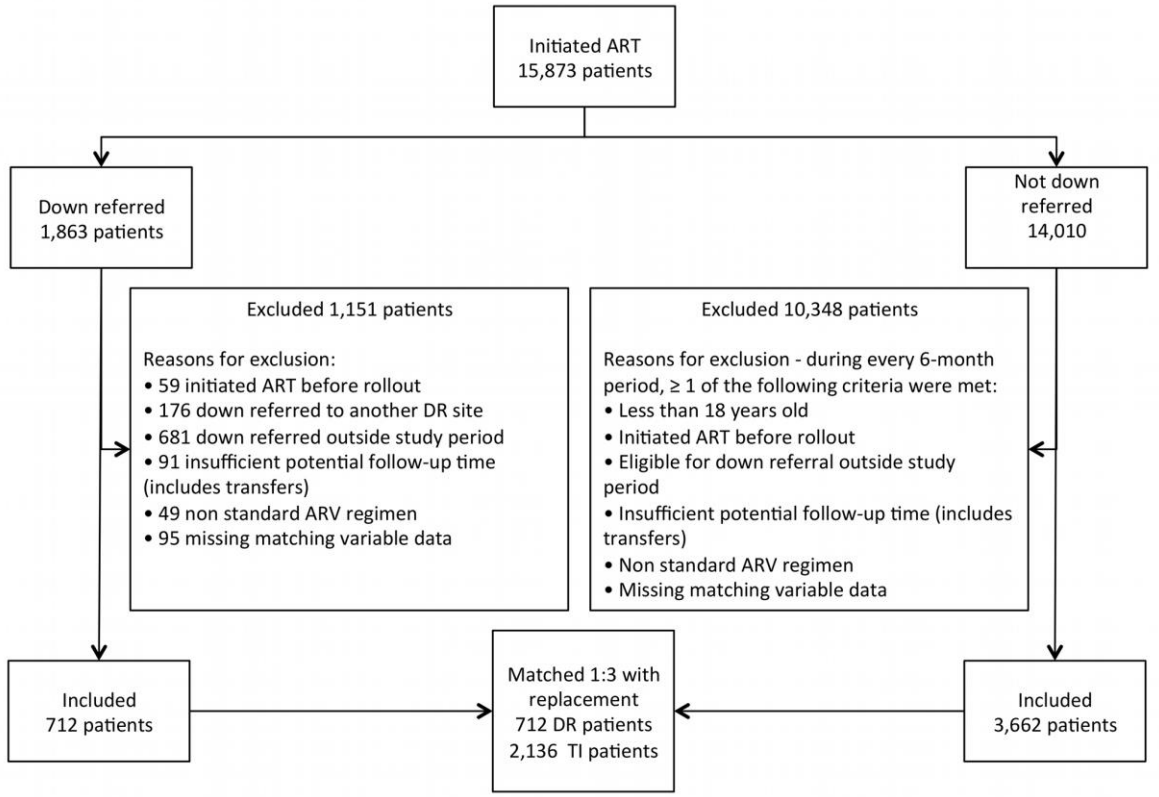

Figure 7-2. Selection of study participants.

All patients initiated on ART at the treatment-initiation site were considered for this study. The patient population was divided into those down-referred and those not down-referred (maintained at the treatment-initiation site). Patients were excluded if they (1) had missing matching variables, (2) were on non-standard ARV regimens, (3) had insufficient potential follow-up time, (4) were eligible/down- referred outside the study period, (5) initiated ART prior to the national rollout, (6) were down-referred to another site (i.e., not the study site), or (7) were ,18 y old. Those down-referred patients included in the study were matched 1:3 with patients maintained at the treatment-initiation site. DR, down-referral; TI, treatment-initiation site.

Table 7-2. Characteristics of ART patients at the time of eligibility for down-referral to nurse-managed care.

Variable	Treatment-initiation group	Down-referral group
Number	2,136	712
Mean age at study eligibility, years (IQR)[a]	38.5 (32.7-43.68)	38.5 (33.06-42.03)
Sex, % female[a]	65.5	65.3
Median CD4 count at ART initiation, cells/mm^3 (IQR)[b]	94 (36 - 163)	103 (41 - 168)
Median CD4 count at study eligibility, cells/mm^3 (IQR)[a]	397 (309 – 521)	404 (318 - 526)
Mean duration on ART at study eligibility, years (IQR)[a]	2.3 (1.8 – 3.3)	2.3 (1.8 – 3.3)
ARV regimen at study eligibility (%)[a]		
Stavudine-lamivudine-efavirenz	64.8	63.8
Zidovudine-lamivudine-efavirenz	27.1	27.1
Other	8.1	9.1

[a] These characteristics were matched between the two samples.
[b] Note that 15.4% of subjects in the treatment-initiation sample and 11.5% in the down-referral sample did not have baseline CD4 counts reported.
IQR, inter-quartile range.

7.4.2 Treatment outcomes

Treatment outcomes are reported in Table 7-3. Both groups showed very good outcomes 12 mo after down-referral eligibility, with well over 90% of patients remaining in care. The down- referral site experienced fewer deaths and losses to follow up, losing just 2% of its patients during the observation period. As a result, the relative risk of no longer being in care in the down- referral group was markedly lower than in the treatment-initiation group (relative risk = 0.27, 95% CI 0.15–0.49). The adjusted hazard ratio was estimated, but it showed no difference from the relative risk estimate. In total, 122 patients in the down-referral group (17.1%) were up-referred within the 12-mo period, after an average of 6.1 mo at the down-referral site. These participants remained in the down-referral group for this analysis. Most of them met the criteria for ‘‘in care and responding’’ after up-referral and are categorized as such in Table 7-3.

Table 7-3. HIV treatment outcomes 12 mo after down-referral eligibility.

Outcome	Treatment-initiation (n=2,136)	Down-referral (n=712)	RR (95% CI)[a]
Total	2,136 (100%)	712(100%)	-
In care and responding	1,912 (89.5%)	680 (95.5%)	1.07 (1.04-1.09)
In care but not responding	91 (4.3%)	20 (2.8%)	0.66 (0.39-1.06)
No longer in care	133 (6.2%)	12 (1.7%)	0.33 (0.18-0.60)
Died	25 (1.2%)	0 (0.0%)	
Lost to follow up	108 (5.1%)	12 (1.7%)	

[a]Relative risk of outcome at down-referral site, with treatment-initiation site as reference.

7.4.3 Resource utilization

Average resource utilization by patients who remained in care at 12 mo is shown in Table 7-4, which also provides unit cost estimates for the resources for which unit cost varied by site. Usage of viral loads and CD4 counts varied little between the samples. Down-referred patients made nearly twice as many clinic visits as patients remaining at the treatment-initiation site, but at a cost per visit of less than half. Fixed costs were also much lower at the down-referral site than at the treatment-initiation site.

Table 7-4. Average resource utilization and selected unit costs for the study sample (n=2,160) over 12 mo from the date of down referral eligibility.

Resource	Treatment-initiation site	Down-referral site
Average utilization per patient-year in care		
Treatment-initiation site visit	4.4	1.5
Down-referral site visit	0.0	5.6
CD4 count	1.6	1.5
Viral load test	1.6	1.4
Unit costs[a]		
Average cost per outpatient visit, US$	14	7
Average fixed cost per patient per month, US$	98	59

[a]Costs were converted to US dollars at a rate of R8.40 to $1.00.

7.4.4 Costs and cost-effectiveness

The average cost per patient by outcome, and the breakdown of total cost by major cost components for patients who remained in care and responding at 12 mo, are reported in Table 7-5. For a patient who remained in care and responding for the 12 mo following down-referral eligibility, treatment at the down-referral site cost an average of US$59 (95% CI US$49–US$70, p<0.001) per year less than at the treatment-initiation site, a savings of 11%. The down-referral site spent less on every component of cost except ARVs. Differences in non-ARV drug and lab test costs can be attributed to the greater latitude doctors have in prescribing drugs and diagnostics beyond what is mandated by guidelines. Despite the larger number of clinic visits per patient-year by down-referral patients, the down-referral

site still saved money on outpatient visits because of its much lower unit cost per visit.

Table 7-5. Average cost per patient, HIV treatment outcome and cost component.

Outcome or Cost Component	Cost[†], in US Dollars	
	Treatment-Initiation Patients	Down-Referral Patients
Outcome, mean (standard deviation)		
All patients in group	539 (141)	486 (98)[a]
In care and responding	551 (128)	492 (88)[a]
In care but not responding	589 (163)	481 (97)[a]
No longer in care	330 (147)	175 (103)[a]
Cost component, value (proportion of total)[b]		
Drugs - ARV	237 (43%)	262 (53%)
Drugs – non ARV	16 (3%)	7 (1%)
Lab tests	120 (22%)	101 (21%)
Outpatient visits	80 (15%)	60 (12%)
Fixed costs	98 (18%)	62 (13%)
Total	551 (100%)	492 (100%)

[a] p<0.001 for difference between treatment-initiation and down-referral patients.
[b] Only patients who were still in care and responding at 12 mo were included.
[†]Costs are given in 2009 US dollars at a rate of R8.40 to US$1.00.

Using the data in Table 7-3 and Table 7-5, we estimate that the down-referral site spends an average of US$509 (95% CI US$500–US$519) to produce a patient who is in care and responding 1 y after down-referral, taking into account the resources invested in those who do not respond, die, or are lost to follow up, and including the costs of treatment-initiation site treatment for those up-referred. The treatment-initiation site spends an average of US$602 (95% CI US$592–US$612). For this pair of sites in South Africa, down-referral to a PHC is the cost-effective strategy for eligible patients.

7.5 Discussion

There is general agreement in the literature and in reports from international agencies that some combination of task-shifting from higher to lower level care providers and decentralization from higher to lower level facilities is essential if targets for HIV/AIDS treatment access in resource-constrained countries are to be met in the face of still-rising patient numbers and declining donor budgets [166]. In this study comparing the outcomes and costs of treatment provided by PHCNs at a PHC with those of treatment provided by doctors at a hospital-based clinic, we

found that, for those patients eligible for down-referral, the down-referral site achieved better outcomes at consistently lower costs than the treatment- initiation site.

Both sites produced very good outcomes for the patients sampled. To some extent this is not surprising, as only stable patients who had been on ART for at least 11 mo were eligible for the study. The relatively large number of patients who die, are lost to follow up, or fail treatment in the first year on ART were thus deliberately excluded. Even considering the strict inclusion criteria, however, outcomes at the down-referral site, where almost 95% of patients remained in care, were exceptional.

A major impetus for task-shifting and decentralization, in South Africa and elsewhere, is cost. There is a clear expectation that moving treatment to lower level clinical staff and facilities will cost less than the status quo. In this study, we observed a cost reduction of roughly 11% per patient-year in care. Although this percentage may be smaller than hoped for, the scale of the treatment program in South Africa makes the potential for absolute savings large. South Africa currently has nearly one million patients on ART [175]. If even a quarter of these could be down-referred, and if the cost difference we found is applicable to sites across the country, the estimated difference in cost of US$59 per patient per year would result in program-wide savings of more than US$14 million per year, enough to support an additional 25,000–30,000 patients on ART per year. Using electronic data from the treatment-initiation site where we conducted the study, we estimated that roughly 43% of all patients who initiated ART in the first half of 2008 met eligibility criteria for down-referral by the end of 2009, suggesting that savings could exceed US$25 million per year. These savings would offset roughly 10%–15% of the cost of adding the 400,000 new patients per year called for by the country’s national plan for achieving universal treatment access [176].

7.5.1 Limitations of the study

Our study had a number of limitations. It looked at only one pair of sites, which may or may not be representative of other facilities in South Africa. Both were high volume, well-resourced, urban sites in one of South Africa's wealthier provinces. Because the treatment-initiation and down-referral sites in the study were located close together, most patients did not face different obstacles in accessing the sites, such as higher transport costs. This is unlikely to be the case in many settings. Both sites were government health facilities and followed the prescribed treatment regimens and monitoring algorithms as outlined in the national treatment guidelines. In these respects, the study sites were comparable to the many public sector treatment sites within South Africa. Both sites did receive some external donor support, however, and our findings might not pertain to under-resourced sites. The generalizability of our findings to other African countries may also be limited because of the diverse conditions under which care and treatment are offered across sub-Saharan Africa. For example, South Africa relies on doctors, rather than clinical officers, to provide routine care and has access to a wider range of diagnostics (e.g., viral load tests) than do many other countries.

A well-designed randomized clinical trial usually produces the most unbiased outcome estimates (internal validity), but may have a low degree of external validity, or relevance to the real world [1]. While using observational data generated through routine practice may have allowed some bias in our study, it also strengthened the relevance of our findings. In addition, by matching participants in our study, we reduced the potential for any strong bias. Still, while we matched down-referred and non- down-referred patients on known and measured factors affecting treatment outcomes, there is the potential that our populations differed with respect to some unmeasured factor. In order to determine the sensitivity of our results to changes in patient outcomes as a result of such a factor we varied (decreased) the proportion of patients in care and responding in the down-referred arm. The proportion of patients in care and responding would have to drop from 96% to 77% in this arm, with no changes to the initiation-site arm, for the costs per patient in care and responding to be equal. If we take the more likely scenario of equivalent outcomes as seen in the CIPRA

clinical trial [170], the cost per nurse-managed patient in care and responding would still be lower than the cost of those managed by doctors ($509 versus $602), and nurse-managed care would therefore still be the preferred choice.

The study reflects treatment guidelines that were in effect until 2010, including the use of stavudine in first-line treatment. In the revised guidelines, new ART patients and those experiencing stavudine toxicities will be prescribed tenofovir. The much greater tolerability of tenofovir may alter the relative effectiveness of doctors and nurses in managing ART patients. While we would expect this to make it even easier for nurses to manage treatment, we cannot be certain. We also cannot evaluate the extent to which the relatively low patient volumes seen at the down-referral site affected the quality of care delivered. Very large down-referral sites, and those that have exceeded their service delivery capacity, may achieve poorer patient outcomes than those we observed. Finally, as has been noted in recent publications, the rate of reported ‘‘loss to follow up’’ from any one treatment facility may overstate actual patient attrition from treatment, as many patients who are reported as lost have actually re-started treatment somewhere else [177]. If this phenomenon was more common at the treatment-initiation site in our study than at the down-referral site, the actual difference in outcomes between our two sites may be less than we observed.

7.5.2 Conclusions

In addition to the financial cost savings estimated in this study, transferring patients to nurse-managed, primary-level clinics has the additional advantage of freeing up the time and resources of more highly trained doctors and well-equipped facilities to focus on patients who are not responding to treatment or have other complications. Task-shifting allows more health care workers to provide ART care, and this in turn increases the treatment coverage available to meet the large unmet need. Although South Africa faces a shortage of both doctors and nurses, the scarcity of doctors is greater [178], and this scarcity may not be fully reflected in the salary differential between the two job grades. The

financial cost-effectiveness analysis presented here thus does not capture the full opportunity costs of the intervention evaluated.

The national treatment guidelines adopted in 2010 allow nurses to initiate, as well as manage, ART, under a model known as NIMART (Nurse-Initiated and Managed ART). This policy change was based on modeled estimates of the cost savings from task-shifting but with little empirical evidence confirming that these savings will indeed be realized. This study provides strong evidence that at least part of the NIMART model—the management of stable patients by PHCNs—will reduce overall treatment program costs in South Africa, without compromising patient outcomes.

7.6 References

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CHAPTER 8 – Paper 2: Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa

At the time of this thesis submission, Paper 2 was under review at PLoS One. For the purposes of this thesis the paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university. See Appendix A for a PDF version of the submitted article.

Reference: LONG L, ROSEN S, BRENNAN A, MOYO F, SAULS C, EVANS D, MODI S, SANNE I, FOX MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

8.1 Abstract

Background: In 2010 South Africa revised its HIV treatment guidelines to allow the initiation and management of patients on antiretroviral therapy (ART) by nurses, rather than solely doctors, under a program called NIMART (Nurse Initiated and Managed Antiretroviral Therapy). We compared the outcomes and costs of NIMART between the two major public sector HIV treatment delivery models in use in South Africa today, primary health clinics and hospital-based HIV clinics.

Methods and findings: The study was conducted at one hospital-based outpatient HIV clinic and one primary health clinic (PHC) in Gauteng Province. A retrospective cohort of adult patients initiated on ART at the PHC was propensity-score matched to patients initiated at the hospital outpatient clinic. Each patient was assigned a 12-month outcome of alive and in care or died/lost to follow up. Costs were estimated from the provider perspective for the 12 months after ART initiation. The proportion of patients alive and in care at 12 months did not differ between the PHC (76.5%) and the hospital-based site (74.2%). The average annual cost per patient alive and in care at 12 months after ART initiation was significantly lower at the PHC (US$238) than at the hospital outpatient clinic (US$428).

Conclusions: Initiating and managing ART patients at PHCs under NIMART is producing equally good outcomes as hospital-based HIV clinic care at much lower cost. Evolution of hospital-based clinics into referral facilities that serve complicated patients, while investing most program expansion resources into PHCs, may be a preferred strategy for achieving treatment coverage targets.

8.2 Introduction

With over 2.6 million people on HIV treatment, South Africa has had unprecedented success in rolling out its public sector antiretroviral therapy (ART) program [22]. Despite this success, further expansion to 5.7 million patients on treatment by 2018/2019 [179] will be needed for South Africa to reach the "90-90-90" targets established by the World Health Organization [180], and current budgetary resources are not sufficient [179]. Expanding access to ART at the lowest possible cost is therefore essential, for South Africa and for many other countries facing similar challenges.

When the South African national antiretroviral therapy (ART) program began in 2004, it relied primarily on hospital-based HIV clinics with services delivered by doctors [4]. In 2010, in the face of increasing demand for care and limited personnel, South Africa revised its treatment guidelines to allow the initiation and management of patients on ART by nurses at both hospitals and primary health clinics (PHCs) [5, 181] under a program known as Nurse Initiated and Managed Antiretroviral Therapy (NIMART).

NIMART shifted the focus of the South African treatment program from doctors to nurses and from hospitals to PHCs, increasing the number of accredited ART delivery facilities sites from 496 to 4333 [30]. With the advent of NIMART, South Africa now has two major public sector ART delivery models: centralized, hospital-based HIV outpatient clinics, which serve roughly 12% of patients; and decentralized, full service, primary health clinics, which serve about 85% (authors' data). Both decentralization and task shifting have been shown to generate health outcomes equivalent to or better than centralized, doctor-led care [116, 169, 182-184]. A recent Cochrane review concluded that there was moderate evidence showing that task shifting for HIV management did not decrease the quality of care and, for patients who were initiated on ART by nurses, may reduce patient loss to follow-up [125].

While several studies have examined outcomes of task shifting and decentralization in South Africa [55, 129, 131-134, 139, 150, 151, 162, 166], few

have included both ART initiation and management by nurses in routine public sector care without external resources. Neither of the two available cost estimates, moreover, reflect routine NIMART implementation [131, 163]. There is therefore little evidence of how NIMART fares, relative to traditional hospital-based, doctor-led care, under the normal conditions and constraints of a typical public sector setting. We used routinely collected patient data and actual resource utilization and cost records to evaluate the outcomes and costs of the two public sector HIV treatment delivery models and provide evidence to guide future program expansion.

8.3 Methods

8.3.1 Study sites

The study was conducted at one hospital-based outpatient HIV treatment clinic and one primary health clinic. Both sites are situated in the same municipality (pop. 360,000) in West Rand District of Gauteng Province, South Africa. The district was one of the early adopters of NIMART across all its facilities. The two sites are seven kilometers apart and serve similar populations.

The hospital-based HIV clinic is a large regional hospital hereafter referred to as the 'HIV outpatient clinic'. As of March 2014 it had 4,396 patients actively on ART and saw an average of 1,956 ART patients per month. It originally provided ART initiation and management by doctors, with nurse support for screening and monitoring. With the introduction of NIMART, responsibility for these services was progressively shifted to nurses. During the study period, the HIV outpatient clinic had one dedicated, full time doctor and sixteen nurses (including enrolled nurse assistants and managers).

The primary health clinic (PHC), hereafter referred to as "the PHC", had as of March 2014 1,958 patients actively on ART and saw approximately of 884 HIV patients for ART pickup in March 2014, which was roughly 11% of the patient load. As of January 2012, HIV was fully integrated into general chronic disease care at

the site. During the study period (2012) it had fifteen clinical staff (nurses and a doctor) serving all patients seeking care at the clinic for all conditions.

8.3.2 Sample selection and matching

We constructed a retrospective cohort of adult (≥18 years) patients initiated on ART at the PHC and matched them to patients initiated at the HIV outpatient clinic. To be included in the cohort, patients had to have at least 15 months of potential follow up as of the date of data collection, not have transferred to another site during their first year after initiation, having initiated after 1 January 2011 (NIMART policy in place) and have a complete patient record available for review. Data collection commenced on 15 January 2014 at the PHC and 1 March 2014 at the HIV outpatient clinic, resulting in the cohorts including patients initiated prior to 15 October 2013 and 1 December 2013 at the PHC and HIV outpatient clinic respectively. At the PHC we enrolled the first 260 patients who met these inclusion criteria. These patients were then matched to hospital outpatient clinic patients 1:3 on gender, age at initiation (18–30, 31-40, 41-50, >50 years), baseline ART regimen, and baseline CD4 count (0-100, 101-200, 201-350, 350 cells/mm^3). We used propensity score matching without replacement [171] using the Vmatch macro in SAS [185] to identify a comparison population from among all patients in the HIV outpatient clinic database who initiated ART after 1 January 2011 and met the study inclusion criteria.

8.3.3 Outcomes data and analysis

Clinical data were collected from paper files and the national electronic HIV register (Tier.net) at the primary health clinic and from a separate electronic patient record (TherapyEdge ™) at the HIV outpatient clinic. All three of these sources contained only routinely collected data. Fields collected for the first 12 months following ART initiation for each patient included baseline CD4 count, date of ART initiation, resource usage (visits, laboratory tests, drugs), and outcome at 12 months. CD4 count and viral load results up to 15 months were also collected to assign 12-month outcomes.

Each patient was assigned a single primary, 12-month outcome of either “alive and in care” or “died / lost to follow-up (LTFU)”. If a patient died before 12 months or was >3 months late for their last scheduled visit within the 12-month follow up period (lost to follow-up) then the patient was assigned to the outcome “died / LTFU”. All other patients were considered “alive and in care”. Secondary outcomes based on virologic and immunologic status were also assigned. Patients with a viral load ≥ 1,000 copies/mm^3 between 9-15 months after treatment initiation were classified as “virologic failure”. Patients with a CD4 count in month 9-15 showing a decrease of >30% from the highest recorded CD4 count between 0-12 months or below the CD4 count at ART initiation were classified as “immunologic failure”. For laboratory results we used the test result reported between 9 and 15 months that was closest to the 12-month endpoint. We then compared the primary and secondary outcomes over the first 12 months of treatment between sites using crude risk ratios with corresponding 95% confidence intervals.

Through sensitivity analysis, we investigated the effect of missing paper files excluded at the PHC (no patients were excluded at the HIV outpatient clinic because of missing files). Data on age, gender, baseline CD4 count, and 12-month primary outcome were collected from Tier.net for patients with missing files, where possible. In the sensitivity analysis, all primary health clinic patients were then matched on age, gender and baseline CD4 count to the hospital outpatient clinic and outcomes were compared.

Cost data and analysis

Costs were estimated from the provider perspective for the 12 months after ART initiation using standard costing methods, as outlined in Table 8-1. Methods for estimating costs and described in previous publications [131, 173]. Resources incurring costs included drugs, diagnostics, clinical staff, space, equipment and other shared services (i.e. other staff, utilities, etc.). Variable resource usage was determined from patient records; utilization of fixed resources, such as space and shared services, was estimated from site records. The quantity of each resource used by each patient was then multiplied by the associated unit cost to determine

a total cost per patient. All unit costs were in 2014 South African Rand (ZAR) or adjusted to 2014 and reported costs were converted to United States Dollar (USD) at the average exchange rate prevailing during 2014 of 10.83:1 (ZAR:USD). Average resource utilization per patient year is presented by site; average cost per patient is presented by site, cost category, and primary outcome.

Table 8-1. Methods for estimating costs.

Type of cost	Method for estimating cost
VARIABLE COSTS (RESOURCES RECORDED IN PATIENT MEDICAL RECORDS)	
Drugs, diagnostics, and other services reported in individual subjects' medical records	Unit cost obtained from suppliers or site and multiplied by actual resource usage for each patient.
Staffing (visits)	The specific staff cadres providing service for each patient visit is not recorded in patient files. A uniform staffing cost is estimated per patient visit at each site based on total staff cost divided by the total visits during the period. The actual number of visits made by the patient is then multiplied by this cost.
FIXED COSTS (RESOURCES USED FOR CLINIC OPERATION, NOT ALLOCATED TO INDIVIDUAL PATIENTS)	
Buildings and utilities	The space of the building was measured and an average rental cost per square metre obtained from the property market for commercial properties in the area was applied. Utilities were not measured at the study sites and so an estimated utility cost per square metre was determined based on a property with basic utility demands (i.e. basic electronic equipment and lighting, air-conditioning, water for cleaning and sanitation).
Equipment	All computer and related equipment was inventoried and costed using the appropriate unit costs and expected working life. Basic furnishings and equipment were costed by including a 10% markup on the rental.
Supplies	This included all non-drug and non-diagnostic related supplies (i.e. gloves, paper, pens). Supply usage was not well recorded at the facilities. The available information was captured and an estimated cost was calculated per month per patient visit. The same supply cost per visit was applied to both sites in order to prevent the costs being biased towards a site with incomplete supply records.

The study protocol was reviewed by the Institutional Review Boards of the University of Witwatersrand and Boston University, who approved the collection of the data without informed consent and the use of an anonymous analytic dataset.

8.4 Results

8.4.1 Sample characteristics

Sample selection is outlined in Supplementary Figure 1. A sample of 260 patients was selected from the primary health clinic, of whom 60 were excluded (55 missing files, 3 missing baseline CD4 count, 2 transferred within 12 months of initiating). The final analytic data set therefore included 200 patients from the primary health clinic matched with 600 patients from the HIV outpatient clinic. The patients excluded from the PHC sample because of missing data were similar to those included in terms of age and gender but had a slightly higher baseline median (IQR) CD4 count (208 cells/mm^3 (122-269 cells/mm^3)) than those included (162 cells/mm^3 (87-257 cells/mm^3)).

Characteristics of the sample are described in Table 8-2. The median age was 34 years (IQR: 28-41 years) and median CD4 count 151 cells/mm^3 (IQR: 69.5-239.5 cells/mm^3); two thirds were female. Most patients were initiated on a baseline regimen of lamivudine and tenofovir with either efavirenz (83%) or nevirapine (8%). There were no important differences in sample characteristics between the two sites.

Table 8-2. Baseline characteristics at HIV treatment initiation.

Characteristics	Total n=800		HIV Outpatient Clinic n=600		Primary Health Clinic n=200	
BASELINE CHARACTERISTICS AT HIV TREATMENT INITIATION[1]						
Gender, n (%)						
Male	275	(34.4)	206	(34.3)	69	(34.5)
Female	525	(65.6)	394	(65.7)	131	(65.5)
Age, n (%)						
18-30	273	(34.1)	206	(34.3)	67	(33.5)
31-40	324	(40.5)	233	(38.8)	91	(45.5)
41-50	141	(17.6)	112	(18.7)	29	(14.5)
>50	62	(7.8)	49	(8.2)	13	(6.5)
Age, median (IQR)	34	(28-41)	34	(29-39)	34	(28-41)
Baseline ART Regimen, n (%)						
3TC-TDF-EFV	663	(82.9)	506	(84.3)	157	(78.5)
3TC-TDF-NVP	62	(7.8)	33	(5.5)	29	(14.5)
Other	75	(9.4)	61	(10.2)	14	(7.0)
Baseline CD4 Count, n (%)						
≤100 cells/mm^3	248	(31.0)	192	(32.0)	56	(28.0)
101-200 cells/mm^3	263	(32.9)	202	(33.7)	61	(30.5)
201-350 cells/mm^3	261	(32.6)	181	(30.2)	80	(40.0)
>351 cells/mm^3	28	(3.5)	25	(4.2)	3	(1.5)
Baseline CD4 Count, median (IQR)	151	(69.5-239.5)	148	(61-236.5)	161.5	(86.5-256.5)

ART: antiretroviral therapy, 3TC: stavudine, TDF: tenofovir, EFV: efavirenz, NVP: nevirapine
[1]All the baseline characteristics were matched using propensity scores

8.4.2 Outcomes

The primary and secondary outcomes are presented in Table 8-3. The majority of patients at both the HIV outpatient clinic (72%) and the PHC (82%) were reported to be alive and in care at 12 months. Being a patient at the primary health clinic appeared to be somewhat protective against death or loss to follow-up (RR: 0.66, 95% CI: 0.48-0.91). However, as Supplementary Figure 1 indicates, 55 patient files from the original sample selected for the PHC were missing and were excluded from the primary analysis. After excluding two patients who transferred to other facilities and six for whom no baseline CD4 count was available, in sensitivity analysis we considered the impact of the missing files on patient outcomes at the PHC. We found that patients with missing files were more likely to be lost to follow up or dead than were those included in the main analysis.

When the outcomes of the patients with missing files were included in the analysis, the difference between the sites in the proportion of patients not in care disappeared (RR: 0.91, 95% CI: 0.71-1.18). There was no difference between the sites in outcomes stratified by baseline CD4 count. We also found no difference in virologic or immunologic failure rates between the sites for those patients who had the necessary diagnostics reported in their files (238/800 and 205/800 for viral load and CD4 count, respectively). We thus conclude that the primary outcomes were comparable between the sites.

Table 8-3. Outcomes at 12 months after ART initiation with relative risk.

Outcomes	Total n/N (%)		HIV Outpatient Clinic n/N (%)		Primary Health Clinic n/N (%)		Relative Risk[a] (95% CI)	
Primary Outcome								
Alive and in care	595/800	(74.4)	432/600	(72.0)	163/200	(81.5)	-	
Dead / LTFU	205/800	(25.6)	168/600	(28.0)	37/200	(18.5)	0.66	(0.48-0.91)
≤100 cells/mm^3	89/248	(35.9)	74/192	(38.5)	15/56	(26.8)	0.70	(0.44-1.11)
101-200 cells/mm^3	61/262	(23.3)	45/201	(22.4)	7/61	(11.5)	0.51	(0.24-1.08)
201-350 cells/mm^3	80/261	(30.7)	45/181	(24.9)	14/80	(17.5)	0.70	(0.41-1.21)
>351 cells/mm^3	3/29	(10.3)	4/26	(15.4)	1/3	(33.3)	2.17	(0.35-13.6)
Secondary Outcome								
Virologic failure*	59/238	(24.8)	36/167	(21.6)	23/71	(32.4)	1.50	(0.96-2.34)
Immunologic failure**	10/205	(4.9)	8/139	(5.8)	2/66	(3.0)	0.53	(0.12-2.41)
SENSITIVITY ANALYSIS* **								
Primary Outcome								
Alive and in care	741/988	(75.0)	550/741	(74.2)	189/247	(76.5)	-	
Dead / LTFU	247/988	(25.0)	191/741	(25.8)	58/247	(23.5)	0.91	(0.71-1.18)

[a]Relative risk of outcome at primary health clinic, with HIV outpatient clinic as reference
**Only includes those with CD4 counts between 9-15 months
***Newly matched sample including missing files

8.4.3 Resource utilization and costs

Table 8-4 compares baseline CD4 counts, duration in care, and utilization of clinic visits and laboratory tests by site and outcome category. Not surprisingly, at both sites patients alive and in care at 12 months had a higher median baseline CD4 count than those not in care. More surprisingly, patients who did not remain in care for 12 months at the PHC spent almost twice as much time in care (7.5 months) as did patients at the HIV outpatient clinic (3.7 months). Resource

utilization by site and outcome reflects these differences in duration of care. In general, resource utilization was slightly higher at the PHC than at the HIV outpatient clinic, primarily because patients at the PHC who ultimately died or were lost to follow up remained in care for an average of nearly four more months, long enough to make at least one more clinic visit and undergo an additional set of laboratory tests. For patients who did remain in care, differences between the sites were modest, with the PHC reporting slightly fewer clinic visits and slightly more laboratory tests.

Table 8-4. Time in care (months) and resource utilization for study period by outcome and facility.

	All patients		Alive in care		Dead / LTFU	
	HIV Outpatient Clinic	Primary Health Clinic	HIV Outpatient Clinic	Primary Health Clinic	HIV Outpatient Clinic	Primary Health Clinic
Patients, n	600	200	432	163	168	37
CD4 count (cells/mm^3), median	148	161.5	155	164	120.5	142
RESOURCES USED IN STUDY PERIOD						
Average months in care	9.7	11.2	12.0	12.0	3.7	7.5
Number of visits	7.0	6.6	8.7	7.3	2.7	3.5
Laboratory tests						
Alanine aminotransferase	0.6	1.0	0.8	1.0	0.2	0.9
CD4 count	0.5	1.7	0.7	1.9	0.1	1.1
Creatinine	0.7	2.2	0.8	2.4	0.3	1.2
Full blood count	0.6	1.0	0.8	1.0	0.2	1.0
Viral load	0.5	0.7	0.7	0.9	0.0	0.9
Total unit cost per visit (USD*)	31	9	31	9	31	9
Staffing cost per visit (USD*)	25	8	25	8	25	8
Fixed cost per visit (USD*)	6	1	6	1	6	1

*Costs are given in 2014 US dollars, converted at a rate of R10.83 to US$1.00

Costs by site, outcome, and cost category are presented in Table 8-5. Drugs and diagnostic tests are procured centrally by government and thus have identical unit costs between sites; higher costs in these categories between sites indicate higher resource usage. Patients who spend 12 months in care have similar drug and diagnostic costs between sites, indicating similar resource utilization. Unit costs for staffing and fixed costs are specific to the site, reflecting staffing composition, infrastructure, equipment, and patient volume. Differences in these cost categories can thus reflect differences in unit costs and/or resource usage.

Table 8-5. Mean 12 month cost per patient (USD) by outcome and facility, broken down by cost category.

Cost category (mean, %)	All patients (USD)				Alive in care (USD)				Dead / LTFU (USD)			
	HIV Outpatient Clinic		Primary Health Clinic		HIV Outpatient Clinic		Primary Health Clinic		HIV Outpatient Clinic		Primary Health Clinic	
Drugs	85	(25%)	100	(47%)	108	(25%)	113	(47%)	28	(23%)	43	(43%)
Diagnostics	41	(12%)	51	(24%)	53	(12%)	57	(24%)	11	(9%)	24	(24%)
Staffing	177	(52%)	56	(26%)	219	(51%)	62	(26%)	68	(56%)	30	(30%)
Fixed	39	(11%)	6	(3%)	48	(11%)	7	(3%)	15	(12%)	3	(3%)
Average cost per patient (95% CI)	342	(326, 358)	213	(204, 222)	428	(422, 452)	238	(233, 244)	122	(106, 137)	100	(87, 113)

[1]Costs are given in 2014 US dollars, converted at a rate of R10.83 to US$1.00

The average cost per patient initiated on ART over the 12 months following initiation was significantly lower at the PHC ($213) than at the HIV outpatient clinic ($342). This finding of lower costs at the PHC held for all outcomes and remained valid even when the longer duration of care for those ultimately not in care was taken into account: $20 v. $36 per month at the PHC and HIV outpatient clinic, respectively, for patients in care and $13 v. $33 per month for patients not in care. Most of this difference derives from the higher costs of staff and infrastructure at the HIV outpatient clinic. While patients at the HIV outpatient clinic made slightly more visits, the cost per visit was substantially more ($31 v. $9).

8.5 Discussion

In this analysis of outcomes and costs of providing antiretroviral therapy under South Africa's two major models of service delivery, we found that both models achieved similar proportions of patients alive and in care 12 months after initiation, but the primary health clinic model cost substantially less per patient treated, despite providing more months of patient care overall. This cost difference is due largely to the higher staff and infrastructure costs incurred in a hospital-based clinic, and reflect the fact that ART patients rarely require the more specialized services and equipment available at a hospital.

Other studies in South Africa have consistently found that decentralization to PHCs from centralized clinics and task shifting to nurses produce favorable or equivalent results for patients [55, 132-134, 151, 166]. We previously showed that down-referral of stable ART patients to PHCs after initiation at a hospital-based HIV outpatient clinic reduced the costs of managing stable patient [131]. The study reported here, which demonstrated both equivalent patient outcomes and lower costs for PHC-level, nurse-led initiation and management, stands in contrast to the only other cost estimate of this model we discovered, from the STRETCH trial in South Africa's Free State Province. The STRETCH trial found that nurse initiation and management can improve health outcomes and quality of care somewhat, but at a higher mean cost [134, 163] that reflected high setup and implementation costs and more clinic visits per patient in the nurse-led arm. Patients in the STRETCH trial were enrolled prior to the advent of NIMART and were managed under the constraints of a randomized controlled trial. Our study is therefore more likely to reflect current, actual conditions in the public sector since NIMART became the standard of care. The knowledge that PHCs can deliver equally good care, at much lower cost, will help the South African Government, neighboring governments, and their partners to make cost-effective decisions about program design.

Shifting ART responsibilities from doctors to nurses has occurred to varying degrees across all treatment facilities in South Africa. At PHCs, nurses provide nearly all HIV services, with only occasional referral, and HIV care is largely integrated with other primary health care. HIV outpatient clinics at hospitals remain stand-alone services with relatively significant doctor involvement, with NIMART trained nurses working alongside but not always replacing doctors. We found that this staffing mix, which also affects patient volume and the efficiency of staff time use, is one of the two main causes of the high cost of HIV outpatient clinics (the other is simply the higher cost of hospital infrastructure). The importance of the staff complement suggests that a re-allocation of responsibilities, with complicated patients (e.g. patients with very low CD4 counts at initiation, patients failing first line therapy, patients on second line therapy) referred to hospital-based HIV clinics and the vast majority of uncomplicated patients initiated and managed at PHCs. Supporting this recommendation, a study of the NIMART rollout in the City of

Johannesburg found that NIMART increased ART initiations at PHCs and reduced them at hospital-based HIV clinics, allowing the hospital clinics to focus on more difficult cases [162].

Although we estimated both costs and effectiveness of the two models of ART delivery, our study was not designed as a cost-effectiveness analysis (CEA), as we do not believe that a choice can be made between the two models. In view of the vast demand for HIV treatment in South Africa, both models will continue to be required for years to come. The information we report will help support efficient allocation of patients between facilities, decisions about future expansion of treatment capacity, and planning and budgeting.

This study had a number of limitations, most of which are common to retrospective, observational cohort studies. Most important, the study was limited to a single pair of sites in one province, which limits geographic generalizability. The study sites are, however, public sector treatment facilities following the national treatment guidelines, and are thus likely to be typical of the public sector in other provinces in South Africa, if not of other countries. Although we matched our samples carefully using a rigorous matching algorithm, moreover, unobserved differences between the samples may bias our estimates. Our results are dependent on the accuracy and completeness of routinely collected patient records, which may also have varied by site. Finally, despite our access to relatively recent data, the rapid pace of change of national and global treatment guidelines makes it nearly impossible for research to “keep up” with the current treatment landscape.

In spite of these limitations, we conclude that initiating and managing ART patients at primary health clinics under South Africa’s NIMART policy is producing equally good outcomes as hospital-based HIV outpatient clinic care at much lower cost. Evolution of the country’s hospital-based clinics into well-resourced, centralized, expert referral facilities that focus on complicated patients, while investing program expansion resources into PHCs, may thus be the country’s preferred strategy. There are currently no widely-utilized guidelines for how to triage patients between

routine PHC care and specialized HIV clinic care. Developing guidance in this area may thus be a priority for policy makers.

While our findings should support the continued expansion of NIMART, we conclude by noting that the impact of the program on non-HIV care must also be considered. So far, nurses appear to have incorporated HIV care into their workloads smoothly, but there is no evidence to suggest how much additional capacity remains on the system or that the addition of HIV care has not been to the detriment of other patients. While we have looked specifically at the provider costs of ART, a full evaluation of the NIMART program—and of similar decentralizing and task-shifting initiatives in other countries—should take into account both the impact of the program on non-HIV care and its benefits and costs to patients themselves.

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SECTION 3 – INPATIENT HIV TREATMENT

Section 3 Aims

- To examine the impact (costs and outcomes) of a large scale antiretroviral treatment program on HIV related inpatient care and treatment, by
  - Determining the burden and cost of HIV related inpatient admissions, and
  - Determining the HIV related inpatient mortality

This section is divided in to two chapters (Chapters 9 and 10), which focus on the cost and outcomes of HIV related inpatient care and treatment, respectively. Chapter 9 determines the burden of HIV on an urban inpatient facility, by estimating the HIV related admissions and their associated costs. Chapter 10 uses routine patient data to determine the HIV related inpatient mortality at an urban inpatient facility.

CHAPTER 9 – Paper 3: The high cost of HIV-positive inpatient care at an urban hospital in Johannesburg, South Africa

At the time of this thesis submission, Paper 3 was published in PLoS One. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university. See Appendix C for a PDF version of the published article.

Reference: LONG LC, FOX MP, SAULS C, EVANS D, SANNE I, ROSEN SB. 2016. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. *PLoS One*. 11(2): e0148546. *http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0148546*

9.1 Abstract

Background: While most HIV care is provided on an outpatient basis, hospitals continue to treat serious HIV-related admissions, which is relatively resource-intensive and expensive. This study reports the primary reasons for HIV-related admission at a regional, urban hospital in Johannesburg, South Africa and estimates the associated lengths of stay and costs.

Methods and Findings: A retrospective cohort study of adult, medical admissions was conducted. Each admission was assigned a reason for admission and an outcome. The length of stay was calculated for all patients (N = 1,041) and for HIV-positive patients (n = 469), actual utilization and associated costs were also estimated. Just under half were known to be HIV-positive admissions. Deaths and transfers were proportionately higher amongst HIV-positive admissions com- pared to HIV-negative and unknown. The three most common reasons for admission were tuberculosis and other mycobacterial infections (18%, n = 187), cardiovascular disorders (12%, n = 127) and bacterial infections (12%, n = 121). The study sample utilized a total of 7,733 bed days of those, 55% (4,259/7,733) were for HIV-positive patients. The average cost per admission amongst confirmed HIV-positive patients, which was an average of 9.3 days in length, was $1,783 (United States Dollars).

Conclusions: Even in the era of large-scale antiretroviral treatment, inpatient facilities in South Africa shoulder a significant HIV burden. The majority of this burden is related to patients not on ART (298/469, 64%), and accounts for more than half of all inpatient resources. Reducing the costs of inpatient care is thus another important benefit of expanding access to ART, promoting earlier ART initiation, and achieving rates of ART retention and adherence.

9.2 Introduction

Although widespread access to antiretroviral therapy (ART) is commonly assumed to have reduced the need for HIV-related hospital inpatient care, there is little published evidence confirming this in low- and middle-income countries. In South Africa, where an estimated 6.3 million people are HIV-infected and more than 2.6 million are on ART [22], the national HIV treatment program places a significant burden on the public healthcare system. While most HIV care is provided on an outpatient basis at public primary health clinics, hospitals continue to treat serious HIV-related admissions but the current extent and cost of this is unknown. Compared to outpatient care, inpatient care is resource-intensive and expensive. It is thus important to describe the main reasons for HIV-related admissions and the associated costs.

Before the availability of public HIV treatment in South Africa, inpatient facilities saw an increasing number of HIV patients presenting with serious HIV-related complications and AIDS [72, 75, 81, 186]. South Africa launched large-scale, public HIV treatment in 2004 through outpatient facilities, and most recent studies of the costs of HIV care in South Africa have been limited to outpatient services[173, 187-189]. Studies estimating inpatient costs have typically included them as part of the overall cost of HIV treatment [67, 109-113, 156]. Only two have looked specifically at inpatient costs [76, 82], and both relied on data from the earliest years of the ART rollout. Similarly, only a few published studies have examined the share of overall inpatient resource utilization attributable to HIV since the advent of public sector ART in 2004 [69, 82, 102], and none have estimated this in more recent years. As a result, the current extent of HIV-related inpatient admissions and its associated cost in public sector hospitals is not known.

To provide current information to policy makers and program managers about the burden of HIV-related inpatient care in a setting of widespread ART access, this study reports the primary reasons for HIV-related admission at a regional, urban hospital in South Africa during 2010 by HIV and ART status and estimates the associated lengths of stay and costs. Data are drawn from medical records and

hospital invoices, providing more detailed and accurate information than has been available thus far.

9.3 Methods

9.3.1 Study population and data

We conducted a retrospective cohort study of admissions at a regional, urban, public sector hospital in Johannesburg, South Africa. The hospital, with 11 inpatient medical wards and 347 beds, falls under the Gauteng Province Department of Health and serves a large urban catchment area that includes both formal and informal settlements.

The study population included all adult (≥ 18 years old) admissions that occurred at the medical admission wards between January 1 and August 31, 2010. This time period (mid summer to late winter) was selected to capture seasonal variation in inpatient medical admissions. Admissions into other specialist wards (e.g. gynecology) were excluded. We created a sampling frame from the medical admission ward registers, then drew a random 12% sample of admissions for analysis, with an aim of 10% and an additional 2% selected to compensate for anticipated missing files. Repeat admissions of the same individual patient were recorded as two separate admissions.

Data were collected from three sources, reflecting the hospital's record keeping system. Medical admission ward registers provided the date of admission, preliminary diagnosis, and final ward assignment. Patient demographic characteristics and all the care that the patient received during the admission were drawn from inpatient files. Finally, the electronic laboratory system was used to verify and update diagnostic tests done during the admission. Final data collection for a patient occurred at least 6 months after admission to ensure sufficient time for the admission to be completed and the patient file stored. Up to three attempts were made to locate missing inpatient admission files over a 3-month period. If

the files could still not be located, the admissions were classified as missing. Missing or otherwise incomplete files were excluded.

Patient data were extracted from the inpatient files and entered directly into a CS Pro™ database. For patients known to be HIV-negative or of unknown HIV status, only demographic and basic admission data were extracted. For HIV-positive patients, we also extracted detailed resource usage data, including length of stay, drugs prescribed, intravenous fluids prescribed, diagnostics performed, and any other recorded procedures.

9.3.2 Outcomes and HIV status

For each admission in the sample, we started by assigning a reason for admission, corresponding to the final discharge diagnosis. Final discharge diagnosis was extracted from the paper patient discharge summary. If the discharge summary was incomplete or missing then the patient medical notes were reviewed to see if a final discharge diagnosis was noted. In the absence of a clear discharge diagnosis the diagnosis was classified as “Unknown”. Each admission was assigned one of four admission outcomes: transfer, unknown, died, discharged. Transfers were those patients sent to other facilities for additional treatment. Patients with unknown outcomes did not have a date of discharge, death, or transfer; their data is included in the base- line cohort description and analysis of reasons for admission but not in average length of stay or cost estimates. Deaths and discharges were as recorded in the inpatient record.

We then categorized each enrolled subject into one of three groups. ‘HIV-positive’ contained known HIV-positive patients determined by a conclusive result in the inpatient file, the presence of HIV monitoring diagnostics, and/or ARV prescriptions. This categorization does not specify whether or not the reason for admission was HIV related, rather the status of the person being admitted. ‘HIV-negative’ included patients with known HIV-negative status in their admission records. ‘HIV unknown’ encompassed all other patients, including undiagnosed HIV-positive patients for whom HIV status was not recorded in the inpatient file.

We report demographic characteristics and primary reason for admission, categorized by major disease area, by HIV status.

9.3.3 Resource utilization and costs

For inpatient care, a substantial portion of total admission cost is attributable not to variable resources, such as drugs, diagnostics, and procedures, but rather to the resources associated with the stay itself, often called the “hotel” costs and including the hospital infrastructure, general staffing, and so on. For each HIV status group and primary reason for admission, we first estimated and compared the mean length of stay and hotel cost associated with it, with 95% confidence intervals.

For HIV-positive patients, we also estimated actual utilization and associated costs for variable resources as well as hotel costs, and we report these admission costs by cost category with means and proportions. Costs were measured from the provider (hospital) perspective and included the cost of all resources from the date of admission of an HIV-positive patient to the date of outcome (i.e. discharge, death, transfer out). A bottom up costing approach was used, including drugs, fluids, diagnostics, surgical procedures and hotel costs (including bed cost, support staff, and medical staff). Bed cost included equipment, space, shared staff, administration and overhead at the study site. Unit costs of drugs, diagnostics, lab charges, procedures, and other variable inputs were recorded from the most recent available invoices / price lists. All unit costs were in 2013 South African Rand (ZAR) or adjusted to 2013.

For medical staff costs, the complement of medical staff in the medical wards was estimated during the study period and 2013 government salary costs applied [190]. Since doctors do not spend all their time in the medical wards, we allocated 20%, 40% and 60% of specialist/consultant, registrar, and medical officer time to the medical wards, respectively. Nurses were assumed to spend all their time in the medical wards. Total personnel costs were then divided by the number of annual bed days to estimate the medical staff cost per day of medical admission.

Annual costs of inpatient care (including all hotel and standard care costs but excluding variable costs for condition-specific drugs, diagnostics, and procedures and medical staff costs) were taken from the hospital's annual accounts for the relevant year (2012–2013) and apportioned either by percentage of medical beds to overall hospital beds or by physical space in the medical wards to overall space in the hospital. Equipment in the medical wards was inventoried, unit costs applied, and an annual equivalent cost calculated using a working life of 8 years and a discount rate of 5%. For all other shared space, equipment was estimated at 20% of the cost of the space, the same percentage as in the medical ward. Space costs were estimated by obtaining minimum rental costs per square metre from the surrounding area at 2013 prices. The hotel, equipment, and space costs are reported together as fixed costs. The reported costs were converted from South African Rand (ZAR) to United States Dollar (USD) at the average exchange rate prevailing during 2013, which was 9.6:1 (ZAR:USD) [191]. Note that costs included may be paid by any combination of patient fees, government budgets, donor grants, and other sources of funding.

The study protocol was reviewed by the Institutional Review Boards of the University of Witwatersrand and Boston University, who approved the collection of the data without informed consent and the use of an anonymous analytic dataset.

9.4 Results

During the eight-month study period there were 10,801 admissions to the medical wards. A random sample of 1,343 (12%) was selected; 302 (2.8%) were then excluded because their files were missing or incomplete, leaving an analytic sample of 9.2% of all admissions. The excluded admissions were matched to the hospital death register and the electronic laboratory records and did not differ from the analytic sample, suggesting that the excluded admissions were not sicker or more likely to be HIV positive than those included. The remaining 1,041 constituted the analytic dataset, with just under half (45%, n = 469) of the sample having a confirmed HIV-positive diagnosis. (See Supplementary Figure 2)

The baseline characteristics of the sample are shown in Table 9-1. Just under half were known to be HIV-positive patients; the rest were HIV-negative (20%) or of unknown HIV status (35%). Almost two thirds (59%) of patients admitted were between 25–50 years of age; amongst HIV-positive patients more than four out of five (82%) were in this age range, consistent with national HIV prevalence by age group. Patients with unknown HIV status were substantially older than those with a known HIV status, suggesting that older patients are less likely to have been tested for HIV. For the HIV-positive patients with CD4 counts (n = 399/469), 36% were at very high risk for HIV-related illness (CD4 count < 50 cells/mm^3) and only 37% were recorded as being on treatment. The percentages of deaths (17%) and transfers (2%) were higher amongst HIV-positive admissions compared to HIV-negative (6% and 0%) and unknown (9% and 1%). Unknown outcomes were evenly distributed by HIV status.

Table 9-1. Baseline characteristics of admission cohort.

	Overall n = 1041		HIV status					
			Positive n = 469		Negative n = 206		Unknown n = 366	
Gender, n (%)								
Male	486	(46.7)	216	(46.1)	114	(55.3)	156	(42.6)
Female	555	(53.3)	253	(53.9)	92	(44.7)	210	(57.4)
Age, n (%)								
18-24	65	(6.2)	16	(3.4)	28	(13.6)	21	(5.7)
25-30	139	(13.4)	81	(17.3)	27	(13.1)	31	(8.5)
31-40	281	(27.0)	194	(41.4)	41	(19.9)	46	(12.6)
41-50	199	(19.1)	113	(24.1)	42	(20.4)	44	(12.0)
51-60	156	(15.0)	44	(9.4)	29	(14.1)	83	(22.7)
61-70	102	(9.8)	21	(4.5)	22	(10.7)	59	(16.1)
>70	99	(9.5)	0	0	17	(8.3)	82	(22.4)
Age, median (IQR)	42	(32, 56)	37	(32, 45)	42	(29, 55)	55	(39, 68)
Most recent* CD4 count (cells/mm^3), n (%)								
Missing	-	-	70	(14.9)	-	-	-	-
<=50	-	-	142	(30.3)	-	-	-	-
51-100	-	-	63	(13.4)	-	-	-	-
101-200	-	-	79	(16.8)	-	-	-	-
201-350	-	-	65	(13.9)	-	-	-	-
>350	-	-	50	(10.7)	-	-	-	-
Most recent* CD4 count (cells/mm^3), median (IQR)	-	-	90	(30, 237)	-	-	-	-
ARV Status, n (%)								
Not on ARVs	870	(83.6)	298	(63.5)	206	(100.0)	366	(100.0)
On ARVs	171	(16.4)	171	(36.5)	-	-	-	-
Outcome, n (%)								
Discharged	876	(84.1)	368	(78.5)	188	(91.3)	320	(87.4)
Died	126	(12.1)	80	(17.1)	13	(6.3)	33	(9.0)
Transferred	13	(1.2)	11	(2.3)	-	-	2	(0.5)
Unknown	26	(2.5)	10	(2.1)	5	(2.4)	11	(3.0)

* Done during or within the 3 months prior to admission

9.4.1 Reason for admission

There were 326 unique reasons for admission, which were categorized into 25 major disease areas. (See Supplementary Table 1.) The top 5 reasons for admission for each HIV status resulted in 9 unique reasons and accounted for more than 75% of all admissions.
Figure 9-1 presents these results by reason for admission. (See Supplementary Table 2.)

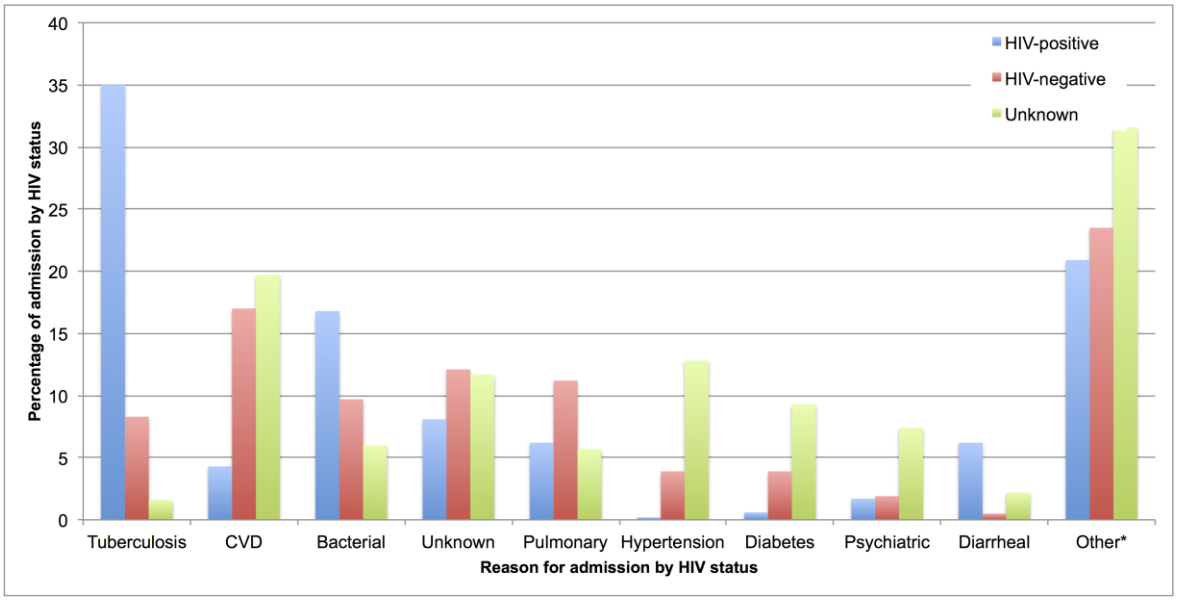

Figure 9-1. Summary of reasons for admission by HIV status.

This figure presents the top 5 reasons for admission for each HIV status category. All other reasons were collapsed into the other category.* Tuberculosis was the most prevalent reason for admission amongst HIV-positive admissions accounting for 35%. CVD was the single most prevalent reason for admission amongst HIV-negative admissions accounting for 17%, while it only accounted for 4% of all HIV-positive admissions.

The three most common reasons for admission were tuberculosis and other mycobacterial infections (18%, n = 187), cardiovascular disorders (12%, n = 127) and bacterial infections (12%, n = 121). The majority of tuberculosis (87%) and bacterial infections (65%) were found among HIV-positive patients, while the majority of cardiovascular disorders (57%) were reported amongst those with unknown HIV status. Pulmonary disease was proportionately almost double in the HIV status unknown patients, which may be explained by the higher median age of this group. Non-communicable diseases such as hypertension, diabetes, and psychiatric illness were much more common amongst those with an unknown HIV

status compared to either HIV-positive or negative patients. The reason for admission for 10% (n = 106) of admissions was unknown. This was either because the information was missing from the patient record or the attending physician did not record a conclusive discharge diagnosis.

We also stratified reason for admission by ART status and baseline CD4 count for those with HIV. (See Supplementary Table 3.) Although most (63%) HIV-positive admissions were not on ART, the 5 most common reasons for admission were the same regardless of treatment status, with the exception of bacterial infection, which comprised a smaller share of admissions among patients on ARVs (9.4%) than not (21.1%) (prevalence difference 11.7%; 95% CI 5%, 18%).

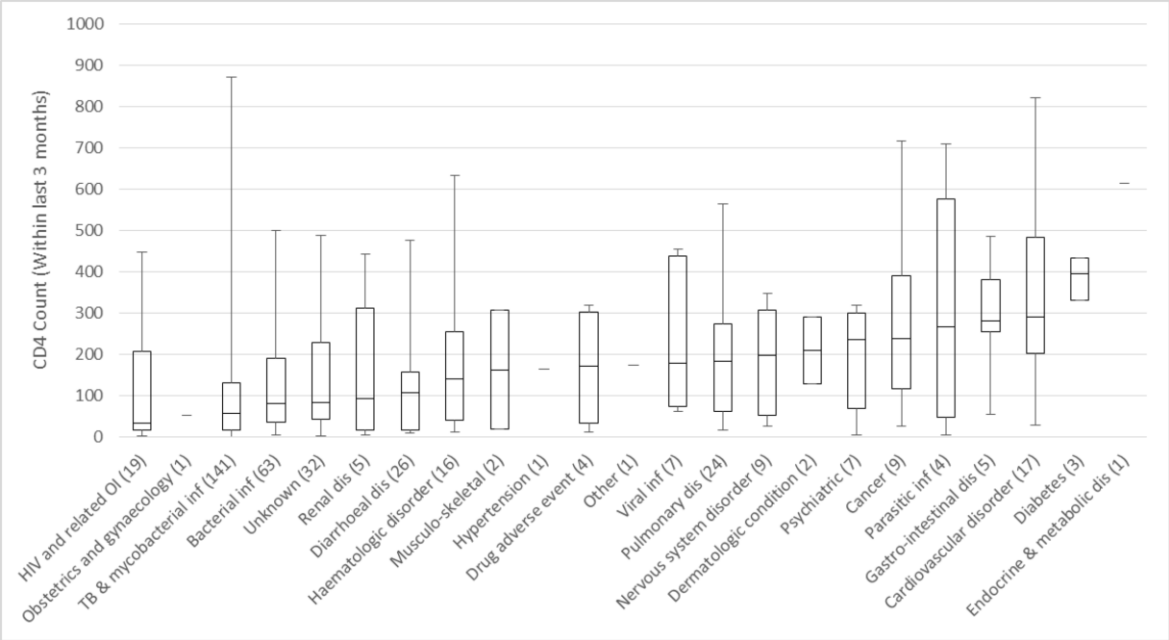

Figure 9-2. Box and whisker plot of CD4 count by reason for admission.

The distribution of CD4 count at admission shows that all HIV positive admissions with one exception had a median CD4 count below 500 cells/mm3. This suggests that boosting the CD4 count of HIV positive patients by starting treatment early and ensuring adherence while on treatment may reduce the frequency and severity of admission.

As Figure 9-2 indicates, the top 5 reasons for HIV-positive admissions all had a median CD4 count below 200 cells/mm^3, which was the threshold for ART initiation at the time of the study. As might be expected, TB and other mycobacterial infections, which account for a major portion of HIV-related inpatient admissions, become less frequent as baseline CD4 count rises. Nearly half (48%) of admissions among patients with CD4 counts ≤ 50 cells/mm^3 were attributable

to TB and mycobacterial infections (51–100 cells/mm^3: 38%, 101–200 cells/mm^3: 34%, 201–350 cells/mm^3: 23%, >350 cells/mm^3: 14%).

9.4.2 Length of stay and distribution of bed days

Among all admissions with a known outcome (n = 1,015), the overall mean length of stay (95% CI) was 7.6 days (7.2, 8.0). The longest average length of stay was for HIV and related OIs at 13.2 days (8.9, 17.3). HIV-positive admissions had a longer average length of stay overall of 9.3 days, compared to 7.3 and 5.6 days for HIV-negative and HIV unknowns. Among HIV-positive patients, renal disease (18 days), gastro-intestinal disease (15 days), and drug adverse events (14 days) resulted in the longest average stays. For HIV-negative and HIV unknown admissions, cancer resulted in the longest average stay (23 and 10 days respectively). (Full details in Supplementary Table 4 and Supplementary Table 5.)

The admissions included in the study sample utilized a total of 7,733 bed days and the top 5 contributors to bed days by HIV status are included in Table 9-2. (Full details in Supplementary Table 6.) Of those, 55% (4,259/7,733) were for HIV-positive patients, 19% (1,469/7,733) were not related to HIV, and 26% (2,005/7,733) were for patients of unknown HIV status. TB and other mycobacterial infections accounted for the most (18%) bed days, driven largely by the HIV- positive admissions of which 36% were as a result of TB and other mycobacterial infections. Cardiovascular disease was the leading reason for bed day usage amongst HIV-negative and HIV unknown patients, accounting for 17% and 20% respectively.

Table 9-2. Distribution of bed days by HIV status and reason for admission.

Reason for admission Total bed days (%)	Overall		HIV status					
			Positive		Negative		Unknown	
TB and other mycobacterial infections	1852	(18.3)	1617	(35.5)	201	(8.5)	34	(1.7)
Cardiovascular disorder	936	(12.5)	197	(4.4)	249	(17.4)	490	(20.3)
Bacterial infection	887	(11.9)	625	(17.2)	136	(10.0)	126	(6.2)
Unknown reason for admission	687	(8.0)	356	(6.3)	131	(10.0)	200	(9.0)
Pulmonary disease	480	(7.2)	207	(6.3)	151	(11.4)	122	(5.9)
Hypertension	273	(5.5)	1	(0.2)	47	(4.0)	225	(13.2)
Diabetes	253	(4.4)	27	(0.7)	46	(4.0)	180	(9.6)
Diarrheal disease	205	(3.7)	175	(6.3)	2	(0.5)	28	(2.3)
Psychiatric	180	(3.8)	57	(1.7)	28	(2.0)	95	(7.6)
Other*	1980	(24.5)	997	(21.4)	478	(32.3)	505	(24.2)
Total**	**7733**	**(100.0)**	**4259**	**(100.0)**	**1469**	**(100.0)**	**2005**	**(100.0)**

* Includes all other reasons which were not amongst the top 5 highest contributors towards total bed days.
** All admission where them outcome is unknown are exclude, as they do not have a discharge date.

9.4.3 Cost of HIV-positive admissions

Table 9-3 presents the top ten most expensive reasons for admission for the HIV-positive patients. (Full details in Supplementary Table 7.) The average cost per admission amongst confirmed HIV-positive patients, which was an average of 9.3 days in length, was $1,783. This resulted in an average cost per bed day of approximately $192, which is just slightly less than the patient day equivalent (PDE) cost reported for Gauteng Province hospitals of $225 [192]. The majority of the cost can be attributable to medical staff (42%) and fixed costs (35%). Laboratory and drugs costs accounted for only 11% and 3% respectively. Although 36% of all HIV-related admissions were reported to be on antiretrovirals, almost none were dispensed during the hospital admission, suggesting that either patients brought their ARVs with them or treatment was interrupted during the hospital stay.

Table 9-3. Cost for HIV-positive admissions (HIV-positive only), by cost category in United States Dollars (USD).

Reason for admission	N	All admissions (USD)		Mean per admission (USD)					
		Total	(%)	Fixed*	Medical staff	Lab	Drug & ARV	Fluid	Total
Renal disease	6	23,661	(2.9)	1,241	1,459	372	110	762	3,944
Drug adverse event	5	12,881	(1.6)	961	1,129	234	21	232	2,576
Endocrine and metabolic disease	1	2,472	(0.3)	905	1,063	363	140	1	2,472
HIV and related OI	21	51,141	(6.3)	918	1,079	218	83	137	2,435
Gastro-intestinal disease	5	11,972	(1.5)	1,030	1,211	132	20	2	2,394
Unknown reason for admission	29	68,150	(8.3)	652	766	219	69	198	2,350
Hematologic disorder	16	32,612	(4.0)	648	762	241	52	336	2,038
Parasitic infection	5	9,637	(1.2)	696	818	189	98	126	1,927
TB and other mycobacterial infections	163	313,318	(38.3)	686	806	198	66	165	1,922
Musculo-skeletal	2	3,761	(0.5)	800	941	93	44	3	1,880
Other	206	288,553	(35.3)	515	605	162	52	67	1,401
All	***459***	***818,156***	***(100.0)***	***632***	***743***	***188***	***61***	***134***	***1,783***

* Fixed costs include hotel, equipment and space costs.

Renal disease generated the most expensive admission ($3,944 per admission, 17.8 days) driven by the length of stay, but this was relatively infrequent (6/459). TB and other mycobacterial infections are ranked ninth by average cost per admission but occurred much more frequently (163/459). As a result TB accounts for the largest portion of HIV-related admission costs, more than a third of the total.

9.5 Discussion

In a random sample of 1,041 inpatient admissions at a regional hospital in Johannesburg in 2010, nearly half (45%) were for patients known to be HIV-positive. These patients accounted for at least 55% of all resources utilized (bed days) by the sampled admissions. Since some proportion of the admissions for patients of unknown HIV status were bound to have been for HIV-positive patients, these figures represent the minimum burden placed on the hospital by HIV-positive patients during the time of the study. They are comparable to the results of a 2005 study of another Johannesburg hospital [82], suggesting that the burden of HIV on South African hospitals may not have changed substantially since the rollout of ART in 2004.

Only 36% of HIV-positive patients were reported to be on ART at the time of the admission, despite 71% being eligible for ART based on their CD4 count. A recent report [76] on an HIV- positive cohort in South Africa found that the majority (64%) of hospitalizations occurred prior to the initiation of ART, which may explain the findings of this paper. In our study, only 12% of HIV-positive admissions occurred when the CD4 count > 350 cells/mm^3. Earlier treatment initiation, at the higher CD4 count thresholds adopted by the South African Government in 2011 and again in 2015, may therefore substantially reduce the number of HIV-related admissions in future years.

In our sample, tuberculosis accounted for almost a fifth of all inpatient medical resources used. Given the low median CD4 count at admission, it is not surprising that tuberculosis and other similar infections were the leading reason for admission and death of HIV-positive patients causing one fourth of all HIV-related deaths. Similar results have been seen in other studies both in sub Saharan Africa prior to treatment availability [193-195] and in South Africa soon after treatment was made available [76, 82, 102]. Cardiovascular disease was the leading reason for admission amongst those who had a known HIV-negative or unknown status, who were also older than those with HIV. This profile is more typical of areas or countries where the population is not severely immune compromised. The UK reported ischemic heart disease as the third primary reason for admission after cancer and pneumonia [196]. The US reported congestive heart disease as the fourth primary reason for admission after live births, pneumonia and osteoarthritis [197].

Within the HIV-positive patients, reason for admission did not vary by ART status. The CD4 count profile for HIV-positive patients by treatment status was also similar, which could account for the similar admission profile and also could suggest that those on ART are recent initiates. Leisegang and colleagues followed HIV-positive patients both prior to and after ART initiation and showed that the highest inpatient costs occurred in the period immediately prior to, during and after ART initiation [109].

A number of papers have indicated that it is the non-curative costs (i.e. hotel costs, not drugs and diagnostics) which drive the cost of medical admissions, meaning that length of stay is an accurate proxy for cost of admission [82, 102]. Overall HIV-positive patients had longer average medical admissions compared to other patients and as a result could on average be expected to use more resources and cost more per admission than HIV-negative patients. Renal disease and cancer had the longest average medical admissions amongst the HIV-positive and negative patients, respectively.

The cost of HIV-related admissions to the South African healthcare system is not trivial, either in terms of the facility resources it takes from other potential patients nor in financial terms. Another recent study reported that for South African patients on ART, the hospitalization rate was 6.9 admissions per 100 patient years [76]. With over 2 million patients on ART in South Africa, this suggests that there are some 138,000 medical admissions in the country per year just for patients already on ART. We estimated an average cost of $1,783 per admission, bringing the annual cost of ART medical admissions to $246 million. With a year of ART estimated to cost approximately $404 [198], the annual funds spent on HIV inpatient admissions while on ART could pay for the annual cost of over 600,000 patients on ART, more than a quarter of the patients on treatment in 2013 [22].

If South African inpatient healthcare facilities are operating at capacity, then a high HIV inpatient burden may lead to the crowding out or displacement of patients with other conditions [195]. The Gauteng HIV prevalence in 2012 for adults (15–49 years old) was 17.8% [164], yet in our sample, HIV positive patients utilized 55% of inpatient resources. In other words, less than a fifth of the population consumed more than half of the available resources, creating a large excess burden of HIV on inpatient facilities. Diminishing this excess burden through earlier ART initiation and better medication adherence—high priorities of the South African government—may free up additional capacity and reduce the cost of treating HIV patients, adding further evidence of the importance of these goals.

Our study had a number of limitations. Other research has suggested that specialist wards may also experience a large HIV burden [87], but this study

focused on medical ward admissions only. The retrospective nature of the study meant that we relied on routine hospital files and a number of these were missing or incomplete. In order to minimize the impact of this missing information alternative data sources (hospital death register, electronic laboratory records) were used to provide additional information on these patients. While we believe the length of stay to be accurate, the estimated costs are based on resource usage extracted from medical records, which may not report all resources utilized. Given that the majority of costs are driven by length of stay, missed variable resources are unlikely to have a major effect on results, however.

9.6 Conclusion

Even in the era of large-scale antiretroviral treatment rollout, we found that inpatient facilities in South Africa are still shouldering a significant HIV burden. We found that the majority of the burden of HIV inpatient care on hospitals is related to patients not on ART, and that this burden is large, accounting for more than half of all inpatient resources. Reducing the costs of inpatient care is thus another important benefit of expanding access to ART, promoting earlier ART initiation, and achieving rates of ART retention and adherence. Having regular reports on HIV-related hospital admissions would provide critical insight into the success of the national treatment program in reducing both HIV-related morbidity and healthcare costs.

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CHAPTER 10 – Paper 4: Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV

At the time of this thesis submission, Paper 4 was under review at JIAS. For the purposes of this thesis the published paper is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the thesis style as prescribed by the university. See Appendix D for a PDF version of the submitted article.

Reference: LONG LC, EVANS DH, ROSEN SB, SAULS C, BRENNAN A, SANNE IM, FOX MP. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. *Under review.*

10.1 Abstract

Introduction: South Africa has one the largest HIV treatment programs, which should be associated with an increase in life expectancy and a reduction in HIV-related mortality. There are a number of discrepancies between the various reported South African HIV-related mortality estimates. A complementary approach to monitoring changes in HIV-related mortality may be to use inpatient care records to examine trends in causes of death and HIV status over time. We investigated the natural mortality experienced in the medical ward of a hospital during 2010 to estimate the contribution of HIV to mortality.

Methods: We conducted a cross-sectional study of inpatient mortality at a regional, hospital in Johannesburg, South Africa. The study population included all adult deaths due to natural causes amongst medical ward inpatients. Cause of death was recorded from the mortuary register. HIV status was ascertained directly from the mortuary register or from laboratory tests specific for HIV diagnosis or monitoring. Resource utilization and cost were based on length of stay in hospital and a reported patient day equivalent cost.

Results: 1,167 inpatient deaths were included in the study, the majority of which were HIV positive (58%). HIV prevalence amongst the males (55%) was slightly lower than that amongst the females (61%) and HIV positive patients were younger (40 years old) than those HIV negative (56 yo) and of unknown HIV status (68 yo). “Infections and parasites” was the most common cause of natural deaths (29%). On average HIV positive patients were admitted for slightly longer (10.5 days) than HIV negative (9.6 days) and HIV status unknown (8.9 days), yet HIV positive inpatient deaths accounted for the majority (62%) of the total bed days. The mean cost per admission was USD 1,976 (95% CI: USD 1,877–USD 2,096).

Conclusions: Even with widespread access to ART, the majority of inpatient natural deaths at a large public sector hospital in 2010 were among HIV positive patients and were likely related to HIV. In view of the importance of accurate data on causes of death, both for HIV interventions and to track other diseases, large-scale expansion of this approach over a longer period is needed.

10.2 Introduction

South Africa has a large generalized HIV epidemic, with over 6 million HIV positive citizens, and one the world's largest HIV treatment programs, with an estimated 2.6 million patients on treatment [22]. Key indicators used to measure the success of this program include an increase in life expectancy and a reduction in HIV-related mortality for antiretroviral therapy (ART) patients. Tracking changes in the contribution of HIV to overall mortality over time is thus an important component of evaluating the national HIV treatment program.

Mortality reporting in South Africa is managed by the Department of Home Affairs and governed by the Births and Deaths Registration Act 1992 (Act No 51 of 1992) [199]. In 2013 Statistics South Africa (StatsSA) reported that 90% of all deaths were due to natural causes and 44% of all deaths occurred in hospitals [200]. In 2011 they reported the percentage of mortality attributable to HIV to be 3.4% and showed this percentage increasing between 2011 and 2013 [200]. This is in contrast to the results of the Thembisa model, an integrated demographic and epidemiologic model of the South African HIV/AIDS epidemic, which shows a decreasing percentage of deaths attributable to AIDS since 2005 with the introduction of antiretroviral treatment [10]. Thembisa estimates that in 2011 there were 169,000 AIDS deaths, which would put the percentage of mortality attributable to HIV to be almost 10 times that estimated in the StatsSA report (169,000/514,480=32%) [10, 200]. Bradshaw and colleagues estimated that fewer than 10% (20,012/207,685) of deaths due to HIV/AIDS in 2010 were registered with HIV as the primary cause of death [201], which supports the discrepancy between the results of StatsSA and modeled estimates. The inconsistency between Deaths Registry data, as reported by StatsSA; modeling estimates of HIV-attributable mortality; and analyses of the registration data suggests that other sources of information are needed to understand the role of HIV in mortality as ART access expands [202].

Data on the contribution of HIV to total mortality from other sources than the Deaths Registry are scarce. The majority of mortality with a known place of death occurs within hospitals. In 2010 and 2013, 52% and 57% of mortality with a known place of death occurred in hospitals, respectively [200, 203]. A complementary approach to monitoring changes in HIV-related mortality may be to use the relatively detailed information available from inpatient care records to examine trends in causes of death and HIV status over time. We investigated the natural mortality experienced in the medical ward of a large, urban, public sector hospital during 2010 to estimate the contribution of HIV to mortality.

10.3 Methods

10.3.1 Study Population and Data

We conducted a retrospective, cross-sectional study of inpatient mortality at a regional, Gauteng Province Department of Health hospital in Johannesburg, South Africa. The hospital serves an urban population of both formal and informal settlements and has 11 inpatient medical wards with 347 beds.

The study population included all adult (≥18 years old) deaths due to natural causes (attributed to illness or an internal malfunction of the body) amongst patients admitted to a medical ward between January 1 and August 31, 2010, an 8-month period intended to capture seasonal variation. Deaths from other (non-natural) causes (e.g. motor vehicle accident) or which occurred during admission to specialist wards (e.g. casualty, surgery) were excluded. Inpatient deaths, which were missing the data required to determine study eligibility, such as date of admission, were excluded. Deaths among pregnant women were also excluded because pregnant women requiring admission were routinely referred to another hospital.

10.3.2 Cause of Death and HIV Status

All persons who die in hospital are taken to the hospital mortuary where the details of death are recorded in the mortuary register. This register includes date of death, gender, age, date of admission, hospital ward, and primary cause of death. In some instances, additional information about co-morbid conditions potentially related to the cause of death is also recorded. South Africa classifies and codes deaths according to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [203, 204]. We assigned a three character ICD-10 code to each primary cause of death. If the cause of death was classified as code R00-R99 ("symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified"), other co-morbid conditions were examined and if available coded as the primary cause of death. Patients whose final primary cause of death is classified as signs or symptoms (R00-R99), heart failure, unspecified renal failure or malignant neoplasms of ill-defined sites are often not reported on individually and classified as 'ill defined' causes of death. We include these deaths and report these codes to allow for full comparison with other publications.

HIV status was determined independently of the listed cause of death and co-morbid conditions. Patients were classified as HIV-positive if a positive HIV status was noted in the mortuary register or if laboratory test results specific for HIV diagnosis or monitoring (e.g. HIV test, CD4 count, or viral load test) could be retrieved from National Health Laboratory Services (NHLS) records. Patients were classified as HIV-negative if a negative HIV test was recorded in the mortuary register, during the current admission or in the month prior to admission. Patients for whom HIV status could not be definitively determined (i.e. no positive HIV test, no HIV monitoring tests, no negative HIV test during the admission or within the month prior to admission) were classified as having an unknown HIV status.

10.3.3 Resource Utilization and Costs

To estimate resource utilization and cost of care, we first captured length of stay (date of admission to date of death), an accepted proxy for inpatient resource usage. The total bed day utilization (sum of all admission lengths) by patients in the data set was divided by the total available at the facility (number of beds x number of days in the follow up period) to estimate the burden of HIV-related deaths on facility capacity. We then used the published patient day equivalent (PDE) cost to translate the length of stay and total bed days into an average cost per admission and total cost by cause of death. The patient day equivalent (PDE) cost for hospitalization in Gauteng for 2013/2014 was ZAR 2,164 (South African Rand) [192]. This was converted into United States dollars (USD) using the average 2014 USD:ZAR weekly exchange rate of 10.84.

The study received ethical approval from the Institutional Review Boards of the University of Witwatersrand and Boston University.

10.4 Results

10.4.1 Baseline description

Baseline characteristics of the study population are presented in Table 10-1. Over the 8-month period 1,201 natural inpatient deaths met study inclusion criteria. Of these, 34 had a missing admission date and were excluded. The final analytic cohort included 1,167 inpatient deaths, an average of 145 deaths per month. The majority of inpatient deaths were HIV positive (n=682, 58%), less than a third had an unknown HIV status (n=343, 29%) and just over a tenth were confirmed HIV negative (n=142, 12%).

Table 10-1. Baseline characteristics of inpatient mortality.

	Overall N=1,167		HIV status					
			Positive n=682		Negative n=142		Unknown n=343	
Gender, n (%)								
Male	595	(51.0)	331	(48.5)	99	(69.7)	165	(48.1)
Female	571	(48.9)	350	(51.3)	43	(30.3)	178	(51.9)
Missing	1	(0.1)	1	(0.1)	0	0	0	0
Age in years, n (%)								
18-19	11	(0.9)	7	(1.0)	1	(0.7)	3	(0.9)
20-24	30	(2.6)	22	(3.2)	4	(2.8)	4	(1.2)
25-29	81	(6.9)	65	(9.5)	7	(4.9)	9	(2.6)
30-34	129	(11.1)	112	(16.4)	6	(4.2)	11	(3.2)
35-39	154	(13.2)	134	(19.6)	4	(2.8)	16	(4.7)
40-44	133	(11.4)	111	(16.3)	10	(7.0)	12	(3.5)
45-49	117	(10.0)	86	(12.6)	12	(8.5)	19	(5.5)
50-54	98	(8.4)	61	(8.9)	16	(11.3)	21	(6.1)
55-59	74	(6.3)	27	(4.0)	24	(16.9)	23	(6.7)
60-64	86	(7.4)	32	(4.7)	23	(16.2)	31	(9.0)
65-69	69	(5.9)	19	(2.8)	19	(13.4)	31	(9.0)
70-74	49	(4.2)	4	(0.6)	5	(3.5)	40	(11.7)
75-79	58	(5.0)	2	(0.3)	7	(4.9)	49	(14.3)
80-84	51	(4.4)	0	0	4	(2.8)	47	(13.7)
85-89	17	(1.5)	0	0	0	0	17	(5.0)
>=90	10	(0.9)	0	0	0	0	10	(2.9)
Age, median (IQR)	46	(36, 62)	39.5	(33, 48)	56	(46, 64)	68	(53, 79)
Length of stay in days, n (%)								
1	103	(8.8)	48	(7.0)	11	(7.7)	44	(12.8)
2-5	452	(38.7)	254	(37.2)	66	(46.5)	132	(38.5)
6-10	240	(20.6)	159	(23.3)	20	(14.1)	61	(17.8)
11-15	133	(11.4)	75	(11.0)	13	(9.2)	45	(13.1)
>=16	239	(20.5)	146	(21.4)	32	(22.5)	61	(17.8)
Length of stay, mean (95% CI)	9.9	(9.4-10.5)	10.5	(9.8-11.3)	9.6	(8.1-11.1)	8.9	(8.1-9.6)
Month of death, n (%)								
January	92	(7.9)	53	(7.8)	16	(17.4)	23	(6.7)
February	119	(10.2)	79	(11.6)	20	(16.8)	20	(5.8)
March	142	(12.2)	94	(13.8)	16	(11.3)	32	(9.3)
April	168	(14.4)	105	(15.4)	25	(14.9)	38	(11.1)
May	147	(12.6)	102	(15.0)	21	(14.3)	24	(7.0)
June	145	(12.4)	94	(13.8)	26	(17.9)	25	(7.3)
July	183	(15.7)	77	(11.3)	10	(5.5)	96	(28.0)
August	171	(14.7)	78	(11.4)	8	(4.7)	85	(24.8)

There were a similar number of males and females in the sample, but the HIV prevalence amongst the males (55%, 331/595) was slightly lower than that amongst the females (61%, 350/571), which reflects what is seen in the

general population. The median (inter-quartile range) age of the cohort was 46 (36-62) years, with HIV positive patients younger (40, IQR: 33-48) than those HIV negative (56, IQR: 46-64) and of unknown HIV status (68, IQR: 53-79).

Figure 10-1 plots inpatient mortality by age group as well as national HIV prevalence estimates by age group [164]. Mortality occurred at much younger ages in HIV-positive patients than in those of negative or unknown status, as illustrated in Figure 1. The percentage of subjects with a confirmed HIV status (HIV-positive + HIV-negative / Total patients) fell rapidly by age group, with 89% of 18-49 year-olds having a confirmed status and only 24% of those who are 65 years and older. In other words, patients of unknown HIV status were older. Similarly, known HIV prevalence (confirmed HIV-positive /total patients) in the cohort fell from 82% amongst 18-49 year-olds to 10% amongst those who are 65 years and older.

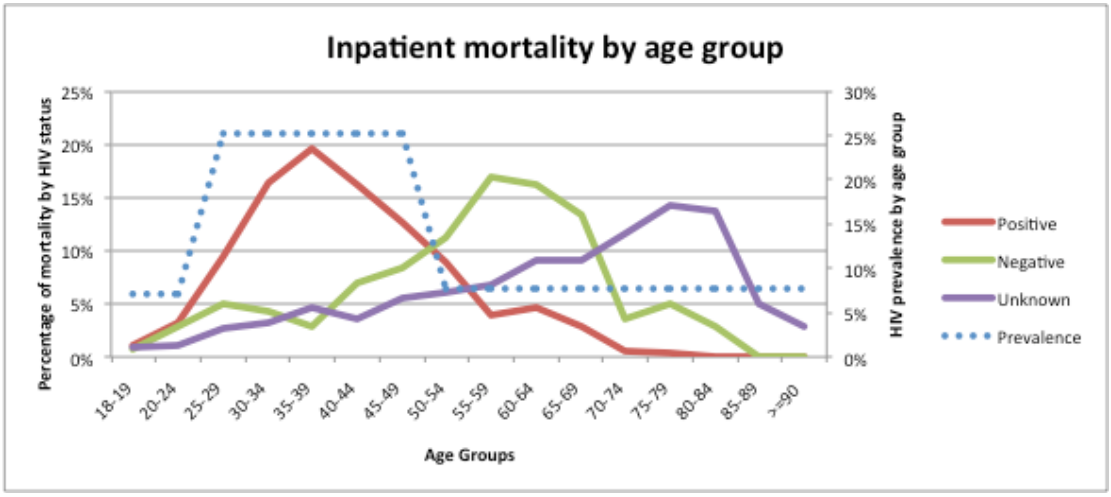

Figure 10-1. Inpatient mortality by HIV status and age group.

Patients who have compromised immune systems (such as those with HIV and the elderly) may be more likely to be admitted and die during months when infectious diseases like influenza are more prevalent. To explore this, mortality is plotted by calendar month of death and HIV status in Figure 10-2. The peak of the annual severe acute respiratory illness (influenza) infections in 2010 occurred in July and August [205], coincident with the peak of

mortality in the HIV unknown group (elderly). Mortality due to influenza, acute lower respiratory infections and chronic respiratory infections showed raised rates during the months of July and August (Data not presented). Mortality in the HIV negative and HIV positive groups, in contrast, showed no clear seasonal patterns.

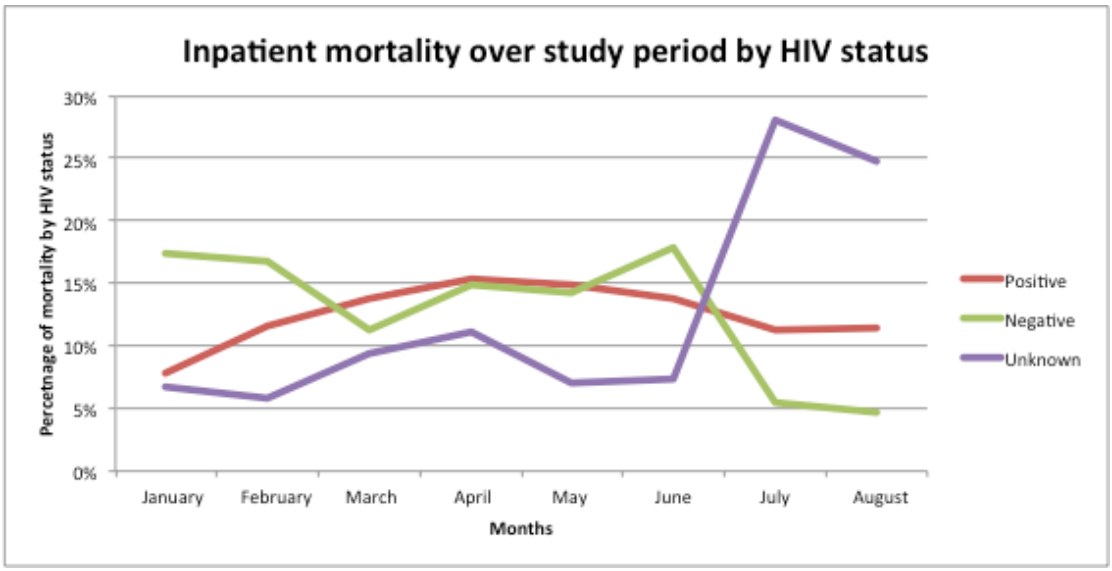

Figure 10-2. Inpatient mortality by calendar month of death.

10.4.2 Description of causes of death

Table 10-2 describes the major causes of death using ICD-10 code chapters by HIV status as well as the top 3 specific causes of death by ICD 10 block for each HIV status group. “Infections and parasites” was the most common cause of natural deaths (29%), followed by “Respiratory” (21%) and “Circulatory” (17%) conditions. HIV positive patients accounted for nearly 9 out of every 10 deaths related to infections and parasites (294/334), despite comprising just 58% of all deaths.

Table 10-2. Cause of death by HIV status.

The top 3 specific causes of death (ICD10 blocks) for each HIV status group are shown as subsets of the chapters they form part of and are shown in *italics*. The top 3 specific causes of death for each HIV status group are marked with an asterisk.

Cause of death (ICD10 chapter / block) n (%)	Overall N=1,167		HIV status					
			Positive n=682		Negative n=142		Unknown n=343	
Infections & parasites (I: A00-B99)	334	(28.6)	294	(43.1)	9	(6.3)	31	(9.0)
Tuberculosis (A15-A19)	*224*	*(19.2)*	*204*	*(29.9)**	*4*	*(2.82)*	*16*	*(4.7)*
Respiratory (X: J00-J99)	241	(20.7)	132	(19.4)	28	(19.7)	81	(23.6)
Influenza and pneumonia (J09-J18)	*97*	*(8.3)*	*67*	*(9.8)**	*7*	*(4.9)*	*23*	*(6.7)*
Other acute lower respiratory tract infections (J20-J22)	*80*	*(6.9)*	*44*	*(5.0)**	*9*	*(6.3)**	*27*	*(7.9)**
Chronic lower respiratory diseases (J40-J47)	*42*	*(3.6)*	*9*	*(1.3)*	*7*	*(4.9)*	*26*	*(7.6)**
Circulatory (IX: I00-I99)	202	(17.3)	40	(5.9)	45	(31.7)	117	(34.1)
Other forms of heart disease (I30-I52)	*112*	*(9.6)*	*19*	*(2.8)*	*25*	*(17.6)**	*68*	*(19.9)**
Cerebrovascular diseases (I60-I69)	*39*	*(3.3)*	*6*	*(0.9)*	*7*	*(4.9)*	*26*	*(7.6)**
Signs & symptoms (XVIII: R00-R99)	77	(6.6)	30	(4.4)	15	(10.6)	32	(9.3)
Nervous system (VI: G00-G99)	61	(5.2)	45	(6.6)	7	(4.9)	9	(2.6)
Genitourinary system (XIV: N00-N99)	55	(4.7)	33	(4.8)	11	(7.7)	11	(3.2)
Renal failure (N17-N19)	*53*	*(4.5)*	*32*	*(4.7)*	*10*	*(7.0)**	*11*	*(3.2)*
Endocrine, nutritional & metabolic (IV: E00-E99)	55	(4.7)	23	(3.4)	10	(7.0)	22	(6.4)
Hematological & immune mechanism (III: D50-D89)	48	(4.1)	40	(5.9)	2	(1.4)	6	(1.7)
Neoplasms (II: C00-D48)	42	(3.6)	16	(2.3)	8	(5.6)	18	(5.2)
Digestive system (XI: K00-K93)	34	(2.9)	20	(2.9)	5	(3.5)	9	(2.6)
Mental & behavioral (V: F00-F99)	11	(0.9)	5	(0.7)	2	(1.4)	4	(1.2)
Skin and subcutaneous tissue (XII: L00-L99)	4	(0.3)	2	(0.3)	0	(0.0)	2	(0.6)
Congenital & chromosomal (XVII: Q00-Q99)	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.3)
Factors influencing health status (XXI: Z00-Z99)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)
Musculoskeletal & connective tissue (XIII: M00-M99)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)
Total	***1167***	***(100.0)***	***682***	***(100.0)***	***142***	***(100.0)***	***343***	***(100.0)***

*Top 3 specific causes of death in that HIV category

Despite infections and parasites accounting for 43% of deaths among HIV-positive patients, only one patient had HIV listed as the primary cause of death. The most common infectious disease across all groups was tuberculosis, responsible for 19% of deaths overall and nearly a third (30%) of deaths amongst HIV positive patients. Heart disease, in contrast, was the leading cause of death amongst HIV negative (18%) and unknown patients (20%). Further details on cause of death by age group are reported in Table 10-3.

Table 10-3. Specific cause of death by broad age category.

Cause of death (based on ICD-10 block)	18-49 n = 655 HIV+ = 82%			50-64 n = 258 HIV+ = 47%			65+ n = 254 HIV+ = 10%		
	Rank	n	%	Rank	n	%	Rank	n	%
Tuberculosis (A15-A19)*	1	191	29%	1	29	11%			
Influenza and pneumonia (J09-J18)	2	54	8%	3	25	10%	4	18	7%
Human immunodeficiency virus disease (B20-B24)									
Intestinal infectious diseases (A00-A09)	6	29	4%	7	11	4%			
Other viral diseases (B25-B34)									
Certain disorders involving the immune mechanism (D80-D89)									
Other forms of heart disease (I30-I52)	7	26	4%	1	29	11%	1	57	22%
Inflammatory diseases of the central nervous system (G00-G09)	5	32	5%						
Other acute lower respiratory infections (J20-J22)	3	51	8%	7	11	4%	4	18	7%
Aplastic and other anaemias (D60-D64)	4	34	5%						
Cerebrovascular diseases (I60-I69)	11	10	2%	9	10	4%	3	19	7%
Diabetes mellitus (E10-E14)				10	9	3%	8	11	4%
Hypertensive diseases (I10-I15)				5	15	6%	6	14	6%
Chronic lower respiratory diseases (J40-J47)				4	18	7%	2	22	9%
Ischaemic heart diseases (I20-I25)									
Malignant neoplasm of digestive organs (C15-C26)									
Renal failure (N17-N19)	7	26	4%	5	15	6%	7	12	5%
Protozoal diseases (B50-B64)	9	23	4%						
Metabolic disorders (E70-E90)	10	17	3%				10	6	2%
Abnormal findings on examination of blood, without diagnosis (R70-R79)							9	8	3%
Other natural causes		162	25%		86	33%		69	27%
All natural causes		***655***	***100%***		***258***	***100%***		***254***	***100%***

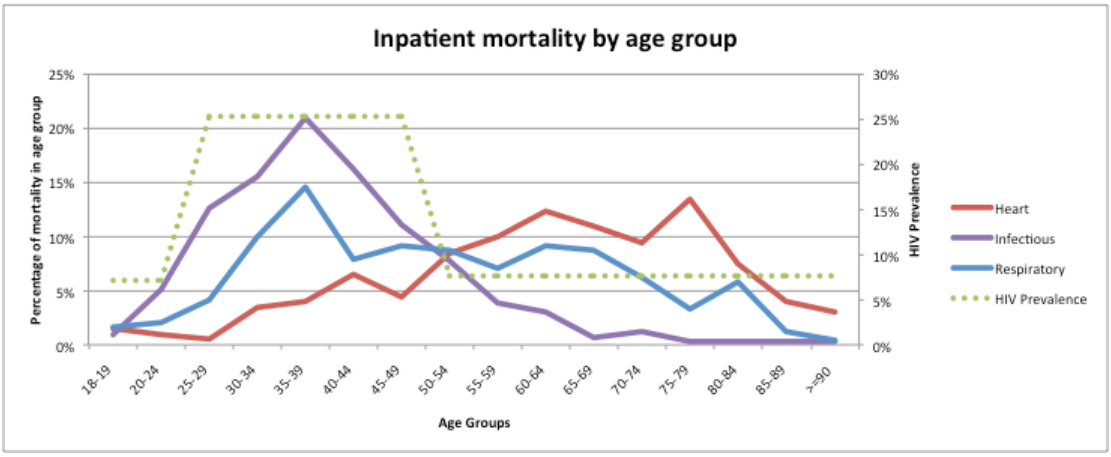

Figure 10-3. Heart disease compared to infectious disease by group.

In Figure 10-3, distribution of mortality by major cause is illustrated across age groups, revealing a distinct pattern of mortality by age and cause, which

would be expected in a population with a high HIV prevalence. Infectious diseases follow the same mortality profile as that of the HIV positive group shown in Figure 1, with the peak in the mortality in the younger age groups. Bradshaw et al dub this type of characteristic age specific mortality profile the 'AIDS signature' [201]. Diseases of the circulatory system, which are not directly related to HIV, show steadily increasing mortality with increasing age. Respiratory disease appears more evenly spread among HIV positives, HIV negatives, and those with unknown HIV status (Figure 3).

10.4.3 Bed days and cost of admissions

On average, patients in the sample were admitted for 9.9 days prior to death. HIV positive patients were admitted for slightly longer (mean 10.5 days, 95% confidence interval: 9.8-11.3 days) than HIV negative (9.6, 95% CI: 8.1-11.1) and HIV status unknown (8.9, 95% CI: 8.1-9.6) patients. However, because HIV positive inpatient deaths were more common HIV positive inpatient deaths accounted for the majority (62%) of the bed days (costs) associated with inpatient deaths (Total HIV-positive bed days / Total bed days), compared to HIV negative and HIV status unknown inpatient deaths (12% and 26% respectively).

"Infections and parasites," which accounted for the majority of deaths, had a mean length of stay in HIV positive patients that was almost double (11.2, 95% CI: 9.97 -12.33) that of the negatives (5.9, 95% CI: 2.28 - 9.50) and unknowns (6.9, 95% CI: 4.51-9.29). Overall the disease categories "infections and parasites" (31%), "respiratory" (16%) and "cardiovascular" (13%) accounted for more than half (60%) of all the bed days associated with inpatient deaths.

Applying a bed day equivalent cost of USD 200 (ZAR 2,164), the mean cost per admission was USD 1,976 (95% CI: USD 1,877 – USD 2,096).

10.5 Discussion

In 2010 South Africa's national ART program was 5 years old, and more than 1.2 million people were estimated to be on ART. This equated to ART coverage of over 60% at the prevailing eligibility threshold of a CD4 count <200 cells/ul [206]. Despite relatively high levels of access to care, however, the results of this study suggest that HIV-positive inpatient medical mortality remained high in 2010, accounting for at least 58% of all deaths during the 8-month study period.

The role of HIV in inpatient mortality in 2010 can be compared to results of a similar study at the same study site covering the years just preceding the national rollout of ART in South Africa (2000-2003) [207]. That study examined all 2,138 inpatient deaths occurring over three months of each year over a four-year period. A large majority (94%) were natural-cause deaths, and most (75%) were from the medical wards, making them comparable to the sample in our study. The numbers of deaths per month and the gender and age distribution were similar between the two studies. The proportion of patients known to be HIV positive more than doubled from 20% in 2000-2003 to 58% in 2010. This is likely due in part to poor ascertainment of HIV status prior to 2004, but the large increase in HIV positives could also suggest a real increase in the proportion of HIV positive deaths over this time period.

Statistics South Africa (StatsSA) reported that there were 28,660 natural deaths in the City of Johannesburg Metropolitan Municipality in 2010 [203]. Our sample of 1,167 thus covers 4% (1,167/28,660) of the natural deaths in Johannesburg that year [203] (Appendix Table A.3). The StatsSA report also notes that in Gauteng Province, where Johannesburg is located, HIV disease [ICD10 B20-B24] was the 7th leading cause of natural death, accounting for 3.4% of all natural deaths. This is equivalent to only 15% of the 21,548 deaths classified as "Infections and parasites (A00 – B99)" [200]. Our study, in contrast, found that 88% of all deaths classified as "Infections and parasites (A00 – B99)" were among HIV positive patients. If we very conservatively

assume that only those HIV positive deaths classified as “Infections & parasites” can be directly attributed to HIV (that is, we assume that 56% of deaths among HIV positive patients are not caused by HIV), then 25% of all natural deaths in our study would be directly attributable to HIV, a seven-fold increase over the StatsSA estimate for the province. While deaths due to HIV may be over-represented in hospital admissions compared to the population at large the largest contributor to this difference is likely the under reporting of HIV as a cause of death, even when the HIV status of patients is known.

StatsSA reported that in 2010 44% of all deaths occurred in hospitals, which translates into approximately 91,381 AIDS deaths in hospitals [201, 203]. The mean hospital cost associated with an inpatient related death was USD 1,976 in our cohort, therefore these deaths equate to a cost of approximately USD 180 million. While it is impossible to remove inpatient AIDS deaths completely it is reasonable to assume that this can be reduced substantially with earlier ART initiation and better treatment adherence. If the cost of ART for a year costs USD 358 [198] then for every inpatient AIDS death averted a patient could receive just over 5.5 years of treatment.

Limitations

Our study had several limitations. As noted above, the mortality reported here accounts for only 4% of natural cause mortality in the City of Johannesburg Metropolitan Municipality in 2010. When compared with national mortality statistics, however, the distribution by major causes of death is similar, which suggests that the findings have relevance beyond a single site. Of more concerns is that only 70% of the sample had a verified HIV status, and older patients were more likely to be of unknown HIV status. The mortality attributed to HIV here should thus be regarded as a lower boundary on true HIV-related mortality, as it is likely that at least a few patients of unknown status were in fact HIV-positive. Finally, while every attempt was made to match methods for assigning cause of death to those used by Statistics South Africa and we believe that the chance of misclassification is low, it is possible that patients may have been assigned the wrong cause of death.

10.6 Conclusions

In conclusion, we found that even with widespread access to ART, the majority of inpatient natural deaths at a large public sector hospital in 2010 were among HIV positive patients and were likely related to HIV. Our results provide support to the contention that HIV related mortality is dramatically under-reported [201, 202] in national statistics. A solution to this problem may be the introduction of an electronic mortuary register would allow for rapid, real time identification of any trends observed in the mortality of patients, both HIV positive and negative. In view of the importance of accurate data on causes of death, both for HIV interventions and to track other diseases, research on this or other solutions is needed.

10.7 References

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SECTION 4 – GENERAL DISCUSSION

Section 4 Aims

- Collate and discuss the significant findings from each of the research chapters
- Identify and discuss broader research themes based on full body of research
- Discuss implications of the research
- Discuss limitations of the research and possible future directions
- Draw conclusions based on full body of research

This section is divided into two chapters and brings together the findings from the four research chapters (Chapters 7 - 10) in an attempt to gain a broader understanding of the results and to identify major themes running through the chapters. Chapter 11 provides a brief discussion of the major findings from each of the chapters and how these findings meet the original aim and objectives of the thesis. It then identifies and discusses some broader research themes identified across the research chapters. Based on this, Chapter 12 highlights the methodological and practical implications of the research, in particular with regards to public health policy. It then identifies and describes the limitations of this body of research and future research opportunities based on these findings. Finally, the unique contribution of this thesis to the body of knowledge is noted.

CHAPTER 11 – Discussion

11.1 Introduction

The overall aim of this thesis was to examine how the costs and outcomes of the current HIV treatment delivery model in South Africa have changed in the context of a large scale, national treatment program. In particular the research focused on the two major components of the HIV treatment program: inpatient and outpatient treatment. This chapter collates the research findings to show how the thesis met the objectives and how this contributed to the overall aim. In addition it identifies and explores common themes across the four research chapters (Chapters 7 – 10).

Detailed discussion sections, specific to each objective, can be found in the respective research chapter (Chapters 7 – 10).

11.2 Overview and summary of significant findings

11.2.1 Objective 1

Evaluate the treatment outcomes and cost-effectiveness of shifting the management of stable ART patients to nurses at a primary health care facility in South Africa.

Prior to the publication of the research presented in Chapter 7 there was very little evidence in South Africa relating to the use of partial task shifting and partial decentralization for the outpatient treatment of HIV. The evidence that was available is tabulated in Appendix I (Supplementary Table 9), which shows that there were four papers examining the partial task shifting and partial decentralization of HIV outpatient treatment prior to this research [118, 129, 130, 208]. Of these four papers none of them reported costs and only one had a comparator (this was a randomized clinical trial)[129]. There was no study that conducted a full economic evaluation of such an approach in

South Africa, which is required in order answer questions of efficiency (costs and outcomes). The research presented in Chapter 7 was unique as it provided a full economic evaluation and evidence to support policy around task shifting in South Africa. We found that it was possible to shift the management of stable patients on antiretrovirals to nurses, while reducing costs without compromising treatment outcomes. This suggested that it was possible to increase treatment capacity through the use of nurses at primary health clinics for maintenance of stable patients. This conclusion was however dependent on the availability of spare capacity at primary health clinics, which was not answered by this research. The success of partial task shifting and partial decentralization meant that exploring full task shifting and decentralization in South Africa might also yield gains in terms of costs and outcomes. The cost effectiveness results of this study added to the body of evidence, which supported the introduction of nurse managed antiretroviral treatment in South Africa [54]. The cost estimates were adapted and used in various iterations of the National ART Cost Model to provide national budget estimates for the South Africa national antiretroviral program [198].

11.2.2 Objective 2

Evaluate the cost and cost effectiveness of nurse initiated and managed antiretroviral therapy (NIMART) at a primary health care facility in South Africa.

Objective 2 was originally designed to investigate the cost effectiveness of full task shifting and decentralization to nurses at primary health clinics for the initiation and management of antiretroviral treatment compared to the original outpatient treatment model of doctor initiated and managed care at HIV specialist clinics. Increasing pressure on government to expand antiretroviral treatment in South Africa led to rapid policy changes resulting in nurse initiation and management of antiretroviral treatment (NIMART) becoming the standard of care in South Africa across all facilities [5, 54]. This occurred despite the fact that there was no local, full economic evaluation to support its

cost effectiveness. This policy change reduced the relevance of the original objective and also made it impossible to conduct such an evaluation in a routine setting given that there was no longer doctor initiated and managed treatment to act as a comparison.

The objective was therefore adapted to examine the costs and outcomes associated with routine NIMART in two public facilities: a primary health clinic and a specialist HIV clinic. The primary health clinic was nurse led while the specialist HIV clinic, although having implemented NIMART, still utilized full time doctors to facilitate and manage care alongside the nurses. The evidence that was available is tabulated in Appendix I (Supplementary Table 9), which shows that there are only 3 papers dealing with the full task shifting and decentralization of HIV outpatient treatment in South Africa prior to this research [55, 134, 163]. The first paper was a demonstration project run by a non-governmental organization and while it showed effectiveness, it did not report costs [55]. The remaining two papers report the effectiveness [134] and costs [163] of a trial conducted in the Free State province. The study design was a pragmatic trial in a routine setting, which resulted in the reported difference between the intervention and control arm being unclear.

There is no evaluation in South Africa that has estimated the costs and outcomes of routine implementation of NIMART, nor has this been done by facility type. So while the research presented in Chapter 8 is no longer a cost effectiveness analysis, it adds new relevant information for the budgeting and effectiveness of NIMART in South Africa. It also explores the possibility that patients could be triaged by need to different facility types. The results show that NIMART at primary health clinics is producing equally good outcomes when compared to NIMART at hospital-based specialist HIV clinics at much lower cost. This suggests that making primary health clinics the focus for achieving treatment coverage targets and using specialist clinics for the management of complicated patients may be a preferred strategy. This recommendation is supported by a study showing that the roll out of NIMART in the City of Johannesburg resulted in an increase in ART initiations at primary health clinics and a reduction at hospital-based HIV clinics, allowing

the hospital clinics additional capacity to focus on complicated cases [162]. The cost estimates of NIMART by facility in this thesis allow for more accurate budgeting of the national treatment program and highlight the shift in cost drivers from antiretroviral drugs to staffing as the program has increased in scale.

11.2.3 Objective 3

Determine the disease and cost burden of HIV on an inpatient facility in South Africa.

In order to determine the disease and cost burden of HIV on an inpatient facility it is necessary to have a cohort that includes HIV positive and HIV negative patients, the reasons for admission and the associated resource usage (cost). Supplementary Table 8 (Appendix I) outlines the available literature regarding HIV related inpatient burden in South Africa. Of the 38 studies identified only five focused on adult, medical ward admissions, including both HIV positive and HIV negative patients [73, 78, 82-84]. Only one study published in 2007 (based on a cohort from 2005) compared HIV negative patients versus HIV positive patients [82]. This study was also the only one of the five to include the associated resource usage and costs [82]. As this cohort covered a period less than one year after the roll out of public antiretroviral treatment in South Africa [82], it did not reflect the impact of antiretroviral treatment. There have been no studies that examine the burden of HIV (including cost) on an inpatient facility by HIV status and reason for admission during a period that would be representative of large-scale antiretroviral treatment access.

The research presented in Chapter 9 is the only study to present data like this for South Africa. The results show that the burden of HIV on the study inpatient facility had not reduced since the introduction of large-scale antiretroviral treatment. Further it showed that more than half of all admission days were related to a HIV positive admission and most of these patients

were not on antiretrovirals. Tuberculosis was the leading cause of admission amongst HIV positive admissions. This suggests that while the outpatient treatment program has grown significantly along with access, the effects of this have not been seen by the inpatient facilities. A recent publication that studied a more contemporary HIV inpatient cohort (2012-2013) reported that the majority of medical inpatient admissions were HIV positive and that the leading cause of admission amongst HIV positive admissions (the publication did not report on HIV negative admissions) remained tuberculosis [70]. This supports the results of the research presented in this thesis and suggests that the inpatient burden of HIV remains. This works highlights that while HIV treatment in South Africa is focused around chronic outpatient treatment, it is essential to include acute HIV related inpatient treatment in order to understand the full impact of the antiretroviral treatment program on the epidemic and the public health system.

11.2.4 Objective 4

Estimate the changes in the mortality profile of an inpatient facility in South Africa since the large-scale roll out of Highly Active Antiretroviral Therapy (HAART).

Current national statistics show very low HIV related mortality, yet the reasons for mortality by age show strong correlations with HIV prevalence by age [200], suggesting that HIV related mortality may be under reported. A number of reports in South Africa have disputed the reported HIV mortality estimates suggesting true HIV mortality may be more than ten fold what is currently being reported [10, 201, 202]. Inpatient mortality covers almost half (44%) of all deaths, but is still only a subset of national mortality [200]. That said, inpatient mortality is better captured and has more complete records of HIV status and reason for death when compared to deaths that occur outside of hospitals. These data therefore provide a unique opportunity to estimate HIV related mortality based on confirmed HIV status for a significant proportion of all deaths in South Africa.

The results presented in Chapter 10 show that 5 years after the rollout of antiretroviral treatment in South Africa, the majority (58%) of inpatient deaths were amongst HIV positive admissions. This supports the argument that HIV related mortality in South Africa is significantly under reported. A similar study 10 years prior had reported less than a quarter of inpatient mortality (20%) being HIV related [207], which in part may be due to poor ascertainment of HIV status but also suggests a real increase in HIV related inpatient mortality. HIV related mortality is a critical indicator of the success of the national HIV treatment program as it is the only indicator that captures patients who may never have been part of the antiretroviral treatment program (i.e. treatment naïve). If antiretroviral status is known it also is way of verifying the HIV related deaths reported for the antiretroviral treatment program. The use of this routine data should become a key part of monitoring national HIV treatment programs and verifying national statistics in the future.

11.2.5 Aim

Examine how the costs and outcomes of the current HIV treatment model in South Africa have changed in the context of a large scale, national treatment program.

These results show the complex relationship between the scale of the antiretroviral treatment program and the costs and outcomes of the associated HIV treatment model. The rapid increase in the scale of the antiretroviral treatment program in the context of limited resources necessitated a change in outpatient treatment delivery models. The change in the outpatient treatment delivery model can be described as treatment task shifting from doctors to nurses and decentralization from hospital-based HIV clinics to primary health clinics. Chapter 7 compared partial task shifting and decentralization and Chapter 8 investigated full task shifting and decentralization. These studies showed the changed costs and outcomes of the outpatient treatment delivery model as the treatment function was

progressively shifted to lower professional cadres and less specialized facilities. The results indicated that task shifting and decentralization in South Africa has until now allowed the expansion of the treatment program at a lower cost per patient treated, while maintaining treatment outcomes. As the treatment program continues to expand and evolve (i.e. primary care service integration, test and treat) it is unclear whether these gains can be maintained given the limited human resources and facilities.

With the rapid increase in the number of patients on antiretroviral treatment in South Africa it was hoped that the burden of HIV inpatient treatment would be reduced, the reason for admission would shift to reflect fewer opportunistic infections and more complications related to antiretroviral treatment and that HIV related inpatient mortality would reduce. Chapter 9 showed that the inpatient burden and reasons for admission related to HIV positive admissions remained largely unchanged by an increase in antiretroviral treatment access and size of the treatment program. Chapter 10 showed that despite national statistics, which reported greatly reduced HIV mortality estimates, HIV positive inpatient mortality remains high (58% confirmed HIV positive). These results suggest that the relationship between HIV inpatient burden and treatment scale and access were not as expected. It may be that the impact of scale and access to antiretroviral treatment on inpatient facilities are not immediate and that in coming years the benefit will be seen at inpatient facilities. It could also be that inpatient facilities cater mostly for those that do not readily engage in outpatient treatment and that access to treatment will not influence their health seeking behavior. If this is the case then there is unlikely to be a significant reduction in the HIV burden on inpatient facilities until there is an effective program that targets these patients.

11.3 Common themes across research chapters

Each of the research chapters addressed a particular objective in order to achieve the overall aim of the thesis. The findings of these chapters were discussed in the previous section and in detail in each of the research chapters. In answering these objectives a number of common themes were consistently noted across each of the research chapters. These themes are identified and described in this section.

11.3.1 Defining a treatment model

In reviewing the literature for the research chapters it became evident that the complete, public HIV treatment model (i.e. all public services related to the treatment of HIV and its associated conditions) is poorly defined in South Africa. Prior to the availability of public antiretroviral treatment, HIV care guidelines did note that the treatment of HIV related conditions should start in the primary health clinics and then depending on severity and response to treatment be referred to higher levels of the public health system [46]. For most HIV positive patients the absence of antiretroviral treatment meant the eventual movement from the primary health clinics to the hospitals, if they were seeking care. With the arrival of public sector antiretroviral treatment the South African guidelines focused on the outpatient treatment of HIV patients with antiretroviral treatment [4]. There was little mention of HIV related inpatient treatment in the national treatment guidelines and no standardized treatment or management protocols for HIV positive patients admitted to the ward as inpatients. The fact that there are no guidelines for the inpatient management of HIV related conditions means that there are no routine statistics on inpatient care by HIV status. As a result it is impossible to monitor the impact of HIV on inpatient facilities without specific research studies. However many such studies [74, 82, 86], including this thesis, make use of routinely collected data to determine the impact, so with some reorganization of existing data it is possible to monitor this.

Even for those HIV outpatient treatment facilities that attempted to record inpatient treatment, there was inconsistent and poor recordkeeping of HIV related inpatient events. There are a number of likely reasons for this poor recordkeeping. The main reason is that the outpatient facility may not be the facility that referred the patient to the hospital. If this were the case then the outpatient facility would have to rely on the inpatient facility or the patient to inform them of the inpatient event. Similarly the inpatient facility would have to rely on the patient and / or the referring outpatient facility to provide information relating to the patient's HIV and treatment status. In both instances the majority of the information available is supplied by the patient and as a result is often sparse and can be inconsistent or inaccurate. Patient provided information may be poor because of stigma related to HIV status, poor patient medical literacy and the fact that providers do not have a way of systematically capturing this (i.e. important clinical information may be recorded in the notes of a patient file). With the exception of referral letters, there are no systems in place that allow the outpatient and inpatient facilities to share information related to the treatment of the same patient. The computerization of basic inpatient admissions using a unique identifier that allows the tracing of a patient within the public health system – even if only to know that a patient was admitted and where – would provide sufficient data to allow both outpatient and inpatient facilities to better use their routinely collected data. The strength of this data is shown in large private sector databases, which clearly show the whole HIV treatment model (i.e. inpatient and outpatient care and treatment) and are able to identify high-risk areas along the HIV care and treatment cascade [109].

Incomplete holistic HIV treatment and patient outcome information (i.e. both inpatient and outpatient HIV related care and treatment) has implications not only for the patient but also the health system. If treatment providers do not have access to the most recent and accurate information related to a patient's treatment it makes appropriate patient management challenging. This applies to treatment providers at outpatient and inpatient facilities and can result in poor patient outcomes. In addition to affecting patient outcomes, the lack of a consolidated HIV treatment model (i.e. a model that incorporates both

inpatient and outpatient HIV related care and treatment) may also have an impact on the health system. The lack of information sharing between the levels of the health system does not encourage the appropriate utilization of scarce treatment resources. For example, diagnostic and monitoring laboratory test results are not easily shared between facilities (i.e. outpatient and inpatient), which can result in duplicate tests being performed that have little or no clinical meaning. Finally, HIV health system research in South Africa focuses predominantly on outpatient treatment and very rarely includes an inpatient component. This reflects the fact that the South African HIV treatment model as defined by the treatment guidelines does not include inpatient treatment and as a result does not track or record the full HIV treatment history (i.e. outpatient and inpatient) making research which incorporates both outpatient and inpatient care complicated. This gap in the HIV research agenda in South Africa masks the true impact of the national program by largely ignoring the impact of HIV on the secondary and tertiary public health system.

11.3.2 Measuring impact – a full economic evaluation

Economic evaluation is critical for allocating scarce resources. Like many other developing countries, the public health sector in South Africa suffers from scarce resources (i.e. staffing, equipment, facilities) [161, 209-211] and as a result economic evaluation should be a key tool for decision-making regarding the allocation of resources across health interventions. According to Drummond a full economic evaluation is the "comparative analysis of alternative courses of action in terms of both their costs and consequences [1]." Studies that do not include both costs and consequences (i.e. benefits, effects) as well as compare viable alternatives are not considered full economic evaluations.

The literature review and research chapters have shown that while South Africa has a relative wealth of local HIV research compared to other sub Saharan African countries; there is very little research that can be considered

true full economic evaluations using primary data. Appendix I (Supplementary Table 8) tabulates the relevant inpatient literature and showed that of 38 publications reporting on the costs or consequences of HIV related inpatient treatment in South Africa only two could be considered an economic evaluation [67, 102]. Eleven publications reported costs but only seven had both costs and outcomes [67, 69, 82, 92, 102, 113, 114] and then of those seven only two [67, 102] had valid alternatives for comparison. Appendix I (Supplementary Table 9) tabulates the relevant outpatient literature for South Africa and shows that the task shifting outpatient research has even fewer economic evaluations. If the research generated in this thesis is excluded, then there were only 17 outpatient publications identified of which only one included costs [163]. This publication also included a valid alternative for comparison and was therefore the only outpatient publication that could be classified as a full economic evaluation [163]. In summary, this implies that although the South African public health sector has a lack of resources and would benefit from full economic evaluations which address the allocation of scarce resources, very little of the current research is sufficient to support evidence based resource allocation and policy change around HIV treatment delivery.

Routine medical data are not typically recorded or presented in a format that readily allows economic evaluation, but as shown with the research papers in this thesis it is possible [131, 212]. The data most readily available are typically the outcome or effectiveness measure, especially when using a standard treatment outcome. For example, in the case of HIV treatment this is often the viral load, which is part of the national treatment guidelines and should be available for all patients on treatment [6]. The resource usage required for the estimation of costs is more complicated in that this is not explicitly recorded in the medical records, but can typically be extracted and aggregated by reviewing medical records (i.e. which laboratory tests were conducted during the study period, which drugs were dispensed during the study period). The research chapters in this thesis show that this approach is not only possible, but may be preferable to controlled trials, which often do not translate to routine settings. If medical data were stored in an electronic

format it would be possible to do this rapidly and on a much larger scale. South Africa has a wealth of data useful to guiding policy, but the lack of a consolidated data system across all public health facilities means that this data are only really accessible when part of labor intensive research projects.

While the effectiveness and cost of health interventions may be obtained relatively easily from routine medical data, finding a viable comparator can prove more difficult. Often policy changes are not implemented individually (i.e. multiple policy changes are made simultaneously) or in a step-wise fashion (i.e. staggered implementation often across multiple sites), which makes identifying the associated effect of a single change challenging. If researchers are involved in the implementation strategy of public policy it is often possible to structure the rollout in such a way that allows the effects of the intervention to be measured. This approach provides evidence in a routine setting without the use of clinical trials, which are expensive, time consuming and may not be good predictors of routine practice. This argues for close collaboration between policy makers (i.e. National Department of Health) and researchers to ensure that new interventions can be critically evaluated to ensure that as a country we make the most of our limited resources.

11.3.3 Task shifting – the next level

The provision of HIV care and treatment requires a number of different services, yet to date most of the interventions and subsequent research has focused specifically on shifting the provision of clinical service from one cadre to another (i.e. from doctors to nurses) and from a specialized, single service HIV clinic to a multi service primary health clinic. Although it is rarely acknowledged or evaluated, there is some degree of task shifting in many of the services associated with HIV care and treatment. For example, HIV counseling and testing was originally the mandate of a clinician with assistance from a trained counselor or social worker. The clinician was required to draw blood and administer the test and the counselor or social

worker was used to provide education, pre-test and post-test counseling. After the amendment of the National Health Act, this service (i.e. blood draw, education and counseling) is now routinely offered by a lay counselor (non-medical personnel) in routine public practice in South Africa [147, 148]. Similarly the dispensing of antiretroviral medication was initially the mandate of a trained pharmacist, but over time this service has been shifted to different cadres. Depending on the site, dispensing of antiretroviral medication can be performed by the treating clinician (i.e. doctor or nurse) or a pharmacy assistant [213]. Pharmacy assistants have no official medical training but have received some basic in-service training to manage the dispensing of medication under supervision. Each of these services (i.e. HIV testing, clinical management, dispensing of antiretroviral treatment) is integral to the success of the HIV care and treatment program yet the focus has been on task shifting for clinical management with little local evidence to support task shifting of other services. The literature rarely speaks to task shifting for services other than clinical management and even when focused on clinical management there is often insufficient detail to assess whether other services are also being task shifted simultaneously. As such the results we see in studies reporting on the task shifting of clinical management may actually be the result of multiple services being simultaneously task shifted. Future research should be held to higher reporting standards that clearly outline all the services included and who provides them. This will allow policy makers to better understand the results and replicate them.

Task shifting of clinical management services for HIV treatment in South Africa has generally only shifted services between cadres of health care workers within traditional health care facilities. In the taxonomy of care models outlined by Duncombe this is the movement from centralized (i.e. HIV clinic) to decentralized (i.e. primary health clinic) [34]. This type of task shifting still makes use of the same limited pool of health care workers and facilities, but shifts the distribution of responsibilities. This is only a viable option for scale up if the lower cadres have unused capacity and / or they are much easier to bring into the workforce (i.e. to train). In South Africa there may have been some truth in this, but the sheer scale of the need means that

task shifting within the traditional health care sector will not be a long term solution for scaling up the national antiretroviral treatment program. The next step would be to task shift beyond the health system – that is to non-medical personnel and to non-health facilities (i.e. Community and home based care) [34]. To some degree this has happened for the non-clinical services (i.e. testing from nurses to lay counselors and dispensing from pharmacists to assistant pharmacists) yet to date the clinical services in South Africa have remained the mandate of health care workers in health care facilities. The South African government has already recognized the limitation of the health system and started the process of putting policies in place to encourage task shifting outside of traditional health care workers and health care facilities [214]. Although government has not labeled the proposed policies task shifting it calls for the management of chronic stable patients outside the traditional health system by non-health care workers. According to the task shifting classification put forward by Kredo and colleagues, this would be partial task shifting and partial decentralization [125, 126]. There is limited economic evaluation that supports these proposed shifts and the decisions appear to be driven by the need to expand access to treatment with limited resources. Evaluating the various proposed policies in order to understand the trade-off between scale and effect will be critical in ensuring the future success of the South African antiretroviral treatment program.

11.4 Summary

The research papers presented here met the objectives and aim of the overall thesis. The first two objectives informed the task shifting strategy that is being used to scale up the outpatient antiretroviral treatment program in South Africa. The second two objectives examined the impact of the increasing scale of the antiretroviral treatment program in South Africa on the HIV burden of an inpatient facility. When combined these objectives showed how the increasing scale of the antiretroviral treatment program brought about a shift in the treatment delivery model and the impact that this had on the costs and outcomes of the HIV treatment model (i.e. outpatient and inpatient) as a

whole. Finally, the thesis highlighted issues around the definition of the HIV treatment model in South Africa, the measurement of impact and the future of task shifting in the treatment of HIV.

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CHAPTER 12 – Conclusions

12.1 Introduction

This chapter takes the findings presented in Chapter 11 and identifies the implications and significance of the research, in particular with regards to policy. The limitations of the research are reviewed and discussed. Based on this and the research findings, future research directions and priorities are outlined. Finally, the unique contribution of this body of work and how it adds to the available literature is summarized.

12.2 Implications of research

The research papers presented in this thesis have a number of broader methodological and practical implications and these are discussed separately below.

12.2.1 Methodological implications

Use of routine data in HIV economic evaluation

Economic evaluation requires data on the effectiveness, resource usage and costs of treatment delivery. Each of the research chapters made use of routinely collected data as the primary data source. While the limitations of these data were noted previously, these limitations stem largely from incomplete adherence to standard record keeping practices rather than inherent gaps in the routine data systems. Economic evaluation outside of a clinical trial setting is often modeled based on expected resource usage and costs rather than using routine patient level data to perform micro costing. This body of work shows that it is possible to use routine public sector health data to perform economic evaluations without the need for modeled estimates. This approach provides more realistic resource

usage and cost estimates that are linked directly to the effectiveness measures and as a result provide more reliable cost effectiveness estimates. Routine data should be used to confirm or challenge the economic evaluations that often precede policy change which tend to be based on clinical trial data and / or modeled estimates. This cyclical process ensures that policy decisions are likely to meet the planned cost and effectiveness targets when under routine, local conditions.

Effectiveness measures in the absence of perfect timing and data

The most objective measure of HIV treatment effectiveness is viral load suppression and South Africa uses this as its primary indicator in its national treatment program [4-6]. Treatment guidelines mandate this test at regular intervals, but routine data show that this is not always followed. Viral load testing at irregular intervals can be the result of many factors, including clinician deviation from the monitoring schedule, patient deviation from the visit schedule and missing data in the patient file. This lack of consistency in the routine data often results in researchers preferring not to use routine data or excluding significant numbers of patients because of missing or incomplete data. In the outpatient papers we developed a patient outcomes algorithm which made use of all the possible information to categorize the patients as either 'in care and responding', 'in care and not responding' or 'no longer in care'. By using this algorithm missing or incomplete data no longer resulted in patients being excluded from the analytic dataset. Using this approach allows routine datasets to be used for the economic evaluation of HIV related treatment interventions without relying on regular effectiveness measures not always available in routine settings.

PDE cost is a good indicator of true HIV related medical admission costs

In the absence of costing individual patient resource usage per admission, hospital costs are often based on the length of stay and a patient day equivalent (PDE) cost. The most basic calculation of the PDE cost takes the total cost of the inpatient facility over a certain period and divides it by the number of patient days (i.e. number of days each inpatient bed was occupied) during the same period. This approach is reasonable if the admission being costed does not use resources significantly in excess or below the average admission. In this thesis, the inpatient

cost of HIV related medical admissions calculation was based on actual resource usage and compared to the patient day equivalent cost reported by the National Department of Health [192]. We found that the majority of HIV related medical inpatient admission costs are related to the cost of being in hospital (i.e. bed and staffing costs) and not to any relatively expensive treatment provided while admitted. This finding suggests that until the reasons for admission change, using the length of stay and the reported PDE cost to estimate the HIV related inpatient costs provides accurate estimates with limited data.

Using salaries to reflect the opportunity cost of human resources

In an economic evaluation the appropriate cost for a resource used is the opportunity cost, which is the value of the forgone benefits for not using the resource for its next best alternative use [1]. Typically market prices are used to reflect the opportunity cost, but in certain instances this may not fully capture the opportunity cost. In South Africa there is generally a shortage of health care workers, yet the scarcity of doctors is greater than that of nurses [178], and this scarcity may not be fully reflected in the salary differential between the two cadres. This discrepancy may occur because the salaries in the public sector are governed by national salary scales and cannot move as freely as those in the private sector. If the opportunity cost between these cadres is larger than estimated it strengthens the case for task shifting further. The use of salaries to reflect the opportunity costs of scarce health worker resources in South Africa should be investigated further.

12.2.2 Practical implications

Use of nurses for the management of stable antiretroviral patients

The economic evaluation presented as part of this thesis showed the cost effectiveness of nurse management compared to doctor management of stable patients on antiretroviral treatment. These results supported in part the change in the South African national treatment model from doctor initiated and managed antiretroviral treatment to nurse initiated and managed antiretroviral treatment (NIMART). The costs estimated in this work were used to provide national level

cost estimates for the roll out of NIMART to South Africa. NIMART is now the primary treatment delivery model used by the National Department of Health in South Africa.

Triage of NIMART patients to effectively use resources

The initiation and management of similar patients (i.e. matched on baseline characteristics) on antiretroviral treatment at primary health clinics under South Africa's NIMART policy are producing equally good outcomes as hospital-based HIV outpatient clinics at much lower cost. The higher cost is driven by the fact that hospital-based clinics are generally better resourced than primary health clinics in terms of staffing (i.e. higher doctor to patient ratios) and infrastructure (i.e. access to advanced diagnostics and drugs) with lower patient to staff volumes. The evolution of these clinics into well-resourced, centralized, expert referral facilities that focus on complicated patients, while investing program expansion resources into primary health clinics, may be the country's preferred strategy. Currently there are no guidelines for how to triage HIV patients between routine primary health clinic care and specialized HIV clinic care. In order to make the most effective use of limited resources developing guidance in this area may be a priority for policy makers.

Expanding treatment access may still reduce HIV related inpatient costs

Although the South African public sector antiretroviral treatment program is the largest in the world [26] and has experienced unprecedented growth since its inception in 2004, we found that inpatient facilities are still shouldering a significant HIV burden. The majority of the HIV related inpatient burden was related to patients who were not on antiretroviral treatment at the time of admission. Getting more patients onto effective antiretroviral treatment through a combination of expanded access to treatment, allowing earlier treatment initiation and improving retention and adherence once on treatment may still lead to a significant reduction in inpatient costs. The success of the national antiretroviral treatment program cannot be evaluated by examining the outpatient treatment component in isolation (i.e. number of patients on treatment), but also needs to include the shifting burden of HIV on inpatient facilities.

Recalibrating national HIV mortality estimates

Although HIV status is not reported routinely for inpatient related mortality, a review of the mortuary register and electronic laboratory records confirmed the HIV status for the majority of inpatient deaths. These data showed that even with widespread access to ART, the majority of inpatient natural deaths were among HIV positive patients and were likely related to HIV. This supports the contention that HIV related mortality is dramatically under-reported [201, 202] in national statistics. Given that these data already exist it would make sense to incorporate them into routine mortality reporting. The introduction of an electronic mortuary register would allow for rapid, real time identification of any trends observed in the mortality of patients, both HIV positive and negative. An accurate HIV related mortality estimate would be an important indicator for the success of the national antiretroviral treatment program.

12.3 Limitations

The research papers presented in this thesis had a number of limitations most of which are common to retrospective, observational cohort studies. The major limitations across the various papers are noted and their possible implications are discussed below. Limitations specific to each research paper can be found in the relevant research chapters (Chapters 7 – 10).

Sampling and size

The thesis was designed to be a case study of urban treatment in South Africa, which meant limited geographic generalizability. The sites chosen were all public treatment facilities following standard treatment guidelines at the time of the study and are thus likely to be typical of other public health facilities serving similar populations. For the outpatient studies the paired sites were purposely chosen to be close together to limit any differences in the populations accessing care. The possible differences in patient populations were also addressed by matching the cohorts on known and measured predictors of outcome. It is however still possible that the populations differed with respect to some unmeasured predictor. Manual data extraction was required for each study and more sites or larger samples

would have required additional funding and time. The sample sizes were set to be able to detect meaningful differences in outcomes and costs wherever possible. The inpatient studies were restricted to patients admitted to the medical wards at a single site, but the literature suggests that the medical wards typically experience the largest HIV burden. In addition to that the distribution of inpatient mortality by major cause closely matched the national statistics, which suggests that the findings have relevance beyond a single site. This is a limitation that affects many studies, but we chose to focus on populations that hold the most policy relevance for the national treatment program and ensured that the sample sizes were adequate to be able to draw accurate estimates.

Rapidly changing treatment landscape

The HIV treatment landscape in South Africa changes rapidly, both in terms of the guidelines but also the HIV treatment delivery model. This means that each of the research papers reflects the treatment guidelines and scale of the national treatment program at the time of that particular study. From the time of developing the thesis proposal to the time of completing the research papers both the treatment guidelines (i.e. drug regimens, eligibility criteria, monitoring tests) and the treatment delivery model (i.e. doctor initiated and managed treatment to nurse initiated and managed treatment) have changed significantly. Each research paper has been able to provide relevant contemporary evidence at the time of publication. This body of work suggests that the South African HIV treatment program is not yet close to full scale and provides insight into what changes policy makers may consider in the HIV treatment delivery model to reach full scale given the limited resources.

Tracing patients between facilities in the public sector

One of the biggest limitations inherent in using public sector data is the fact that there is no standardized unique patient identifier used either within a single facility nor across facilities. This means that it is often difficult to allocate services within a facility to the correct patient (i.e. laboratory tests) or to identify the same patient presenting at a referral facility (i.e. from a clinic to a hospital) or an alternative treatment facility (i.e. from a clinic to another clinic). It is likely that a number of the patients classified as lost to follow-up are actually receiving care at an alternative

clinic or have actually died. A unique patient identifier would allow more accurate patient resource allocation and treatment outcome determination. The National Department of Health has created a technical working group to examine the issues around creating and using a unique patient identifier in the public health sector. They have concluded that the national identity number should be used as the unique identifier for all public health records, but this has not been enforced to date. The use of the national identity number will improve the status quo, but studies have reported that many patients accessing HIV care in South Africa do not have a valid national identity number [215]. Most foreign nationals, with the exception of permanent residents, will not have a valid national identity number and as a result the proposed system will not be able assign them a unique identifier. While many facilities and non governmental organizations get around this by assigning site specific unique identifiers these are not effective in tracing patients outside of the original site. Biometric identification (i.e. fingerprint) is one possible unique identifier that would be consistent across sites without the need for a new system to create and manage unique identity numbers. The effective implementation of a unique patient identifier would dramatically increase the value of the large routine national health databases, which currently exist but are not used because it is difficult to track patients.

Accuracy and completeness of routine data

All of the research papers presented in this thesis relied on routine patient records as the primary source of patient level data. This means that the results are dependent on the accuracy and completeness of routinely collected patient records, which may vary by site or even within a site between treatment programs (i.e. HIV vs. diabetes). One of the strengths of this body of work is to highlight the wealth of information that is available from routinely collected data in the public sector, but it did require significant data cleaning in order to ensure the accuracy and completeness of data; wherever possible patient records were verified with alternative data sources (i.e. hospital death register, electronic laboratory records). Even with extensive data cleaning there were still a significant number of files that had to be excluded or were considered incomplete. Each of the papers presented alternative measures to try and show the possible impact of the missing or incomplete data. In most instances it meant that the estimates presented were

conservative (i.e. HIV mortality was underestimated) and this was noted in the relevant papers.

12.4 Future research directions

Impact of well-resourced facilities on complicated HIV patient outcomes
Given that within the current nurse initiated and managed antiretroviral treatment (NIMART) program the cost of treating patients by facility type (i.e. primary health clinic vs. hospital-based clinic) varies significantly it would be useful to understand whether certain patients might benefit from the additional resources found typically at the hospital-based sites. Using routine data it may be possible to compare the outcomes of complicated patients on antiretroviral treatment at primary health clinics compared to similar complicated patients at hospital-based HIV clinics. This might then identify a particular group of complicated antiretroviral patients who do better at the more well-resourced, hospital-based clinics. If there are benefits in terms of patient outcomes then these data could be used to develop a triage strategy for complicated patients to make the best use of the relatively expensive, well-resourced hospital-based clinics.

Task shifting – taking it beyond the traditional health sector and HIV
The increasing chronic patient burden in South Africa (i.e. HIV, TB, diabetes, hypertension, mental health) has led to the development of alternative strategies for the management of stable chronic patients, as outlined in the draft National Adherence Strategy [214]. For the first time in South Africa an integrated, multi-disease approach has been taken to task shifting for the management of stable chronic patients. This approach utilizes non-medical personnel to manage the patients outside of traditional health facilities. If this strategy reaches its target coverage targets it will be the largest single public health strategy in terms of the number of patients covered - surpassing even that of the HIV program. While there is some limited evidence to support the effectiveness of single disease task shifting interventions for the management of stable chronic patients (mostly within HIV treatment) there is no literature or evidence that speaks to a comprehensive, multi-disease approach. Building this evidence base will be critical for evaluating

the success of the strategy and if necessary adjusting it to improve its effectiveness.

Impact of task shifting with limited human resources

Task shifting is not the final solution for countries with limited human resources in health [121, 123]. If task shifting occurs within the health sector (i.e. from doctors to nurses) and incorporates cadres that were never previously allocated to that service (i.e. incorporation of primary health care nurses as the primary clinicians for HIV patients), but which were previously offering other non-HIV related health services then it is possible that task shifting may crowd out these non-HIV services. So far, nurses appear to have incorporated HIV care into their workloads smoothly, but there is no evidence to suggest how much additional capacity remains or that the addition of HIV care has not been to the detriment of other patients. Future research on task shifting should take into account both the impact of the program on non-HIV care and its benefits and costs to patients themselves. This will be critical to ensure that the resources allocated to the HIV program when compared to other non-HIV health services reflect the relative burden of disease related to HIV.

The link between antiretroviral treatment access and HIV inpatient burden

The clinical evidence shows that HIV positive patients who are on antiretroviral treatment have decreased inpatient admissions, yet six years after national treatment roll out this thesis showed no marked difference in the HIV related inpatient burden in a geographic area that had relatively high treatment coverage. It is possible that the impact of antiretroviral treatment access and uptake is delayed and that future research will start to show a decline in HIV related inpatient burden. It is also possible however that the continued high HIV burden on the inpatient facilities represents a specific segment of the HIV positive population that is slow to or not willing to initiate antiretroviral treatment even when it is readily, freely available. If the latter is true or even partially true then increasing treatment coverage or removing eligibility criteria are not going to address this burden. Research is required to understand why patients in areas of high antiretroviral treatment coverage are still not initiating treatment or initiating very late and then designing interventions to engage this population in treatment.

12.5 Conclusions

The findings presented in this thesis make an original and significant contribution to the body of evidence, which speaks to the impact of large-scale antiretroviral treatment on the associated costs, and outcomes of HIV treatment delivery in South Africa and more generally.

Research Paper 1 (Chapter 7) was the first South African economic evaluation to examine the partial task shifting of stable antiretroviral patients from doctors at a hospital based clinic to nurses at a primary health clinic in a routine setting. This paper provided evidence that supported the shift to nurse initiated and managed antiretroviral treatment (NIMART) as the standard treatment delivery model in South Africa. The unit costs produced in this paper were adapted and used in the National ART Cost Model (NACM) [198], which informed the HIV Conditional Grant budget for the National Department of Health.

Research Paper 2 (Chapter 8) produced the first routine costs and outcomes of the NIMART program in South Africa since its rollout in 2010. All previous estimates were based on modeled or trial data. These data will be used to parameterize future budget models for the National Department of Health. This was also the first paper to highlight the continued dichotomy of treatment facilities within the NIMART program. Although all public health facilities in South Africa use NIMART to deliver antiretroviral treatment the type of facility (i.e. hospital-based vs. primary health clinic) seems to dictate the level of resources used to supply this service and as a result the cost. This knowledge may allow policy makers to better allocate patients so as to effectively utilize scarce resources.

Research Papers 3 and 4 (Chapters 9 and 10) were the first papers to report specifically on the HIV related inpatient burden in South Africa since the large scale roll out of antiretroviral treatment in 2004 – the last paper reporting on this was published in 2007 using a 2005 cohort [82]. Paper 3 included HIV positive and negative admissions and reported the costs and outcomes by reason for admission. This provided a unique opportunity to not only understand the additional burden of increased admissions but also the length of admissions by

cause and HIV status. Paper 4 provided strong evidence to support the growing concerns that HIV related mortality is under reported in the South African national mortality statistics. Traditionally mortality at inpatient facilities in South Africa is not reported by HIV status and this study was the first to do so during the period of large-scale antiretroviral access. Papers 3 and 4 highlighted the importance of considering inpatient treatment as an integral part of the HIV treatment delivery model and how it can be used to provide additional indicators of treatment program success or failure.

Through the use of adapted economic evaluation techniques this thesis has furthered our understanding of the public health issues facing the South African HIV treatment program in the era of large-scale antiretroviral treatment access.

12.6 References

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APPENDIX A: Paper 1 – Published format

Long L, Brennan A, Fox MP, Ndibongo B, Jaffray I, Sanne I, Rosen S. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. **PLoS Med.** 2011;8(7):e1001055.

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Treatment Outcomes and Cost-Effectiveness of Shifting Management of Stable ART Patients to Nurses in South Africa: An Observational Cohort

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Abstract

Background: To address human resource and infrastructure shortages, resource-constrained countries are being encouraged to shift HIV care to lesser trained care providers and lower level health care facilities. This study evaluated the cost-effectiveness of down-referring stable antiretroviral therapy (ART) patients from a doctor-managed, hospital-based ART clinic to a nurse-managed primary health care facility in Johannesburg, South Africa.

Methods and Findings: Criteria for down-referral were stable ART (≥11 mo), undetectable viral load within the previous 10 mo, CD4>200 cells/mm^3, <5% weight loss over the last three visits, and no opportunistic infections. All patients down-referred from the treatment-initiation site to the down-referral site between 1 February 2008 and 1 January 2009 were compared to a matched sample of patients eligible for down-referral but not down-referred. Outcomes were assigned based on vital and health status 12 mo after down-referral eligibility and the average cost per outcome estimated from patient medical record data. The down-referral site ($n=712$) experienced less death and loss to follow up than the treatment-initiation site ($n=2,136$) (1.7% versus 6.2%, relative risk=0.27, 95% CI 0.15–0.49). The average cost per patient-year for those in care and responding at 12 mo was US$492 for down-referred patients and US$551 for patients remaining at the treatment-initiation site ($p<0.0001$), a savings of 11%. Down-referral was the cost-effective strategy for eligible patients.

Conclusions: Twelve-month outcomes of stable ART patients who are down-referred to a primary health clinic are as good as, or better than, the outcomes of similar patients who are maintained at a hospital-based ART clinic. The cost of treatment with down-referral is lower across all outcomes and would save 11% for patients who remain in care and respond to treatment. These results suggest that this strategy would increase treatment capacity and conserve resources without compromising patient outcomes.

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

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Competing Interests: The authors have declared no competing interests. IS is the director and IJ an employee of Right to Care, an organization that provides technical assistance to the study sites.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral drug; CI, confidence interval; PHC, primary health clinic; PHCN, primary health care nurses; TLC, Themba Lethu Clinic

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Introduction

The rapid expansion of large-scale provision of care and treatment for HIV/AIDS in sub-Saharan Africa has placed tremendous pressure on the region's human resources. As a result, the World Health Organization, other international agencies, and national governments are actively encouraging the shifting of clinical care responsibilities to lesser trained, less expensive, and generally less scarce cadres of the clinical workforce [1].

In South Africa, a major component of this "task shifting" strategy is to reduce the role of doctors in managing patients on antiretroviral therapy (ART), in favor of primary health care nurses (PHCNs). Unlike in many countries in the region, South Africa's national treatment program has been largely managed by doctors. Nurses have not been authorized to dispense antiretroviral drugs (ARVs), initiate patients on treatment, or conduct medical examinations in lieu of doctors. The number of accredited sites authorized to provide ART has thus been limited by the availability of doctors. Since most primary health care facilities are staffed entirely by nurses, most accredited ART sites have been located at hospitals rather than primary care clinics.

There is a small but expanding body of evidence from sub-Saharan Africa demonstrating that nurses managing ART patients at primary health care facilities can achieve very good outcomes. A recent systematic review of task-shifting in Africa identified seven cohort studies of nurse-initiated and/or nurse-managed adult treatment [2]. Those that reported outcomes generally showed nurses achieved comparable or superior results to doctor-led treatment in the same general setting, but only one undertook a direct comparison of doctor-managed versus nurse-managed treatment of similar patient populations [3]. Primary health care facilities achieved better outcomes than hospitals in a recent study from South Africa, but patients were treated by doctors at both levels [4]. A prospective controlled evaluation in Swaziland found equally good outcomes amongst stable HIV patients managed by nurses in a primary care facility compared to those receiving routine hospital care [5]. Malawi has shown similar success in decentralizing care and allowing non-physician clinicians to initiate ART [6]. In Kenya a clinical trial evaluated whether the ART management could be partially shifted from health care workers to persons living with HIV/AIDS who would monitor patients within the community [7]. This showed similar clinical outcomes but with fewer clinic visits. No studies have estimated the cost differences between the two approaches using primary data.

In 2010, the South African government revised its HIV treatment guidelines for the first time since the program launched in 2004. Among a host of changes to drug regimens, eligibility criteria, and monitoring protocols, the revised guidelines included the following two objectives: to "enable nurses to initiate ARVs for treatment and prevention" and to "enable primary health care facilities to initiate, manage, monitor, and refer patients." Justification for this change included a recently published randomized trial set in South Africa demonstrating that, under the carefully regulated conditions of a clinical trial, patients initiated on ART by doctors, but monitored by nurses, at primary health care clinics achieved similar treatment outcomes as those managed solely by doctors [8].

Prior to the 2010 guideline revision, a number of interventions to shift treatment delivery to lower level facilities and from doctors to nurses had already been piloted in routine care settings. Among these was a strategy of "down referring" stable, adult ART patients from a central hospital to nearby primary clinics the same strategy tested by the randomized clinical trial in South Africa, but in a routine care setting pioneered by the Gauteng Province Department of Health and Right to Care, a South African nongovernmental organization supported primarily by the United States President's Emergency Plan for AIDS Relief. To evaluate the implications of this down-referral strategy for treatment outcomes and costs, we conducted a cost-effectiveness analysis of the treatment program at the Themba Lethu Clinic in Johannesburg and a nearby primary health clinic serving as a down-referral site.

Methods

Ethics Statement

The University of the Witwatersrand and Boston University provided ethical approval of the study. In order to protect the anonymity of the patients, the study was conducted as an unlinked, retrospective analysis of a patient data set that did not contain any individual identifiers.

Down-Referral Procedures

Under the down-referral strategy evaluated in this study, all patients receive pre-ART care and initiate ART at an accredited, hospital-based HIV/AIDS clinic, which we will refer to as the treatment-initiation site. For patients who are eligible for and accept down-referral, management of their care is moved to a down-referral site, which is a primary health clinic (PHC). PHCs typically provide reproductive, maternal, and child health care, TB treatment, HIV testing, and other basic services but are not typically accredited to provide ART.

To be eligible for down-referral, patients must have been on ART for at least 11 mo; they must have no opportunistic infections, a CD4 cell count >200 cells/mm^3, and a stable weight as reflected by <5% weight loss between the last three visits; and their latest HIV viral load within the last 10 mo must be undetectable (<400 copies/ml). The treatment-initiation site involved in this study performs the first routine viral load test after 4 mo on treatment, and the second at 10 mo, establishing the time intervals used in the down-referral criteria. Treatment-initiation site patients who meet these criteria are invited (but not required) to transfer to a down-referral site. For those who accept down-referral, the treatment-initiation site doctor then writes a prescription for 6 mo of ARVs. Down-referred patients are dispensed a 2-mo supply of ARVs at the treatment-initiation site and make an appointment at the down-referral site for 2 mo later. All subsequent ARV pickups occur at the down-referral site. At both the treatment-initiation and down-referral sites, stable patients are scheduled for medication pickups every 2 mo. Treatment follows South African national guidelines, which during the study period called for a first-line regimen of stavudine, lamivudine, and nevirapine or efavirenz and routine CD4 counts and viral load tests every 6 mo.

The main difference between the routine monitoring conducted at the down-referral site and the treatment-initiation site is the cadre of clinical staff involved. While the treatment-initiation site relies on medical consultations with doctors, patients at the down-referral site see only PHCNs, professional nurses with a qualification in primary health care. Down-referred patients have a nurse consultation at every routine visit (every 2 mo), while patients at the treatment-initiation site have a doctor consultation only every 6 mo. At each visit, the PHCN asks whether the patient has had any unexplained weight loss, experienced symptoms related to hyperlactatemia, and/or visited any other medical facility since the last appointment. If none of these events has

occurred, the patient collects a 2-mo supply of medications and is scheduled for an appointment 2 mo later. Otherwise, if any of these events has occurred, the PHCN conducts a full consultation. The PHCN may prescribe or change non-ARV medications and renew existing ARV prescriptions but cannot alter the patient's original ARV prescription. After a full consultation, the PHCN can continue the patient on the standard drug collection and visit schedule (i.e., every 2 mo), treat the patient and request a follow-up visit before the next scheduled visit, or up-refer (return) the patient to the treatment-initiation site. The PHCN also does a routine blood draw 4 mo into each 6-mo prescription cycle, with samples processed for viral load, CD4 count, full blood count, alanine aminotransferase, aspartate aminotransferase, and, depending on drug regimen, cholesterol, triglycerides, creatinine, and/or lactates. Based on the results of these tests, the PHCN can renew the patient's ARV prescription for another 6 mo, change any concomitant non-ARV medications, draw blood again to confirm the laboratory findings, and/or up-refer the patient immediately. Both sites performed the same routine monitoring tests every 6 mo, but doctors at the treatment-initiation site were allowed to order additional laboratory tests if required, whereas nurses at the down-referral site had a restricted list of laboratory tests available and had to up-refer a patient if non-routine tests were indicated.

Patients who are up-referred to the treatment-initiation site remain under treatment-initiation site care until a treatment-initiation site doctor recommends (re-)down-referral. At both sites, a patient who is more than 3 mo late for the next scheduled visit is classified as lost to follow up.

Study Sites

The treatment-initiation site in this study is the Themba Lethu Clinic (TLC) of Helen Joseph Hospital in Johannesburg, a large public sector ART clinic at a secondary hospital. The site, which has been described in detail elsewhere [9], started providing ART in April 2004 and has since initiated more than 18,500 patients on treatment. Treatment is initiated and managed by doctors, as required by the treatment guidelines in place in South Africa until 2010. The clinic is sponsored by the Gauteng Province Department of Health, with additional support from the United States President's Emergency Plan for AIDS Relief.

Due to increasing patient numbers and shortages of human, financial, and infrastructural resources, TLC began down-referring to PHCs within its patient catchment area in 2008. Its first down-referral site was Crosby Clinic, a PHC of the City of Johannesburg roughly 3 km from TLC. Crosby Clinic established a down-referral wing that has its own ART waiting area, consultation rooms, and pharmacy and operates independently of other PHC departments. It can therefore be closely integrated with the treatment-initiation site and avoid the long patient waiting times that are characteristic of many PHC facilities. Because it is located near the treatment-initiation site, patient transport costs are similar between the two facilities.

The treatment-initiation and down-referral sites make use of the same electronic patient management and data system, Therapy Edge-HIV. The system transfers patient records between the treatment-initiation and down-referral sites when a patient is down- or up-referred, alerts the provider if up-referral is required, and automatically transfers files and schedules appointments as needed.

Sample Selection and Matching

We conducted a secondary analysis of routinely collected data from a cohort of patients followed in a routine care setting. As the intervention had already been implemented, we were unable to randomize to limit confounding. Instead, we used a quasi-experimental design in which we matched down-referred patients (down-referral group) to non-down-referred patients (treatment-initiation group) to attempt to create similar populations at the time of eligibility for down-referral. We included all ART patients down-referred from TLC to Crosby Clinic between 1 February 2008 and 1 January 2009. Down-referred patients were matched to not down-referred patients 1:3 based on gender, age (18 24.99, 25 29.99, 30 39.99, 40 49.99, and ≥50 y), time on ART (in 6-mo intervals), ARV regimen at study eligibility, and CD4 count at study eligibility (0 99 100 199, 200 349, and ≥350 cells/mm^3). Matching was accomplished though propensity scores [10,11]. We allowed treatment-initiation site patients to be used as a match more than once, but not within the same 6-mo time interval. Patients were excluded from both groups if they were (1) down-referred to a site other than Crosby Clinic, (2) had <12 mo of potential follow up after down-referral or down-referral eligibility, (3) initiated treatment outside TLC, (4) had a non-standard treatment regimen; or (5) had missing or erroneous medical record data. In the remainder of this paper, "study eligibility" refers to eligibility for either group.

Data Collection

Methods for data collection and costing have been described previously [12]. Taking the provider's perspective, each study participant's electronic medical record was reviewed, and resource usage data for the 12-mo period following down-referral eligibility were collected. For down-referred patients who returned to the treatment-initiation site during the study period (i.e., were up-referred), resource utilization included resources provided by the treatment-initiation site. Resources captured included ARVs, non-ARV medications, laboratory tests, outpatient visits, infrastructure, equipment and furnishings, data capture, and program management. An outpatient visit at the treatment-initiation site included consultations with both a nurse and a doctor; if a patient also collected medications, an additional pharmacy cost was added to the total visit cost. An outpatient visit at the down-referral site was limited to a consultation with the PHCN, who also dispensed medications. Utilization of fixed resources (e.g., infrastructure and administrative staff) for participants who died or were lost to follow up was prorated based on the number of months the patient remained in care. Unit costs were estimated in 2009 South African rand from service provider price lists and financial information provided by the sites. Costs were converted to US dollars at a rate of R8.40 to US$1.00.

Data Analysis

Each study participant at both sites was assigned to a single outcome category on the basis of patient status 12 mo after down-referral eligibility. Criteria for assigning outcomes were adapted from previous work in South Africa assessing patient outcomes 12 mo after treatment initiation [12]. To cope with inconsistent timing of clinic visits and laboratory tests, medical record information within a 3-mo window on either side of 12 mo (i.e., 9 15 mo after down-referral eligibility) was used in determining outcomes, as shown in Table 1.

Using these criteria, outcome assignments were made hierarchically, as illustrated in Figure 1. Up-referral return of a down-referred patient to the treatment-initiation site for monitoring and care was not considered a discrete outcome. Outcomes for up-referred patients were assigned using the same criteria as for all other patients, as defined in Table 1, and costs incurred at the

Table 1. Criteria for assigning HIV treatment outcomes.

Outcome	Criteria for Assigning Outcome	Comments
Excluded from study	Started treatment prior to public rollout	Patient initiated ART prior to the South African national treatment plan launched in April 2004
	Outside of study period	Down-referred/eligible for down-referral before 1 February 2008 or after 1 January 2009
	Less than 12 mo of potential follow up	Started ART <12 mo prior to data collection or transferred formally to a different site; informal transfers without medical record notation are recognized as loss to follow up
	Non-standard ARV regimen	Patient on a regimen that was not part of the national treatment guidelines during the study
	Missing matching data/erroneous data	Includes patients who do not have a viral load, CD4 count, regimen, weight, age, or gender
No longer in care	Died	Only reported deaths included; deaths never reported to the site are recognized as loss to follow up
	Lost to follow up	≥3 mo late for last scheduled consultation or medication pickup
In care but not responding	Detectable viral load (virologic failure)	Viral load >400 copies/ml in month 9–15
	If no viral load available, insufficient CD4 change (immunologic failure)	CD4 decrease of ≥30% from peak or ≤baseline in month 9–15
In care and responding	Undetectable viral load	Viral load ≤400 copies/ml in month 9–15
	If no viral load available, sufficient CD4 change	CD4 within 30% of peak and >baseline in month 9–15
	If no viral load or CD4 count available, still in care	Default outcome for patients remaining alive and in care but without laboratory results

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treatment-initiation site following up-referral are included in the cost per down-referred patient.

Once an outcome was assigned, we estimated a total cost for each patient based on all resources utilized during the 12-mo study period. We estimated an average cost per patient-year in care for each outcome category by site. The cost-effectiveness of the two sites was compared on the basis of average cost per patient remaining in care and responding at the 12-mo point. We created 95% confidence intervals (CIs) around these estimates using bootstrapping with 10,000 replicates [13].

Results

Sample Selection and Cohort Characteristics

Selection of patients from each site is illustrated in Figure 2, and study participants are described in Table 2. We enrolled 712 study participants from the down-referral site and 2,136 patients from the treatment-initiation site. There was little difference between the groups in the characteristics on which they were matched. Down-referred patients excluded because of missing data were similar to patients in the down-referral group in terms of age, time on ART, CD4 count, and treatment regimen.

Treatment Outcomes

Treatment outcomes are reported in Table 3. Both groups showed very good outcomes 12 mo after down-referral eligibility, with well over 90% of patients remaining in care. The down-referral site experienced fewer deaths and losses to follow up, losing just 2% of its patients during the observation period. As a result, the relative risk of no longer being in care in the down-referral group was markedly lower than in the treatment-initiation group (relative risk = 0.27, 95% CI 0.15 0.49). The adjusted hazard ratio was estimated, but it showed no difference from the relative risk estimate. In total, 122 patients in the down-referral group (17.1%) were up-referred within the 12-mo period, after an average of 6.1 mo at the down-referral site. These participants remained in the down-referral group for this analysis. Most of them met the criteria for "in care and responding" after up-referral and are categorized as such in Table 3.

Resource Utilization

Average resource utilization by patients who remained in care at 12 mo is shown in Table 4, which also provides unit cost estimates for the resources for which unit cost varied by site. Usage of viral loads and CD4 counts varied little between the samples. Down-referred patients made nearly twice as many clinic visits as patients remaining at the treatment-initiation site, but at a cost per visit of less than half. Fixed costs were also much lower at the down-referral site than at the treatment-initiation site.

Costs and Cost-Effectiveness

The average cost per patient by outcome, and the breakdown of total cost by major cost components for patients who remained in care and responding at 12 mo, are reported in Table 5. For a patient who remained in care and responding for the 12 mo following down-referral eligibility, treatment at the down-referral site cost an average of US$59 (95% CI US$49 US$70, $p<0.001$) per year less than at the treatment-initiation site, a savings of 11%. The down-referral site spent less on every component of cost except ARVs. Differences in non-ARV drug and lab test costs can be attributed to the greater latitude doctors have in prescribing drugs and diagnostics beyond what is mandated by guidelines. Despite the larger number of clinic visits per patient-year by down-referral patients, the down-referral site still saved money on outpatient visits because of its much lower unit cost per visit.

Using the data in Tables 3 and 5, we estimate that the down-referral site spends an average of US$509 (95% CI US$500 US$519) to produce a patient who is in care and responding 1 y after down-referral, taking into account the resources invested in those who do not respond, die, or are lost to follow up, and

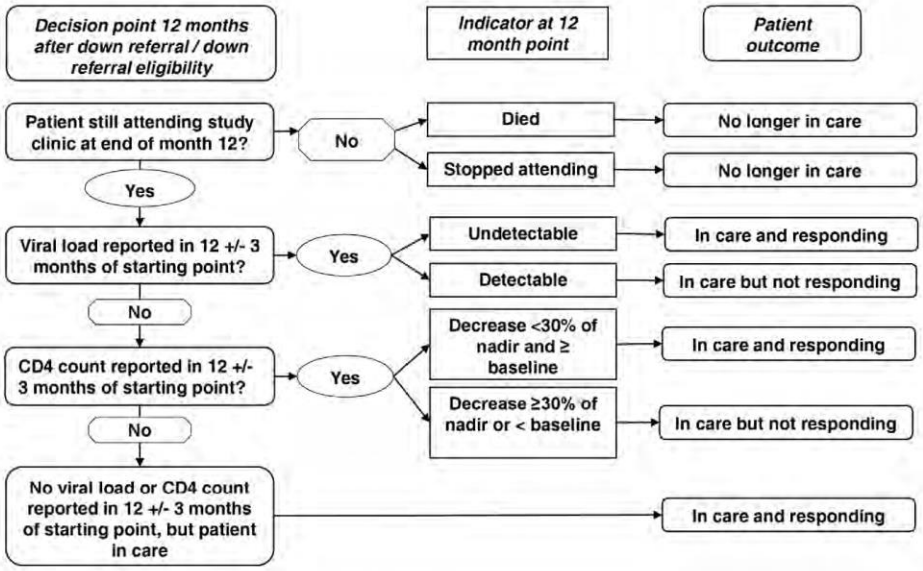

Figure 1. Decision process for assigning HIV treatment outcomes. Patients were placed in a mutually exclusive patient outcome category 12 mo after study enrolment – no longer in care, in care and responding or in care and not responding. Patient outcomes were defined based on the patient's vital status, presence in the clinic, viral load or CD4 count at 12 mo after study enrolment. For those patients alive and in treatment, viral load was the preferred outcome indicator, but in the absence of viral load CD4 count was used and if neither were available then it was assumed the patient was in care and responding based on their presence in the clinic. The diagnostic result closest to 12 mo, but within 3 mo (9–15 mo) was used.
doi:10.1371/journal.pmed.1001055.g001

including the costs of treatment-initiation site treatment for those up-referred. The treatment-initiation site spends an average of US$602 (95% CI US$592 US$612). For this pair of sites in South Africa, down-referral to a PHC is the cost-effective strategy for eligible patients.

Discussion

There is general agreement in the literature and in reports from international agencies that some combination of task-shifting from higher to lower level care providers and decentralization from higher to lower level facilities is essential if targets for HIV/AIDS treatment access in resource-constrained countries are to be met in the face of still-rising patient numbers and declining donor budgets [4]. In this study comparing the outcomes and costs of treatment provided by PHCNs at a PHC with those of treatment provided by doctors at a hospital-based clinic, we found that, for those patients eligible for down-referral, the down-referral site achieved better outcomes at consistently lower costs than the treatment-initiation site.

Both sites produced very good outcomes for the patients sampled. To some extent this is not surprising, as only stable patients who had been on ART for at least 11 mo were eligible for the study. The relatively large number of patients who die, are lost to follow up, or fail treatment in the first year on ART were thus deliberately excluded. Even considering the strict inclusion criteria, however, outcomes at the down-referral site, where almost 95% of patients remained in care, were exceptional.

A major impetus for task-shifting and decentralization, in South Africa and elsewhere, is cost. There is a clear expectation that moving treatment to lower level clinical staff and facilities will cost less than the status quo. In this study, we observed a cost reduction of roughly 11% per patient-year in care. Although this percentage may be smaller than hoped for, the scale of the treatment program in South Africa makes the potential for absolute savings large. South Africa currently has nearly one million patients on ART [14]. If even a quarter of these could be down-referred, and if the cost difference we found is applicable to sites across the country, the estimated difference in cost of US$59 per patient per year would result in program-wide savings of more than US$14 million per year, enough to support an additional 25,000 30,000 patients on ART per year. Using electronic data from the treatment-initiation site where we conducted the study, we estimated that roughly 43% of all patients who initiated ART in the first half of 2008 met eligibility criteria for down-referral by the end of 2009, suggesting that savings could exceed US$25 million per year. These savings would offset roughly 10% 15% of the cost of adding the 400,000 new patients per year called for by the country's national plan for achieving universal treatment access [15].

Limitations of the Study

Our study had a number of limitations. It looked at only one pair of sites, which may or may not be representative of other facilities in South Africa. Both were high volume, well-resourced, urban sites in one of South Africa's wealthier provinces. Because

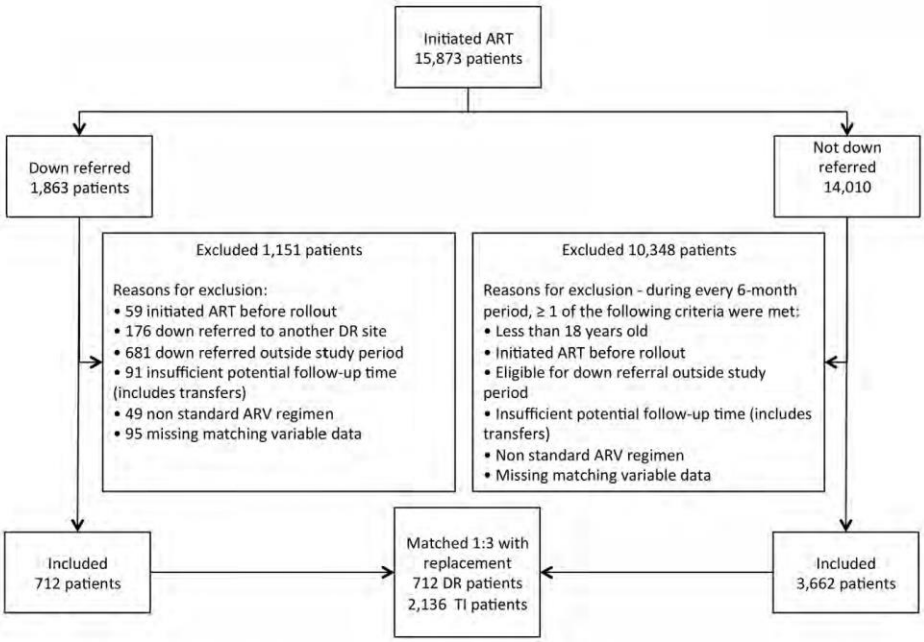

Figure 2. Selection of study participants. All patients initiated on ART at the treatment-initiation site were considered for this study. The patient population was divided into those down-referred and those not down-referred (maintained at the treatment-initiation site). Patients were excluded if they (1) had missing matching variables, (2) were on non-standard ARV regimens, (3) had insufficient potential follow-up time, (4) were eligible/down-referred outside the study period, (5) initiated ART prior to the national rollout, (6) were down-referred to another site (i.e., not the study site), or (7) were <18 y old. Those down-referred patients included in the study were matched 1:3 with patients maintained at the treatment-initiation site. DR, down-referral; TI, treatment-initiation site.
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Table 2. Characteristics of ART patients at the time of eligibility for down-referral to nurse-managed care.

Variable	Treatment-Initiation Group	Down-Referral Group
Number	2,136	712
Mean age at study eligibility, years (IQR)[a]	38.5 (32.7–43.68)	38.5 (33.06–42.03)
Sex, percent female[a]	65.5	65.3
Median CD4 count at ART initiation, cells/mm³ (IQR)[b]	94 (36–163)	103 (41–168)
Median CD4 count at study eligibility, cells/mm³ (IQR)[a]	397 (309–521)	404 (318–526)
Mean duration on ART at study eligibility, years (IQR)[a]	2.3 (1.8–3.3)	2.3 (1.8–3.3)
ARV regimen at study eligibility (percent)[a]		
Stavudine–lamivudine–efavirenz	64.8	63.8
Zidovudine–lamivudine–efavirenz	27.1	27.1
Other	8.1	9.1

[a]These characteristics were matched between the two samples.
[b]Note that 15.4% of participants in the treatment-initiation sample and 11.5% in the down-referral sample did not have baseline CD4 counts reported.
IQR, inter-quartile range.
doi:10.1371/journal.pmed.1001055.t002

Table 3. HIV treatment outcomes 12 mo after down-referral eligibility.

Outcome	Treatment-Initiation Group (n=1,623)	Down-Referral Group (n=540)	Relative Risk (95% CI)[a]
Total	2,136 (100%)	712 (100%)	—
In care and responding	1,912 (89.5%)	680 (95.5%)	1.07 (1.04–1.09)
In care but not responding	91 (4.3%)	20 (2.8%)	0.66 (0.39–1.06)
No longer in care	133 (6.2%)	12 (1.7%)	0.27 (0.15–0.49)
Died	25 (1.2%)	0 (0.0%)	
Lost to follow up	108 (5.1%)	12 (1.7%)	

[a]Relative risk of outcome at down-referral site, with treatment-initiation site as reference.
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the treatment-initiation and down-referral sites in the study were located close together, most patients did not face different obstacles in accessing the sites, such as higher transport costs. This is unlikely to be the case in many settings. Both sites were government health facilities and followed the prescribed treatment regimens and monitoring algorithms as outlined in the national treatment guidelines. In these respects, the study sites were comparable to the many public sector treatment sites within South Africa. Both sites did receive some external donor support, however, and our findings might not pertain to under-resourced sites. The generalizability of our findings to other African countries may also be limited because of the diverse conditions under which care and treatment are offered across sub-Saharan Africa. For example, South Africa relies on doctors, rather than clinical officers, to provide routine care and has access to a wider range of diagnostics (e.g., viral load tests) than do many other countries.

A well-designed randomized clinical trial usually produces the most unbiased outcome estimates (internal validity), but may have a low degree of external validity, or relevance to the real world [16]. While using observational data generated through routine practice may have allowed some bias in our study, it also strengthened the relevance of our findings. In addition, by matching participants in our study, we reduced the potential for any strong bias. Still, while we matched down-referred and non-down-referred patients on known and measured factors affecting treatment outcomes, there is the potential that our populations differed with respect to some unmeasured factor. In order to determine the sensitivity of our results to changes in patient outcomes as a result of such a factor we varied (decreased) the proportion of patients in care and responding in the down-referred arm. The proportion of patients in care and responding would have to drop from 96% to 77% in this arm, with no changes to the initiation-site arm, for the costs per patient in care and responding to be equal. If we take the more likely scenario of equivalent outcomes as seen in the CIPRA clinical trial [9], the cost per nurse-managed patient in care and responding would still be lower than the cost of those managed by doctors ($509 versus $602), and nurse-managed care would therefore still be the preferred choice.

The study reflects treatment guidelines that were in effect until 2010, including the use of stavudine in first-line treatment. In the revised guidelines, new ART patients and those experiencing stavudine toxicities will be prescribed tenofovir. The much greater tolerability of tenofovir may alter the relative effectiveness of doctors and nurses in managing ART patients. While we would expect this to make it even easier for nurses to manage treatment, we cannot be certain. We also cannot evaluate the extent to which the relatively low patient volumes seen at the down-referral site affected the quality of care delivered. Very large down-referral sites, and those that have exceeded their service delivery capacity, may achieve poorer patient outcomes than those we observed. Finally, as has been noted in recent publications, the rate of reported "loss to follow up" from any one treatment facility may overstate actual patient attrition from treatment, as many patients who are reported as lost have actually re-started treatment somewhere else [17]. If this phenomenon was more common at the treatment-initiation site in our study than at the down-referral site, the actual difference in outcomes between our two sites may be less than we observed.

Table 4. Average resource utilization and selected unit costs for the study sample (n=2,160) over 12 mo from the date of down-referral eligibility.

Resource	Treatment-Initiation Site	Down-Referral Site
Average utilization per patient-year in care		
Treatment-initiation site visit	4.4	1.5
Down-referral site visit	0.0	5.6
CD4 count	1.6	1.5
Viral load test	1.6	1.4
Unit costs[a]		
Average cost per outpatient visit, US$	14	7
Average fixed cost per patient per month, US$	98	59

[a]Costs were converted to US dollars at a rate of R8.40 to US$1.00.
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Table 5. Average cost per patient, by HIV treatment outcome and cost component.

Outcome or Cost Component	Cost, in US Dollars	
	Treatment-Initiation Patients	Down-Referral Patients
Outcome, mean (standard deviation)		
All patients in group	539 (141)	486 (98)[a]
In care and responding	551 (128)	492 (88)[a]
In care but not responding	589 (163)	481 (97)[a]
No longer in care	330 (147)	175 (103)[a]
Cost component, value (proportion of total)[b]		
Drugs—ARV	237 (43%)	262 (53%)
Drugs—non-ARV	16 (3%)	7 (1%)
Lab tests	120 (22%)	101 (21%)
Outpatient visits	80 (15%)	60 (12%)
Fixed costs	98 (18%)	62 (13%)
Total	551 (100%)	492 (100%)

Costs are given in 2009 US dollars, converted at a rate of R8.40 to US$1.00.
[a]$p<0.001$ for difference between treatment-initiation and down-referral patients.
[b]Only patients who were still in care and responding at 12 mo were included.
doi:10.1371/journal.pmed.1001055.t005

Conclusions

In addition to the financial cost savings estimated in this study, transferring patients to nurse-managed, primary-level clinics has the additional advantage of freeing up the time and resources of more highly trained doctors and well-equipped facilities to focus on patients who are not responding to treatment or have other complications. Task-shifting allows more health care workers to provide ART care, and this in turn increases the treatment coverage available to meet the large unmet need. Although South Africa faces a shortage of both doctors and nurses, the scarcity of doctors is greater [18], and this scarcity may not be fully reflected in the salary differential between the two job grades. The financial cost-effectiveness analysis presented here thus does not capture the full opportunity costs of the intervention evaluated.

The national treatment guidelines adopted in 2010 allow nurses to initiate, as well as manage, ART, under a model known as NIMART (Nurse-Initiated and Managed ART). This policy change was based on modeled estimates of the cost savings from task-shifting but with little empirical evidence confirming that these savings will indeed be realized. This study provides strong evidence that at least part of the NIMART model the management of stable patients by PHCNs will reduce overall treatment program costs in South Africa, without compromising patient outcomes.

Acknowledgments

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Author Contributions

Conceived and designed the experiments: LL AB MPF IS IJ SR. Analyzed the data: LL AB MPF SR. Wrote the first draft of the paper: LL SR. Wrote the paper: LL AB MPF BN IJ IS SR. ICMJE criteria for authorship read and met: LL AB MPF BN IJ IS SR. Agree with the manuscript's results and conclusions: LL AB MPF BN IJ IS SR.

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Editors' Summary

Background. AIDS has killed more than 25 million people since 1981, and about 33 million people are now infected with HIV, the virus that causes AIDS. Because HIV destroys immune system cells, which leaves infected individuals susceptible to other infections, early in the AIDS epidemic, most HIV-infected people died within ten years of infection. Then, in 1996, antiretroviral therapy (ART), which can keep HIV in check for many years, became available. For people living in developed countries, HIV infection became a chronic condition, but people in developing countries were not so lucky—ART was prohibitively expensive and so a diagnosis of HIV infection remained a death sentence in many regions of the world. 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. As a result, nowadays, more than a third of people in low- and middle-income countries who need ART are receiving it.

Why Was This Study Done? Unfortunately, shortages of human resources in developing countries are impeding progress toward universal ART coverage. In sub-Saharan Africa, for example, where two-thirds of all HIV-positive people live, there are too few doctors to supervise all the ART that is required. Various organizations are therefore encouraging a shift of clinical care responsibilities for people receiving ART from doctors to less highly trained, less expensive, and more numerous members of the clinical workforce. Thus, in South Africa, plans are underway to reduce the role of hospital doctors in ART and to increase the role of primary health clinic nurses. One specific strategy involves "down-referring" patients whose HIV infection is under control ("stable ART patients") from a doctor-managed, hospital-based ART clinic to a nurse-managed primary health care facility. In this observational study, the researchers investigate the effect of this strategy on treatment outcomes and costs by retrospectively analyzing data collected from a cohort (group) of adult patients initially treated by doctors at the Themba Lethu Clinic in Johannesburg and then down-referred to a nearby primary health clinic where nurses supervised their treatment.

What Did the Researchers Do and Find? Patients attending the hospital-based ART clinic were invited to transfer to the down-referral site if they had been on ART for at least 11 months and met criteria that indicated that ART was controlling their HIV infection. Each of the 712 stable ART patients who agreed to be down-referred to the primary health clinic was matched to three patients eligible for down-referral but not down-referred (2,136 patients), and clinical outcomes and costs in the patient groups were compared 12 months after down-referral eligibility. At this time point, 1.7% of the down-referred patients had died or had been lost to follow up compared to 6.2% of the patients who continued to receive hospital-based ART. The average cost per patient-year for those in care and responding at 12 months was US$492 for down-referred patients but US$551 for patients remaining at the hospital. Finally, the down-referral site spent US$509 to produce a patient who was in care and responding one year after down-referral on average, whereas the hospital spent US$602 for each responding patient. Thus, the down-referral strategy (nurse-managed care) was more cost-effective than continued hospital treatment (doctor-managed care).

What Do These Findings Mean? These findings indicate that, at least for this pair of study sites, the 12-month outcomes of stable ART patients who were down-referred to a primary health clinic were as good as or better than the outcomes of similar patients who remained at a hospital-based ART clinic. Moreover, the down-referral strategy saved 11% of costs for patients who remained in care and responded to treatment and appeared to be cost-effective, although additional studies are needed to confirm this last finding. Because this is an observational study (that is, patients eligible for down-referral were not randomly assigned to hospital or primary care facility treatment), it is possible that some unknown factor was responsible for the difference in outcomes between the two patient groups. Nevertheless, these results suggest that the down-referral strategy tested in this study could increase ART capacity and conserve resources without compromising patient outcomes in South Africa and possibly in other resource-limited settings.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/journal.pmed.pmed.1001055.

- This study is further discussed in a *PLoS Medicine* Perspective by Ford and Mills
- The US National Institute of Allergy and Infectious Diseases provides information on HIV infection and AIDS
- HIV InSite has comprehensive information on HIV/AIDS
- Information is available from Avert, an international AIDS charity, on many aspects of HIV/AIDS, including information on 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 its 2010 progress report (in English, French and Spanish)
- Right to Care, a non-profit organization that aims to deliver and support quality clinical services in Southern Africa for the prevention, treatment, and management of HIV, provides information on down-referral

APPENDIX B1: Paper 2 – Submitted format

Long LC, Rosen SB, Brennan A, Moyo F, Sauls C, Evans D, Modi SL, Sanne I, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. ***Submitted to PLoS One.*** *Under review.*

Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa

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Abstract

Background: In 2010 South Africa revised its HIV treatment guidelines to allow the initiation and management of patients on antiretroviral therapy (ART) by nurses, rather than solely doctors, under a program called NIMART (Nurse Initiated and Managed Antiretroviral Therapy). We compared the outcomes and costs of NIMART between the two major public sector HIV treatment delivery models in use in South Africa today, primary health clinics and hospital-based HIV clinics.

Methods and findings: The study was conducted at one hospital-based outpatient HIV clinic and one primary health clinic (PHC) in Gauteng Province. A retrospective cohort of adult patients initiated on ART at the PHC was propensity-score matched to patients initiated at the hospital outpatient clinic. Each patient was assigned a 12-month outcome of alive and in care or died/lost to follow up. Costs were estimated from the provider perspective for the 12 months after ART initiation. The proportion of patients alive and in care at 12 months did not differ between the PHC (76.5%) and the hospital-based site (74.2%). The average annual cost per patient alive and in care at 12 months after ART initiation was significantly lower at the PHC (US$238) than at the hospital outpatient clinic (US$428).

Conclusions: Initiating and managing ART patients at PHCs under NIMART is producing equally good outcomes as hospital-based HIV clinic care at much lower cost. Evolution of hospital-based clinics into referral facilities that serve complicated patients, while investing most program expansion resources into PHCs, may be a preferred strategy for achieving treatment coverage targets.

Introduction

With over 2.6 million people on HIV treatment, South Africa has had unprecedented success in rolling out its public sector antiretroviral therapy (ART) program[1]. Despite this success, further expansion to 5.7 million patients on treatment by 2018/2019 [2] will be needed for South Africa to reach the "90-90-90" targets established by the World Health Organization [3], and current budgetary resources are not sufficient [2]. Expanding access to ART at the lowest possible cost is therefore essential, for South Africa and for many other countries facing similar challenges.

When the South African national antiretroviral therapy (ART) program began in 2004, it relied primarily on hospital-based HIV clinics with services delivered by doctors [4]. In 2010, in the face of increasing demand for care and limited personnel, South Africa revised its treatment guidelines to allow the initiation and management of patients on ART by nurses at both hospitals and primary health clinics (PHCs) [5, 6] under a program known as Nurse Initiated and Managed Antiretroviral Therapy (NIMART).

NIMART shifted the focus of the South African treatment program from doctors to nurses and from hospitals to PHCs, increasing the number of accredited ART delivery facilities sites from 496 to 4333 [7]. With the advent of NIMART, South Africa now has two major public sector ART delivery models: centralized, hospital-based HIV outpatient clinics, which serve roughly 12% of patients; and decentralized, full service, primary health clinics, which serve about 85% (authors' data). Both decentralization and task shifting have been shown to generate health outcomes

equivalent to or better than centralized, doctor-led care [8-12]. A recent Cochrane review concluded that there was moderate evidence showing that task shifting for HIV management did not decrease the quality of care and, for patients who were initiated on ART by nurses, may reduce patient loss to follow-up [13].

While several studies have examined outcomes of task shifting and decentralization in South Africa [14-24], few have included both ART initiation and management by nurses in routine public sector care without external resources. Neither of the two available cost estimates, moreover, reflect routine NIMART implementation [17, 25]. There is therefore little evidence of how NIMART fares, relative to traditional hospital-based, doctor-led care, under the normal conditions and constraints of a typical public sector setting. We used routinely collected patient data and actual resource utilization and cost records to evaluate the outcomes and costs of the two public sector HIV treatment delivery models and provide evidence to guide future program expansion.

Methods

Study sites

The study was conducted at one hospital-based outpatient HIV treatment clinic and one primary health clinic. Both sites are situated in the same municipality (pop. 360,000) in West Rand District of Gauteng Province, South Africa. The district was

one of the early adopters of NIMART across all its facilities. The two sites are seven kilometers apart and serve similar populations.

The hospital-based HIV clinic is a large regional hospital hereafter referred to as the 'HIV outpatient clinic'. As of March 2014 it had 4,396 patients actively on ART and saw an average of 1,956 ART patients per month. It originally provided ART initiation and management by doctors, with nurse support for screening and monitoring. With the introduction of NIMART, responsibility for these services was progressively shifted to nurses. During the study period, the HIV outpatient clinic had one dedicated, full time doctor and sixteen nurses (including enrolled nurse assistants and managers).

The primary health clinic (PHC), hereafter referred to as "the PHC", had as of March 2014 1,958 patients actively on ART and saw approximately of 884 HIV patients for ART pickup in March 2014, which was roughly 11% of the patient load. As of January 2012, HIV was fully integrated into general chronic disease care at the site. During the study period (2012) it had fifteen clinical staff (nurses and a doctor) serving all patients seeking care at the clinic for all conditions.

Sample selection and matching

We constructed a retrospective cohort of adult (≥18 years) patients initiated on ART at the PHC and matched them to patients initiated at the HIV outpatient clinic. To be included in the cohort, patients had to have at least 15 months of potential follow up as of the date of data collection, not have transferred to another site during their first

year after initiation, having initiated after 1 January 2011 (NIMART policy in place) and have a complete patient record available for review. Data collection commenced on 15 January 2014 at the PHC and 1 March 2014 at the HIV outpatient clinic, resulting in the cohorts including patients initiated prior to 15 October 2013 and 1 December 2013 at the PHC and HIV outpatient clinic respectively. At the PHC we enrolled the first 260 patients who met these inclusion criteria. These patients were then matched to hospital outpatient clinic patients 1:3 on gender, age at initiation (18–30, 31-40, 41-50, >50 years), baseline ART regimen, and baseline CD4 count (0-100, 101-200, 201-350, 350 cells/mm^3). We used propensity score matching without replacement [26] using the Vmatch macro in SAS [27] to identify a comparison population from among all patients in the HIV outpatient clinic database who initiated ART after 1 January 2011 and met the study inclusion criteria.

Outcomes data and analysis

Clinical data were collected from paper files and the national electronic HIV register (Tier.net) at the primary health clinic and from a separate electronic patient record (TherapyEdge ™) at the HIV outpatient clinic. All three of these sources contained only routinely collected data. Fields collected for the first 12 months following ART initiation for each patient included baseline CD4 count, date of ART initiation, resource usage (visits, laboratory tests, drugs), and outcome at 12 months. CD4 count and viral load results up to 15 months were also collected to assign 12-month outcomes.

147 Each patient was assigned a single primary, 12-month outcome of either "alive and in
148 care" or "died / lost to follow-up (LTFU)". If a patient died before 12 months or was
149 >3 months late for their last scheduled visit within the 12-month follow up period
150 (lost to follow-up) then the patient was assigned to the outcome "died / LTFU". All
151 other patients were considered "alive and in care". Secondary outcomes based on
152 virologic and immunologic status were also assigned. Patients with a viral load ≥
153 1,000 copies/mm^3 between 9-15 months after treatment initiation were classified as
154 "virologic failure". Patients with a CD4 count in month 9-15 showing a decrease of
155 >30% from the highest recorded CD4 count between 0-12 months or below the CD4
156 count at ART initiation were classified as "immunologic failure". For laboratory
157 results we used the test result reported between 9 and 15 months that was closest to
158 the 12-month endpoint. We then compared the primary and secondary outcomes over
159 the first 12 months of treatment between sites using crude risk ratios with
160 corresponding 95% confidence intervals.
161
162 Through sensitivity analysis, we investigated the effect of missing paper files
163 excluded at the PHC (no patients were excluded at the HIV outpatient clinic because
164 of missing files). Data on age, gender, baseline CD4 count, and 12-month primary
165 outcome were collected from Tier.net for patients with missing files, where possible.
166 In the sensitivity analysis, all primary health clinic patients were then matched on age,
167 gender and baseline CD4 count to the hospital outpatient clinic and outcomes were
168 compared.
169
170 *Cost data and analysis*
171

Outcomes and costs of ART at PHCs v hospital clinics

172 Costs were estimated from the provider perspective for the 12 months after ART
173 initiation using standard costing methods, as outlined in Table 1 and described in
174 previous publications [17, 28]. Resources incurring costs included drugs, diagnostics,
175 clinical staff, space, equipment and other shared services (i.e. other staff, utilities,
176 etc.). Variable resource usage was determined from patient records; utilization of
177 fixed resources, such as space and shared services, was estimated from site records.
178 The quantity of each resource used by each patient was then multiplied by the
179 associated unit cost to determine a total cost per patient. All unit costs were in 2014
180 South African Rand (ZAR) or adjusted to 2014 and reported costs were converted to
181 United States Dollar (USD) at the average exchange rate prevailing during 2014 of
182 10.83:1 (ZAR:USD). Average resource utilization per patient year is presented by
183 site; average cost per patient is presented by site, cost category, and primary outcome.
184
185 **Table 1.** Methods for estimating costs
186

Type of cost	Method for estimating cost
VARIABLE COSTS (RESOURCES RECORDED IN PATIENT MEDICAL RECORDS)	
Drugs, diagnostics, and other services reported in individual subjects' medical records	Unit cost obtained from suppliers or site and multiplied by actual resource usage for each patient.
Staffing (visits)	The specific staff cadres providing service for each patient visit is not recorded in patient files. A uniform staffing cost is estimated per patient visit at each site based on total staff cost divided by the total visits during the period. The actual number of visits made by the patient is then multiplied by this cost.
FIXED COSTS (RESOURCES USED FOR CLINIC OPERATION, NOT ALLOCATED TO INDIVIDUAL PATIENTS)	
Buildings and utilities	The space of the building was measured and an average rental cost per square metre obtained from the property market for commercial properties in the area was applied. Utilities were not measured at the study sites and so an estimated utility cost per square metre was determined based on a property with basic utility demands (i.e. basic electronic equipment and lighting, air-conditioning, water for cleaning and sanitation).
Equipment	All computer and related equipment was inventoried and costed using the appropriate unit costs and expected working life. Basic furnishings and equipment were costed by including a 10% markup on the rental.
Supplies	This included all non-drug and non-diagnostic related supplies (i.e. gloves, paper, pens). Supply usage was not well recorded at the facilities. The available information was captured and an estimated cost was calculated per month per patient visit. The same supply cost per visit was applied to both sites in order to prevent the costs being biased towards a site with incomplete supply records.

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The study protocol was reviewed by the Institutional Review Boards of the University of Witwatersrand and Boston University, who approved the collection of the data without informed consent and the use of an anonymous analytic dataset.

Results

Sample characteristics

Sample selection is outlined in S1 Fig. A sample of 260 patients was selected from the primary health clinic, of whom 60 were excluded (55 missing files, 3 missing baseline CD4 count, 2 transferred within 12 months of initiating). The final analytic data set therefore included 200 patients from the primary health clinic matched with 600 patients from the HIV outpatient clinic. The patients excluded from the PHC sample because of missing data were similar to those included in terms of age and gender but had a slightly higher baseline median (IQR) CD4 count (208 cells/mm^3 (122-269 cells/mm^3)) than those included (162 cells/mm^3 (87-257 cells/mm^3)).

Characteristics of the sample are described in Table 2. The median age was 34 years (IQR: 28-41 years) and median CD4 count 151 cells/mm^3 (IQR: 69.5-239.5 cells/mm^3); two thirds were female. Most patients were initiated on a baseline regimen of lamivudine and tenofovir with either efavirenz (83%) or nevirapine (8%). There were no important differences in sample characteristics between the two sites.

Outcomes and costs of ART at PHCs v hospital clinics

213 **Table 2.** Baseline characteristics at HIV treatment initiation
214

Characteristics	Total n=800		HIV Outpatient Clinic n=600		Primary Health Clinic n=200	
BASELINE CHARACTERISTICS AT HIV TREATMENT INITIATION[1]						
Gender, n (%)						
Male	275	(34.4)	206	(34.3)	69	(34.5)
Female	525	(65.6)	394	(65.7)	131	(65.5)
Age, n (%)						
18-30	273	(34.1)	206	(34.3)	67	(33.5)
31-40	324	(40.5)	233	(38.8)	91	(45.5)
41-50	141	(17.6)	112	(18.7)	29	(14.5)
>50	62	(7.8)	49	(8.2)	13	(6.5)
Age, median (IQR)	34	(28-41)	34	(29-39)	34	(28-41)
Baseline ART Regimen, n (%)						
3TC-TDF-EFV	663	(82.9)	506	(84.3)	157	(78.5)
3TC-TDF-NVP	62	(7.8)	33	(5.5)	29	(14.5)
Other	75	(9.4)	61	(10.2)	14	(7.0)
Baseline CD4 Count, n (%)						
≤100 cells/mm^3	248	(31.0)	192	(32.0)	56	(28.0)
101-200 cells/mm^3	263	(32.9)	202	(33.7)	61	(30.5)
201-350 cells/mm^3	261	(32.6)	181	(30.2)	80	(40.0)
>351 cells/mm^3	28	(3.5)	25	(4.2)	3	(1.5)
Baseline CD4 Count, median (IQR)	151	(69.5-239.5)	148	(61-236.5)	161.5	(86.5-256.5)

215 ART: antiretroviral therapy, 3TC: stavudine, TDF: tenofovir, EFV: efavirenz, NVP: nevirapine
216 [1]All the baseline characteristics were matched using propensity scores

217

218 # Outcomes

219

220 The primary and secondary outcomes are presented in Table 3. The majority of
221 patients at both the HIV outpatient clinic (72%) and the PHC (82%) were reported to
222 be alive and in care at 12 months. Being a patient at the primary health clinic
223 appeared to be somewhat protective against death or loss to follow-up (RR: 0.66, 95%
224 CI: 0.48-0.91). However, as Figure 1 indicates, 55 patient files from the original
225 sample selected for the PHC were missing and were excluded from the primary
226 analysis. After excluding two patients who transferred to other facilities and six for

whom no baseline CD4 count was available, in sensitivity analysis we considered the impact of the missing files on patient outcomes at the PHC. We found that patients with missing files were more likely to be lost to follow up or dead than were those included in the main analysis. When the outcomes of the patients with missing files were included in the analysis, the difference between the sites in the proportion of patients not in care disappeared (RR: 0.91, 95% CI: 0.71-1.18). There was no difference between the sites in outcomes stratified by baseline CD4 count. We also found no difference in virologic or immunologic failure rates between the sites for those patients who had the necessary diagnostics reported in their files (238/800 and 205/800 for viral load and CD4 count, respectively). We thus conclude that the primary outcomes were comparable between the sites.

Table 3. Outcomes at 12 months after ART initiation with relative risk

Outcomes	Total n/N (%)		HIV Outpatient Clinic n/N (%)		Primary Health Clinic n/N (%)		Relative Risk[a] (95% CI)	
Primary Outcome								
Alive and in care	595/800	(74.4)	432/600	(72.0)	163/200	(81.5)	-	
Dead / LTFU	205/800	(25.6)	168/600	(28.0)	37/200	(18.5)	0.66	(0.48-0.91)
≤100 cells/mm^3	89/248	(35.9)	74/192	(38.5)	15/56	(26.8)	0.70	(0.44-1.11)
101-200 cells/mm^3	61/262	(23.3)	45/201	(22.4)	7/61	(11.5)	0.51	(0.24-1.08)
201-350 cells/mm^3	80/261	(30.7)	45/181	(24.9)	14/80	(17.5)	0.70	(0.41-1.21)
>351 cells/mm^3	3/29	(10.3)	4/26	(15.4)	1/3	(33.3)	2.17	(0.35-13.6)
Secondary Outcome								
Virologic failure*	59/238	(24.8)	36/167	(21.6)	23/71	(32.4)	1.50	(0.96-2.34)
Immunologic failure**	10/205	(4.9)	8/139	(5.8)	2/66	(3.0)	0.53	(0.12-2.41)
SENSITIVITY ANALYSIS* **								
Primary Outcome								
Alive and in care	741/988	(75.0)	550/741	(74.2)	189/247	(76.5)	-	
Dead / LTFU	247/988	(25.0)	191/741	(25.8)	58/247	(23.5)	0.91	(0.71-1.18)

[a]Relative risk of outcome at primary health clinic, with HIV outpatient clinic as reference
**Only includes those with CD4 counts between 9-15 months
***Newly matched sample including missing files

Resource utilization and costs

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246

247 Table 4 compares baseline CD4 counts, duration in care, and utilization of clinic visits
248 and laboratory tests by site and outcome category. Not surprisingly, at both sites
249 patients alive and in care at 12 months had a higher median baseline CD4 count than
250 those not in care. More surprisingly, patients who did not remain in care for 12
251 months at the PHC spent almost twice as much time in care (7.5 months) as did
252 patients at the HIV outpatient clinic (3.7 months). Resource utilization by site and
253 outcome reflects these differences in duration of care. In general, resource utilization
254 was slightly higher at the PHC than at the HIV outpatient clinic, primarily because
255 patients at the PHC who ultimately died or were lost to follow up remained in care for
256 an average of nearly four more months, long enough to make at least one more clinic
257 visit and undergo an additional set of laboratory tests. For patients who did remain in
258 care, differences between the sites were modest, with the PHC reporting slightly
259 fewer clinic visits and slightly more laboratory tests.

260

261 **Table 4.** Time in care (months) and resource utilization for study period by outcome and facility
262

	All patients		Alive in care		Dead / LTFU	
	HIV Outpatient Clinic	Primary Health Clinic	HIV Outpatient Clinic	Primary Health Clinic	HIV Outpatient Clinic	Primary Health Clinic
Patients, n	600	200	432	163	168	37
CD4 count (cells/mm^3), median	148	161.5	155	164	120.5	142
RESOURCES USED IN STUDY PERIOD						
Average months in care	9.7	11.2	12.0	12.0	3.7	7.5
Number of visits	7.0	6.6	8.7	7.3	2.7	3.5
Laboratory tests						
Alanine aminotransferase	0.6	1.0	0.8	1.0	0.2	0.9
CD4 count	0.5	1.7	0.7	1.9	0.1	1.1
Creatinine	0.7	2.2	0.8	2.4	0.3	1.2
Full blood count	0.6	1.0	0.8	1.0	0.2	1.0
Viral load	0.5	0.7	0.7	0.9	0.0	0.9
Total unit cost per visit (USD)*	31	9	31	9	31	9
Staffing cost per visit (USD*)	25	8	25	8	25	8

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Fixed cost per visit (USD*)	6	1	6	1	6	1						

*Costs are given in 2014 US dollars, converted at a rate of R10.83 to US$1.00

Costs by site, outcome, and cost category are presented in Table 5. Drugs and diagnostic tests are procured centrally by government and thus have identical unit costs between sites; higher costs in these categories between sites indicate higher resource usage. Patients who spend 12 months in care have similar drug and diagnostic costs between sites, indicating similar resource utilization. Unit costs for staffing and fixed costs are specific to the site, reflecting staffing composition, infrastructure, equipment, and patient volume. Differences in these cost categories can thus reflect differences in unit costs and/or resource usage.

Table 5. Mean 12 month cost per patient (USD) by outcome and facility, broken down by cost category

	All patients (USD)				Alive in care (USD)				Dead / LTFU (USD)			
Cost category (mean, %)	**HIV Outpatient Clinic**		**Primary Health Clinic**		**HIV Outpatient Clinic**		**Primary Health Clinic**		**HIV Outpatient Clinic**		**Primary Health Clinic**	
Drugs	85	(25%)	100	(47%)	108	(25%)	113	(47%)	28	(23%)	43	(43%)
Diagnostics	41	(12%)	51	(24%)	53	(12%)	57	(24%)	11	(9%)	24	(24%)
Staffing	177	(52%)	56	(26%)	219	(51%)	62	(26%)	68	(56%)	30	(30%)
Fixed	39	(11%)	6	(3%)	48	(11%)	7	(3%)	15	(12%)	3	(3%)
Average cost per patient (95% CI)	342	(326, 358)	213	(204, 222)	428	(422, 452)	238	(233, 244)	122	(106, 137)	100	(87, 113)

[1]Costs are given in 2014 US dollars, converted at a rate of R10.83 to US$1.00

The average cost per patient initiated on ART over the 12 months following initiation was significantly lower at the PHC ($213) than at the HIV outpatient clinic ($342). This finding of lower costs at the PHC held for all outcomes and remained valid even when the longer duration of care for those ultimately not in care was taken into account: $20 v. $36 per month at the PHC and HIV outpatient clinic, respectively, for

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patients in care and $13 v. $33 per month for patients not in care. Most of this difference derives from the higher costs of staff and infrastructure at the HIV outpatient clinic. While patients at the HIV outpatient clinic made slightly more visits, the cost per visit was substantially more ($31 v. $9).

Discussion

In this analysis of outcomes and costs of providing antiretroviral therapy under South Africa's two major models of service delivery, we found that both models achieved similar proportions of patients alive and in care 12 months after initiation, but the primary health clinic model cost substantially less per patient treated, despite providing more months of patient care overall. This cost difference is due largely to the higher staff and infrastructure costs incurred in a hospital-based clinic, and reflect the fact that ART patients rarely require the more specialized services and equipment available at a hospital.

Other studies in South Africa have consistently found that decentralization to PHCs from centralized clinics and task shifting to nurses produce favorable or equivalent results for patients [14-16, 20, 21, 24]. We previously showed that down-referral of stable ART patients to PHCs after initiation at a hospital-based HIV outpatient clinic reduced the costs of managing stable patient [17]. The study reported here, which demonstrated both equivalent patient outcomes and lower costs for PHC-level, nurse-led initiation and management, stands in contrast to the only other cost estimate of this model we discovered, from the STRETCH trial in South Africa's Free State Province. The STRETCH trial found that nurse initiation and management can

improve health outcomes and quality of care somewhat, but at a higher mean cost [24, 25] that reflected high setup and implementation costs and more clinic visits per patient in the nurse-led arm. Patients in the STRETCH trial were enrolled prior to the advent of NIMART and were managed under the constraints of a randomized controlled trial. Our study is therefore more likely to reflect current, actual conditions in the public sector since NIMART became the standard of care. The knowledge that PHCs can deliver equally good care, at much lower cost, will help the South African Government, neighboring governments, and their partners to make cost-effective decisions about program design.

Shifting ART responsibilities from doctors to nurses has occurred to varying degrees across all treatment facilities in South Africa. At PHCs, nurses provide nearly all HIV services, with only occasional referral, and HIV care is largely integrated with other primary health care. HIV outpatient clinics at hospitals remain stand-alone services with relatively significant doctor involvement, with NIMART trained nurses working alongside but not always replacing doctors. We found that this staffing mix, which also affects patient volume and the efficiency of staff time use, is one of the two main causes of the high cost of HIV outpatient clinics (the other is simply the higher cost of hospital infrastructure). The importance of the staff complement suggests that a re-allocation of responsibilities, with complicated patients (e.g. patients with very low CD4 counts at initiation, patients failing first line therapy, patients on second line therapy) referred to hospital-based HIV clinics and the vast majority of uncomplicated patients initiated and managed at PHCs. Supporting this recommendation, a study of the NIMART rollout in the City of Johannesburg found that NIMART increased ART

initiations at PHCs and reduced them at hospital-based HIV clinics, allowing the hospital clinics to focus on more difficult cases [22].

Although we estimated both costs and effectiveness of the two models of ART delivery, our study was not designed as a cost-effectiveness analysis (CEA), as we do not believe that a choice can be made between the two models. In view of the vast demand for HIV treatment in South Africa, both models will continue to be required for years to come. The information we report will help support efficient allocation of patients between facilities, decisions about future expansion of treatment capacity, and planning and budgeting.

This study had a number of limitations, most of which are common to retrospective, observational cohort studies. Most important, the study was limited to a single pair of sites in one province, which limits geographic generalizability. The study sites are, however, public sector treatment facilities following the national treatment guidelines, and are thus likely to be typical of the public sector in other provinces in South Africa, if not of other countries. Although we matched our samples carefully using a rigorous matching algorithm, moreover, unobserved differences between the samples may bias our estimates. Our results are dependent on the accuracy and completeness of routinely collected patient records, which may also have varied by site. Finally, despite our access to relatively recent data, the rapid pace of change of national and global treatment guidelines makes it nearly impossible for research to "keep up" with the current treatment landscape.

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In spite of these limitations, we conclude that initiating and managing ART patients at primary health clinics under South Africa's NIMART policy is producing equally good outcomes as hospital-based HIV outpatient clinic care at much lower cost. Evolution of the country's hospital-based clinics into well-resourced, centralized, expert referral facilities that focus on complicated patients, while investing program expansion resources into PHCs, may thus be the country's preferred strategy. There are currently no widely-utilized guidelines for how to triage patients between routine PHC care and specialized HIV clinic care. Developing guidance in this area may thus be a priority for policy makers.

While our findings should support the continued expansion of NIMART, we conclude by noting that the impact of the program on non-HIV care must also be considered. So far, nurses appear to have incorporated HIV care into their workloads smoothly, but there is no evidence to suggest how much additional capacity remains on the system or that the addition of HIV care has not been to the detriment of other patients. While we have looked specifically at the provider costs of ART, a full evaluation of the NIMART program—and of similar decentralizing and task-shifting initiatives in other countries—should take into account both the impact of the program on non-HIV care and its benefits and costs to patients themselves.

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381

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384 data. A.B. and M.F. contributed to the design of the study and provided assistance
385 with statistical analysis. F.M. and C.S. assisted with coordinating field study
386 activities, data collection and data cleaning. S.R. contributed to the original design of
387 the study, provided assistance with the costing analysis and provided supervision.
388 D.E., S.M. and I.S. provided supervision and support on the clinical aspects of the
389 analysis. L.L. did the analysis and prepared the first draft of the manuscript. All
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391

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400

401 # Conflicts of Interest

402

403 There are no conflicts of interest.

404

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Supporting Information

S1 Fig. **Study Samples.**

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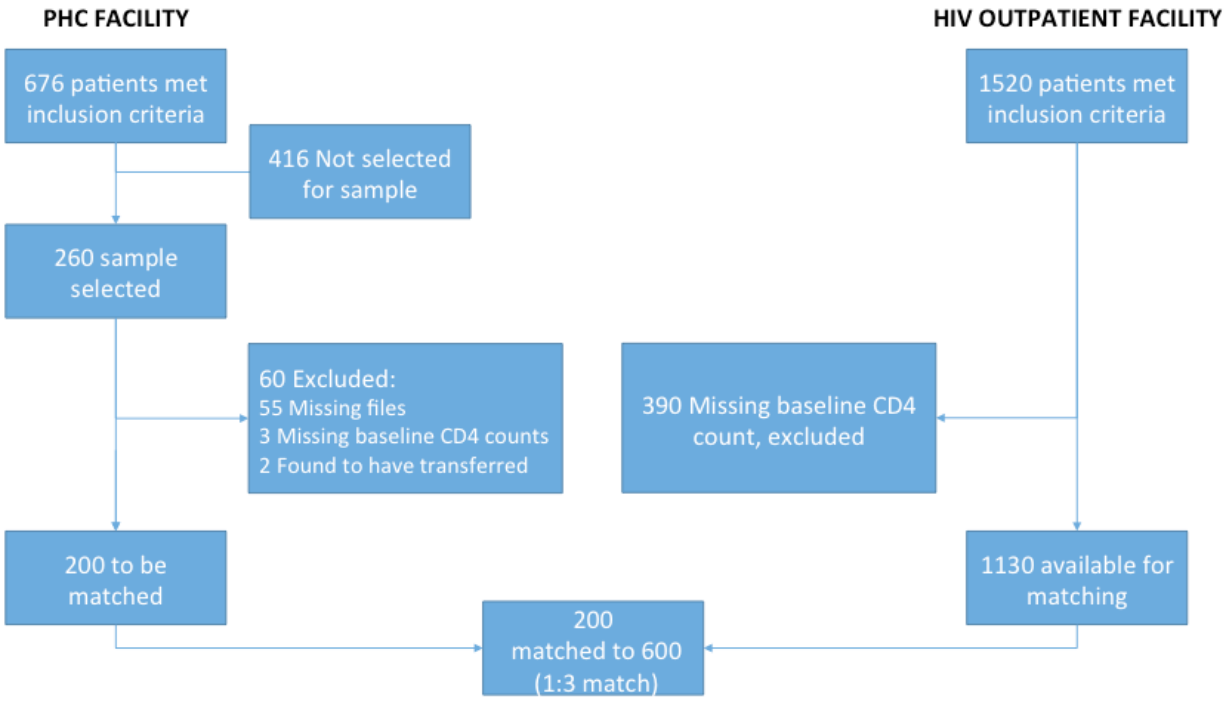
APPENDIX B2: Paper 2 – Supplementary material



Supplementary Figure 1. Study samples.

APPENDIX C1: Paper 3 – Published format

Long LC, Fox MP, Sauls C, Evans D, Sanne I, Rosen SB. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. **PLoS One.** 2016;11(2):e0148546.

PLOS | ONE

RESEARCH ARTICLE

The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa

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Abstract

Background

While most HIV care is provided on an outpatient basis, hospitals continue to treat serious HIV-related admissions, which is relatively resource-intensive and expensive. This study reports the primary reasons for HIV-related admission at a regional, urban hospital in Johannesburg, South Africa and estimates the associated lengths of stay and costs.

Methods and Findings

A retrospective cohort study of adult, medical admissions was conducted. Each admission was assigned a reason for admission and an outcome. The length of stay was calculated for all patients (N = 1,041) and for HIV-positive patients (n = 469), actual utilization and associated costs were also estimated. Just under half were known to be HIV-positive admissions. Deaths and transfers were proportionately higher amongst HIV-positive admissions compared to HIV-negative and unknown. The three most common reasons for admission were tuberculosis and other mycobacterial infections (18%, n = 187), cardiovascular disorders (12%, n = 127) and bacterial infections (12%, n = 121). The study sample utilized a total of 7,733 bed days of those, 55% (4,259/7,733) were for HIV-positive patients. The average cost per admission amongst confirmed HIV-positive patients, which was an average of 9.3 days in length, was $1,783 (United States Dollars).

Conclusions

Even in the era of large-scale antiretroviral treatment, inpatient facilities in South Africa shoulder a significant HIV burden. The majority of this burden is related to patients not on ART (298/469, 64%), and accounts for more than half of all inpatient resources. Reducing

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the costs of inpatient care is thus another important benefit of expanding access to ART, promoting earlier ART initiation, and achieving rates of ART retention and adherence.

Introduction

Although widespread access to antiretroviral therapy (ART) is commonly assumed to have reduced the need for HIV-related hospital inpatient care, there is little published evidence confirming this in low- and middle-income countries. In South Africa, where an estimated 6.3 million people are HIV-infected and more than 2.6 million are on ART [1], the national HIV treatment program places a significant burden on the public healthcare system. While most HIV care is provided on an outpatient basis at public primary health clinics, hospitals continue to treat serious HIV-related admissions but the current extent and cost of this is unknown. Compared to outpatient care, inpatient care is resource-intensive and expensive. It is thus important to describe the main reasons for HIV-related admissions and the associated costs.

Before the availability of public HIV treatment in South Africa, inpatient facilities saw an increasing number of HIV patients presenting with serious HIV-related complications and AIDS [2–5]. South Africa launched large-scale, public HIV treatment in 2004 through outpatient facilities, and most recent studies of the costs of HIV care in South Africa have been limited to outpatient services [6–9]. Studies estimating inpatient costs have typically included them as part of the overall cost of HIV treatment [10–16]. Only two have looked specifically at inpatient costs [17, 18], and both relied on data from the earliest years of the ART rollout. Similarly, only a few published studies have examined the share of overall inpatient resource utilization attributable to HIV since the advent of public sector ART in 2004 [17, 19, 20], and none have estimated this in more recent years. As a result, the current extent of HIV-related inpatient admissions and its associated cost in public sector hospitals is not known.

To provide current information to policy makers and program managers about the burden of HIV-related inpatient care in a setting of widespread ART access, this study reports the primary reasons for HIV-related admission at a regional, urban hospital in South Africa during 2010 by HIV and ART status and estimates the associated lengths of stay and costs. Data are drawn from medical records and hospital invoices, providing more detailed and accurate information than has been available thus far.

Methods

Study Population and Data

We conducted a retrospective cohort study of admissions at a regional, urban, public sector hospital in Johannesburg, South Africa. The hospital, with 11 inpatient medical wards and 347 beds, falls under the Gauteng Province Department of Health and serves a large urban catchment area that includes both formal and informal settlements.

The study population included all adult (≥18 years old) admissions that occurred at the medical admission wards between January 1 and August 31, 2010. This time period (mid summer to late winter) was selected to capture seasonal variation in inpatient medical admissions. Admissions into other specialist wards (e.g. gynecology) were excluded. We created a sampling frame from the medical admission ward registers, then drew a random 12% sample of admissions for analysis, with an aim of 10% and an additional 2% selected to compensate for anticipated missing files. Repeat admissions of the same individual patient were recorded as two separate admissions.

Data were collected from three sources, reflecting the hospital's record keeping system. Medical admission ward registers provided the date of admission, preliminary diagnosis, and final ward assignment. Patient demographic characteristics and all the care that the patient received during the admission were drawn from inpatient files. Finally, the electronic laboratory system was used to verify and update diagnostic tests done during the admission. Final data collection for a patient occurred at least 6 months after admission to ensure sufficient time for the admission to be completed and the patient file stored. Up to three attempts were made to locate missing inpatient admission files over a 3-month period. If the files could still not be located, the admissions were classified as missing. Missing or otherwise incomplete files were excluded.

Patient data were extracted from the inpatient files and entered directly into a CS Pro™ database. For patients known to be HIV-negative or of unknown HIV status, only demographic and basic admission data were extracted. For HIV-positive patients, we also extracted detailed resource usage data, including length of stay, drugs prescribed, intravenous fluids prescribed, diagnostics performed, and any other recorded procedures.

Outcomes and HIV Status

For each admission in the sample, we started by assigning a reason for admission, corresponding to the final discharge diagnosis. Final discharge diagnosis was extracted from the paper patient discharge summary. If the discharge summary was incomplete or missing then the patient medical notes were reviewed to see if a final discharge diagnosis was noted. In the absence of a clear discharge diagnosis the diagnosis was classified as "Unknown". Each admission was assigned one of four admission outcomes: transfer, unknown, died, discharged. Transfers were those patients sent to other facilities for additional treatment. Patients with unknown outcomes did not have a date of discharge, death, or transfer; their data is included in the baseline cohort description and analysis of reasons for admission but not in average length of stay or cost estimates. Deaths and discharges were as recorded in the inpatient record.

We then categorized each enrolled subject into one of three groups. '*HIV-positive*' contained known HIV-positive patients determined by a conclusive result in the inpatient file, the presence of HIV monitoring diagnostics, and/or ARV prescriptions. This categorization does not specify whether or not the reason for admission was HIV related, rather the status of the person being admitted. '*HIV-negative*' included patients with known HIV-negative status in their admission records. '*HIV unknown*' encompassed all other patients, including undiagnosed HIV-positive patients for whom HIV status was not recorded in the inpatient file. We report demographic characteristics and primary reason for admission, categorized by major disease area, by HIV status.

Resource Utilization and Costs

For inpatient care, a substantial portion of total admission cost is attributable not to variable resources, such as drugs, diagnostics, and procedures, but rather to the resources associated with the stay itself, often called the "hotel" costs and including the hospital infrastructure, general staffing, and so on. For each HIV status group and primary reason for admission, we first estimated and compared the mean length of stay and hotel cost associated with it, with 95% confidence intervals.

For HIV-positive patients, we also estimated actual utilization and associated costs for variable resources as well as hotel costs, and we report these admission costs by cost category with means and proportions. Costs were measured from the provider (hospital) perspective and included the cost of all resources from the date of admission of an HIV-positive patient to the

date of outcome (i.e. discharge, death, transfer out). A bottom up costing approach was used, including drugs, fluids, diagnostics, surgical procedures and hotel costs (including bed cost, support staff, and medical staff). Bed cost included equipment, space, shared staff, administration and overhead at the study site. Unit costs of drugs, diagnostics, lab charges, procedures, and other variable inputs were recorded from the most recent available invoices / price lists. All unit costs were in 2013 South African Rand (ZAR) or adjusted to 2013.

For medical staff costs, the complement of medical staff in the medical wards was estimated during the study period and 2013 government salary costs applied [21]. Since doctors do not spend all their time in the medical wards, we allocated 20%, 40% and 60% of specialist/consultant, registrar, and medical officer time to the medical wards, respectively. Nurses were assumed to spend all their time in the medical wards. Total personnel costs were then divided by the number of annual bed days to estimate the medical staff cost per day of medical admission.

Annual costs of inpatient care (including all hotel and standard care costs but excluding variable costs for condition-specific drugs, diagnostics, and procedures and medical staff costs) were taken from the hospital's annual accounts for the relevant year (2012–2013) and apportioned either by percentage of medical beds to overall hospital beds or by physical space in the medical wards to overall space in the hospital. Equipment in the medical wards was inventoried, unit costs applied, and an annual equivalent cost calculated using a working life of 8 years and a discount rate of 5%. For all other shared space, equipment was estimated at 20% of the cost of the space, the same percentage as in the medical ward. Space costs were estimated by obtaining minimum rental costs per square metre from the surrounding area at 2013 prices. The hotel, equipment, and space costs are reported together as fixed costs. The reported costs were converted from South African Rand (ZAR) to United States Dollar (USD) at the average exchange rate prevailing during 2013, which was 9.6:1 (ZAR:USD) [22]. Note that costs included may be paid by any combination of patient fees, government budgets, donor grants, and other sources of funding.

The study protocol was reviewed by the Institutional Review Boards of the University of Witwatersrand and Boston University, who approved the collection of the data without informed consent and the use of an anonymous analytic dataset.

Results

During the eight-month study period there were 10,801 admissions to the medical wards. A random sample of 1,343 (12%) was selected; 302 (2.8%) were then excluded because their files were missing or incomplete, leaving an analytic sample of 9.2% of all admissions. The excluded admissions were matched to the hospital death register and the electronic laboratory records and did not differ from the analytic sample, suggesting that the excluded admissions were not sicker or more likely to be HIV positive than those included. The remaining 1,041 constituted the analytic dataset, with just under half (45%, n = 469) of the sample having a confirmed HIV-positive diagnosis. (See S1 Fig)

The baseline characteristics of the sample are shown in Table 1. Just under half were known to be HIV-positive patients; the rest were HIV-negative (20%) or of unknown HIV status (35%). Almost two thirds (59%) of patients admitted were between 25–50 years of age; amongst HIV-positive patients more than four out of five (82%) were in this age range, consistent with national HIV prevalence by age group. Patients with unknown HIV status were substantially older than those with a known HIV status, suggesting that older patients are less likely to have been tested for HIV. For the HIV-positive patients with CD4 counts (n = 399/469), 36% were at very high risk for HIV-related illness (CD4 count < 50 cells/mm^3) and only 37% were recorded

Table 1. Baseline characteristics of admission cohort.

	Overall n = 1041		HIV status					
			Positive n = 469		Negative n = 206		Unknown n = 366	
Gender, n (%)								
Male	486	(46.7)	216	(46.1)	114	(55.3)	156	(42.6)
Female	555	(53.3)	253	(53.9)	92	(44.7)	210	(57.4)
Age, n (%)								
18–24	65	(6.2)	16	(3.4)	28	(13.6)	21	(5.7)
25–30	139	(13.4)	81	(17.3)	27	(13.1)	31	(8.5)
31–40	281	(27.0)	194	(41.4)	41	(19.9)	46	(12.6)
41–50	199	(19.1)	113	(24.1)	42	(20.4)	44	(12.0)
51–60	156	(15.0)	44	(9.4)	29	(14.1)	83	(22.7)
61–70	102	(9.8)	21	(4.5)	22	(10.7)	59	(16.1)
>70	99	(9.5)	0	0	17	(8.3)	82	(22.4)
Age, median (IQR)	42	(32, 56)	37	(32, 45)	42	(29, 55)	55	(39, 68)
Most recent* CD4 count (cells/mm^3), n (%)								
Missing	-	-	70	(14.9)	-	-	-	-
< = 50	-	-	142	(30.3)	-	-	-	-
51–100	-	-	63	(13.4)	-	-	-	-
101–200	-	-	79	(16.8)	-	-	-	-
201–350	-	-	65	(13.9)	-	-	-	-
>350	-	-	50	(10.7)	-	-	-	-
Most recent* CD4 count (cells/mm^3), median (IQR)	-	-	90	(30, 237)	-	-	-	-
ARV Status, n (%)								
Not on ARVs	870	(83.6)	298	(63.5)	206	(100.0)	366	(100.0)
On ARVs	171	(16.4)	171	(36.5)	-	-	-	-
Outcome, n (%)								
Discharged	876	(84.1)	368	(78.5)	188	(91.3)	320	(87.4)
Died	126	(12.1)	80	(17.1)	13	(6.3)	33	(9.0)
Transferred	13	(1.2)	11	(2.3)	-	-	2	(0.5)
Unknown	26	(2.5)	10	(2.1)	5	(2.4)	11	(3.0)

* Done during or within the 3 months prior to admission

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as being on treatment. The percentages of deaths (17%) and transfers (2%) were higher amongst HIV-positive admissions compared to HIV-negative (6% and 0%) and unknown (9% and 1%). Unknown outcomes were evenly distributed by HIV status.

Reason for admission

There were 326 unique reasons for admission, which were categorized into 25 major disease areas. (See Table A in S1 File.) The top 5 reasons for admission for each HIV status resulted in 9 unique reasons and accounted for more than 75% of all admissions. Fig 1 presents these results by reason for admission. (See Table B in S1 File)

The three most common reasons for admission were tuberculosis and other mycobacterial infections (18%, n = 187), cardiovascular disorders (12%, n = 127) and bacterial infections (12%, n = 121). The majority of tuberculosis (87%) and bacterial infections (65%) were found among HIV-positive patients, while the majority of cardiovascular disorders (57%) were

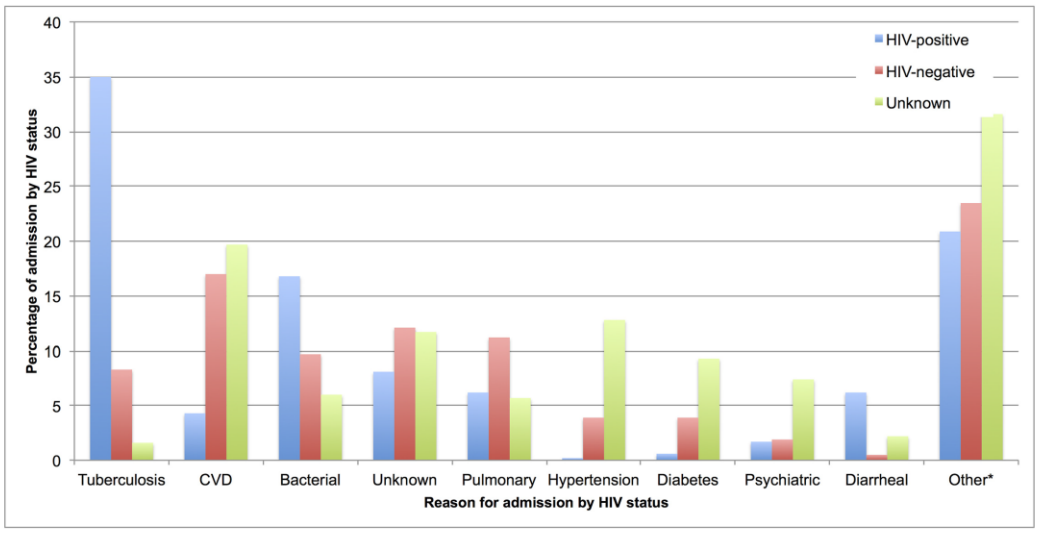

Fig 1. Summary of reasons for admission by HIV status. This figure presents the top 5 reasons for admission for each HIV status category. All other reasons were collapsed into the other category.* Tuberculosis was the most prevalent reason for admission amongst HIV-positive admissions accounting for 35%. CVD was the single most prevalent reason for admission amongst HIV-negative admissions accounting for 17%, while it only accounted for 4% of all HIV-positive admissions.

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reported amongst those with unknown HIV status. Pulmonary disease was proportionately almost double in the HIV status unknown patients, which may be explained by the higher median age of this group. Non-communicable diseases such as hypertension, diabetes, and psychiatric illness were much more common amongst those with an unknown HIV status compared to either HIV-positive or negative patients. The reason for admission for 10% (n = 106) of admissions was unknown. This was either because the information was missing from the patient record or the attending physician did not record a conclusive discharge diagnosis.

We also stratified reason for admission by ART status and baseline CD4 count for those with HIV. (See Table C in S1 File.) Although most (63%) HIV-positive admissions were not on ART, the 5 most common reasons for admission were the same regardless of treatment status, with the exception of bacterial infection, which comprised a smaller share of admissions among patients on ARVs (9.4%) than not (21.1%) (prevalence difference 11.7%; 95% CI 5%, 18%).

As Fig 2 indicates, the top 5 reasons for HIV-positive admissions all had a median CD4 count below 200 cells/mm^3, which was the threshold for ART initiation at the time of the study. As might be expected, TB and other mycobacterial infections, which account for a major portion of HIV-related inpatient admissions, become less frequent as baseline CD4 count rises. Nearly half (48%) of admissions among patients with CD4 counts < = 50 cells/mm^3 were attributable to TB and mycobacterial infections (51–100 cells/mm^3: 38%, 101–200 cells/mm^3: 34%, 201–350 cells/mm^3: 23%, >350 cells/mm^3: 14%).

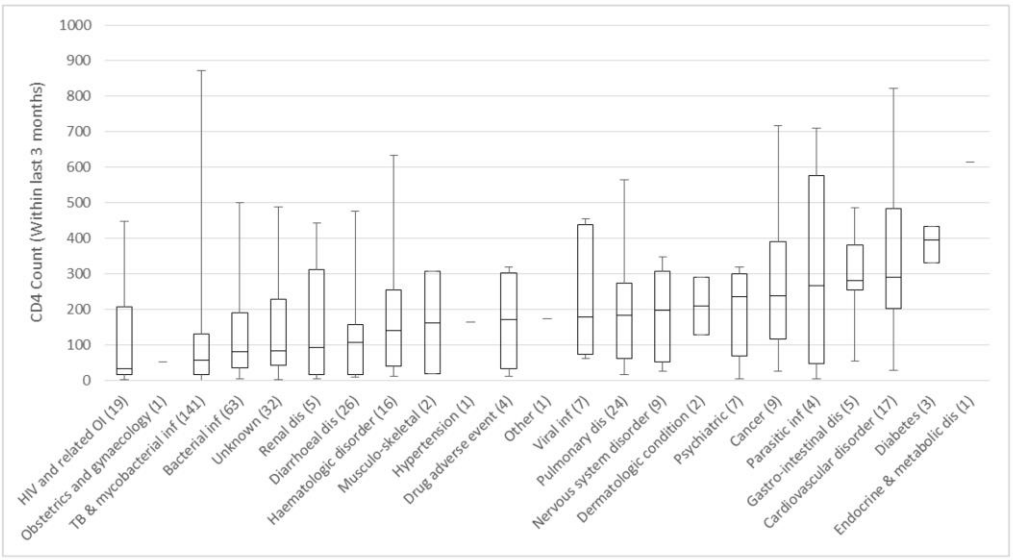

Fig 2. Box and whisker plot of CD4 count by reason for admission. The distribution of CD4 count at admission shows that all HIV positive admissions with one exception had a median CD4 count below 500 cells/mm^3. This suggests that boosting the CD4 count of HIV positive patients by starting treatment early and ensuring adherence while on treatment may reduce the frequency and severity of admission.

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Length of stay and distribution of bed days

Among all admissions with a known outcome (n = 1,015), the overall mean length of stay (95% CI) was 7.6 days (7.2, 8.0). The longest average length of stay was for HIV and related OIs at 13.2 days (8.9, 17.3). HIV-positive admissions had a longer average length of stay overall of 9.3 days, compared to 7.3 and 5.6 days for HIV-negative and HIV unknowns. Among HIV-positive patients, renal disease (18 days), gastro-intestinal disease (15 days), and drug adverse events (14 days) resulted in the longest average stays. For HIV-negative and HIV unknown admissions, cancer resulted in the longest average stay (23 and 10 days respectively). (Full details in Tables D and E in S1 File)

The admissions included in the study sample utilized a total of 7,733 bed days and the top 5 contributors to bed days by HIV status are included in Table 2. (Full details in Table F in S1 File) Of those, 55% (4,259/7,733) were for HIV-positive patients, 19% (1,469/7,733) were not related to HIV, and 26% (2,005/7,733) were for patients of unknown HIV status. TB and other mycobacterial infections accounted for the most (18%) bed days, driven largely by the HIV-positive admissions of which 36% were as a result of TB and other mycobacterial infections. Cardiovascular disease was the leading reason for bed day usage amongst HIV-negative and HIV unknown patients, accounting for 17% and 20% respectively.

Cost of HIV-positive admissions

Table 3 presents the top ten most expensive reasons for admission for the HIV-positive patients. (Full details in Table G in S1 File) The average cost per admission amongst confirmed HIV-

Table 2. Distribution of bed days by HIV status and reason for admission.

Reason for admission	Overall		HIV status					
Total bed days (%)			Positive		Negative		Unknown	
TB and other mycobacterial infections	1852	(18.3)	1617	(35.5)	201	(8.5)	34	(1.7)
Cardiovascular disorder	936	(12.5)	197	(4.4)	249	(17.4)	490	(20.3)
Bacterial infection	887	(11.9)	625	(17.2)	136	(10.0)	126	(6.2)
Unknown reason for admission	687	(8.0)	356	(6.3)	131	(10.0)	200	(9.0)
Pulmonary disease	480	(7.2)	207	(6.3)	151	(11.4)	122	(5.9)
Hypertension	273	(5.5)	1	(0.2)	47	(4.0)	225	(13.2)
Diabetes	253	(4.4)	27	(0.7)	46	(4.0)	180	(9.6)
Diarrheal disease	205	(3.7)	175	(6.3)	2	(0.5)	28	(2.3)
Psychiatric	180	(3.8)	57	(1.7)	28	(2.0)	95	(7.6)
Other*	1980	(24.5)	997	(21.4)	478	(32.3)	505	(24.2)
Total **	***7733***	***(100.0)***	***4259***	***(100.0)***	***1469***	***(100.0)***	***2005***	***(100.0)***

* Includes all other reasons which were not amongst the top 5 highest contributors towards total bed days.

** All admissions where the outcome is unknown are excluded, as they do not have a discharge date.

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positive patients, which was an average of 9.3 days in length, was $1,783. This resulted in an average cost per bed day of approximately $192, which is just slightly less than the patient day equivalent (PDE) cost reported for Gauteng Province hospitals of $225 [23]. The majority of the cost can be attributable to medical staff (42%) and fixed costs (35%). Laboratory and drugs costs accounted for only 11% and 3% respectively. Although 36% of all HIV-related admissions were reported to be on antiretrovirals, almost none were dispensed during the hospital admission, suggesting that either patients brought their ARVs with them or treatment was interrupted during the hospital stay.

Table 3. Cost for HIV-positive admissions (HIV-positive only), by cost category in United States Dollars (USD).

Reason for admission	N	All admissions (USD)		Mean per admission (USD)					
		Total	(%)	Fixed*	Medical staff	Lab	Drug & ARV	Fluid	Total
Renal disease	6	23,661	(2.9)	1,241	1,459	372	110	762	3,944
Drug adverse event	5	12,881	(1.6)	961	1,129	234	21	232	2,576
Endocrine and metabolic disease	1	2,472	(0.3)	905	1,063	363	140	1	2,472
HIV and related OI	21	51,141	(6.3)	918	1,079	218	83	137	2,435
Gastro-intestinal disease	5	11,972	(1.5)	1,030	1,211	132	20	2	2,394
Unknown reason for admission	29	68,150	(8.3)	652	766	219	69	198	2,350
Hematologic disorder	16	32,612	(4.0)	648	762	241	52	336	2,038
Parasitic infection	5	9,637	(1.2)	696	818	189	98	126	1,927
TB and other mycobacterial infections	163	313,318	(38.3)	686	806	198	66	165	1,922
Musculo-skeletal	2	3,761	(0.5)	800	941	93	44	3	1,880
Other	206	288,553	(35.3)	515	605	162	52	67	1,401
All	***459***	***818,156***	***(100.0)***	***632***	***743***	***188***	***61***	***134***	***1,783***

* Fixed costs include hotel, equipment and space costs.

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Renal disease generated the most expensive admission ($3,944 per admission, 17.8 days) driven by the length of stay, but this was relatively infrequent (6/459). TB and other mycobacterial infections are ranked ninth by average cost per admission but occurred much more frequently (163/459). As a result TB accounts for the largest portion of HIV-related admission costs, more than a third of the total.

Discussion

In a random sample of 1,041 inpatient admissions at a regional hospital in Johannesburg in 2010, nearly half (45%) were for patients known to be HIV-positive. These patients accounted for at least 55% of all resources utilized (bed days) by the sampled admissions. Since some proportion of the admissions for patients of unknown HIV status were bound to have been for HIV-positive patients, these figures represent the minimum burden placed on the hospital by HIV-positive patients during the time of the study. They are comparable to the results of a 2005 study of another Johannesburg hospital [17], suggesting that the burden of HIV on South African hospitals may not have changed substantially since the rollout of ART in 2004.

Only 36% of HIV-positive patients were reported to be on ART at the time of the admission, despite 71% being eligible for ART based on their CD4 count. A recent report [18] on an HIV-positive cohort in South Africa found that the majority (64%) of hospitalizations occurred prior to the initiation of ART, which may explain the findings of this paper. In our study, only 12% of HIV-positive admissions occurred when the CD4 count > 350 cells/mm^3. Earlier treatment initiation, at the higher CD4 count thresholds adopted by the South African Government in 2011 and again in 2015, may therefore substantially reduce the number of HIV-related admissions in future years.

In our sample, tuberculosis accounted for almost a fifth of all inpatient medical resources used. Given the low median CD4 count at admission, it is not surprising that tuberculosis and other similar infections were the leading reason for admission and death of HIV-positive patients causing one fourth of all HIV-related deaths. Similar results have been seen in other studies both in sub Saharan Africa prior to treatment availability [24–26] and in South Africa soon after treatment was made available [17–19]. Cardiovascular disease was the leading reason for admission amongst those who had a known HIV-negative or unknown status, who were also older than those with HIV. This profile is more typical of areas or countries where the population is not severely immune compromised. The UK reported ischemic heart disease as the third primary reason for admission after cancer and pneumonia [27]. The US reported congestive heart disease as the fourth primary reason for admission after live births, pneumonia and osteoarthritis [28].

Within the HIV-positive patients, reason for admission did not vary by ART status. The CD4 count profile for HIV-positive patients by treatment status was also similar, which could account for the similar admission profile and also could suggest that those on ART are recent initiates. Leisegang and colleagues followed HIV-positive patients both prior to and after ART initiation and showed that the highest inpatient costs occurred in the period immediately prior to, during and after ART initiation [15].

A number of papers have indicated that it is the non-curative costs (i.e. hotel costs, not drugs and diagnostics) which drive the cost of medical admissions, meaning that length of stay is an accurate proxy for cost of admission [17, 19]. Overall HIV-positive patients had longer average medical admissions compared to other patients and as a result could on average be expected to use more resources and cost more per admission than HIV-negative patients. Renal disease and cancer had the longest average medical admissions amongst the HIV-positive and negative patients, respectively.

The cost of HIV-related admissions to the South African healthcare system is not trivial, either in terms of the facility resources it takes from other potential patients nor in financial terms. Another recent study reported that for South African patients on ART, the hospitalization rate was 6.9 admissions per 100 patient years [18]. With over 2 million patients on ART in South Africa, this suggests that there are some 138,000 medical admissions in the country per year just for patients already on ART. We estimated an average cost of $1,783 per admission, bringing the annual cost of ART medical admissions to $246 million. With a year of ART estimated to cost approximately $404 [29], the annual funds spent on HIV inpatient admissions while on ART could pay for the annual cost of over 600,000 patients on ART, more than a quarter of the patients on treatment in 2013 [1].

If South African inpatient healthcare facilities are operating at capacity, then a high HIV inpatient burden may lead to the crowding out or displacement of patients with other conditions [26]. The Gauteng HIV prevalence in 2012 for adults (15–49 years old) was 17.8% [30], yet in our sample, HIV positive patients utilized 55% of inpatient resources. In other words, less than a fifth of the population consumed more than half of the available resources, creating a large excess burden of HIV on inpatient facilities. Diminishing this excess burden through earlier ART initiation and better medication adherence—high priorities of the South African government—may free up additional capacity and reduce the cost of treating HIV patients, adding further evidence of the importance of these goals.

Our study had a number of limitations. Other research has suggested that specialist wards may also experience a large HIV burden [31], but this study focused on medical ward admissions only. The retrospective nature of the study meant that we relied on routine hospital files and a number of these were missing or incomplete. In order to minimize the impact of this missing information alternative data sources (hospital death register, electronic laboratory records) were used to provide additional information on these patients. While we believe the length of stay to be accurate, the estimated costs are based on resource usage extracted from medical records, which may not report all resources utilized. Given that the majority of costs are driven by length of stay, missed variable resources are unlikely to have a major effect on results, however.

Conclusion

Even in the era of large-scale antiretroviral treatment rollout, we found that inpatient facilities in South Africa are still shouldering a significant HIV burden. We found that the majority of the burden of HIV inpatient care on hospitals is related to patients not on ART, and that this burden is large, accounting for more than half of all inpatient resources. Reducing the costs of inpatient care is thus another important benefit of expanding access to ART, promoting earlier ART initiation, and achieving rates of ART retention and adherence. Having regular reports on HIV-related hospital admissions would provide critical insight into the success of the national treatment program in reducing both HIV-related morbidity and healthcare costs.

Supporting Information

S1 Fig. Cohort enrolment. There were 10,801 medical admissions between January and August 2010. A sample of 10% was targeted with an additional 2% to account for missing or incomplete files. Of the 1,343 files selected 220 could not be found and an additional 82 could be identified but the admission of interest was missing or incomplete in the file. There were 1,041 admissions captured representing 9.6% of all admissions during the period. The majority of the admissions were confirmed as HIV-positive (466, 45%), while the rest were HIV-negative (206, 20%) and

those with an unknown HIV status (366, 35%).
(TIFF)

S1 File. Table A. Reason of admission by HIV status. Table B. Summary of reasons for admission by HIV status. Table C. Primary reason for admission by ART status, HIV-positive only. Table D. Length of stay (days) by reason of admission and HIV status. Table E. Summary length of stay (days) by HIV status and reason for admission. Table F. Distribution of bed days by reason of admission. Table G. Mean cost per admission (HIV-positive only), by cost category in USD.
(DOCX)

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Author Contributions

Conceived and designed the experiments: LCL SBR. Performed the experiments: LCL CS. Analyzed the data: LCL MPF SBR. Contributed reagents/materials/analysis tools: LCL MPF CS DE IS SBR. Wrote the paper: LCL MPF CS DE IS SBR. Technical and clinical oversight: DE IS.

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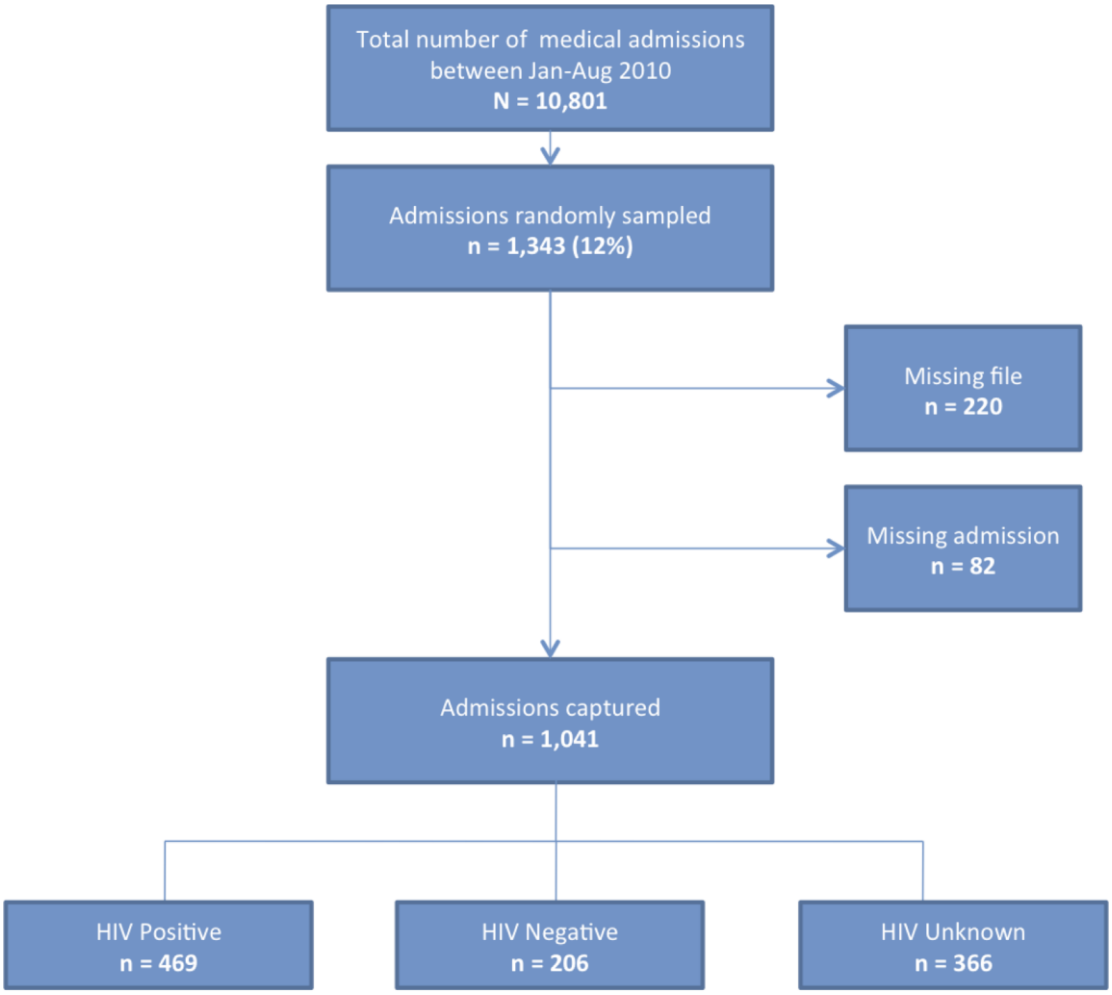
APPENDIX C2: Paper 3 – Supplementary material



Supplementary Figure 2. Cohort enrolment.

There were 10,801 medical admissions between January and August 2010. A sample of 10% was targeted with an additional 2% to account for missing or incomplete files. Of the 1,343 files selected 220 could not be found and an additional 82 could be identified but the admission of interest was missing or incomplete in the file. There were 1,041 admissions captured representing 9.6% of all admissions during the period. The majority of the admissions were confirmed as HIV-positive (466, 45%), while the rest were HIV-negative (206, 20%) and those with an unknown HIV status (366, 35%).

Supplementary Table 1. Reason of admission by HIV status.

Reason for admission n (%)	Overall		HIV status					
			Positive		Negative		Unknown	
TB and other mycobacterial infections*	187	(18.0)	164	(35.0)	17	(8.3)	6	(1.6)
Cardiovascular disorder*	127	(12.2)	20	(4.3)	35	(17.0)	72	(19.7)
Bacterial infection*	121	(11.6)	79	(16.8)	20	(9.7)	22	(6.0)
Unknown*	106	(10.2)	38	(8.1)	25	(12.1)	43	(11.7)
Pulmonary disease*	73	(7.0)	29	(6.2)	23	(11.2)	21	(5.7)
Hypertension*	56	(5.4)	1	(0.2)	8	(3.9)	47	(12.8)
Nervous system disorder	51	(4.9)	12	(2.6)	16	(7.8)	23	(6.3)
Diabetes*	45	(4.3)	3	(0.6)	8	(3.9)	34	(9.3)
Psychiatric*	39	(3.7)	8	(1.7)	4	(1.9)	27	(7.4)
Diarrheal disease*	38	(3.7)	29	(6.2)	1	(0.5)	8	(2.2)
Hematologic disorder	25	(2.4)	16	(3.4)	3	(1.5)	6	(1.6)
Renal disease	24	(2.3)	6	(1.3)	10	(4.9)	8	(2.2)
Viral infections	24	(2.3)	9	(1.9)	9	(4.4)	6	(1.6)
Gastro-intestinal disease	23	(2.2)	5	(1.1)	3	(1.5)	15	(4.1)
Drug adverse event	22	(2.1)	5	(1.1)	4	(1.9)	13	(3.6)
Cancer	21	(2.0)	10	(2.1)	5	(2.4)	6	(1.6)
HIV and related OI	21	(2.0)	21	(4.5)	0	0	0	0
Parasitic infection	12	(1.2)	5	(1.1)	5	(2.4)	2	(0.5)
Musculo-skeletal	9	(0.9)	2	(0.4)	5	(2.4)	2	(0.5)
Endocrine and metabolic disease	5	(0.5)	1	(0.2)	2	(1.0)	2	(0.5)
Dermatologic condition	4	(0.4)	2	(0.4)	2	(1.0)	0	0
Other	3	(0.3)	2	(0.4)	1	(0.5)	0	0
Trauma	3	(0.3)	0	0	0	0	3	(0.8)
Obstetrics and gynecology	2	(0.2)	2	(0.4)	0	0	0	0
Total	***1041***	***(100.0)***	***469***	***(100.0)***	***206***	***(100.0)***	***366***	***(100.0)***

* These were the top 5 unique reasons by HIV status and used in summary Supplementary Table 2

Supplementary Table 2. Summary of reasons for admission by HIV status.

Reason for admission n (%)	Overall		HIV status					
			Positive n = 469		Negative n = 206		Unknown n = 366	
TB and other mycobacterial infections	187	(18.0)	164	(35.0)	17	(8.3)	6	(1.6)
Cardiovascular disorder	127	(12.2)	20	(4.3)	35	(17.0)	72	(19.7)
Bacterial infection	121	(11.6)	79	(16.8)	20	(9.7)	22	(6.0)
Unknown	106	(10.2)	38	(8.1)	25	(12.1)	43	(11.7)
Pulmonary disease	73	(7.0)	29	(6.2)	23	(11.2)	21	(5.7)
Hypertension	56	(5.4)	1	(0.2)	8	(3.9)	47	(12.8)
Diabetes	45	(4.3)	3	(0.6)	8	(3.9)	34	(9.3)
Psychiatric	39	(3.7)	8	(1.7)	4	(1.9)	27	(7.4)
Diarrheal disease	38	(3.7)	29	(6.2)	1	(0.5)	8	(2.2)
Other*	249	(23.9)	98	(20.9)	86	(23.5)	65	(31.6)
Total	***1041***	***(100.0)***	***469***	***(100.0)***	***206***	***(100.0)***	***366***	***(100.0)***

* Includes all other reasons which were not the amongst the top 5 most frequent reasons for any HIV status group

Supplementary Table 3. Primary reason for admission by ART status, HIV-positive only.

Reason for admission	Overall		ARV status			
n (%)			Not on ARV		On ARV	
TB and other mycobacterial infections	164	(35.0)	103	(34.6)	61	(35.7)
Bacterial infection	79	(16.8)	63	(21.1)	16	(9.4)
Unknown	38	(8.1)	26	(8.7)	12	(7.0)
Diarrheal disease	29	(6.2)	17	(5.7)	12	(7.0)
Pulmonary disease	29	(6.2)	15	(5.0)	14	(8.2)
Other*	130	(27.7)	74	(24.8)	56	(32.7)
Total	**469**	**(100.0)**	**298**	**(100.0)**	**171**	**(100.0)**

* Includes all other reasons which were not the amongst the top 5 most frequent reasons

Supplementary Table 4. Length of stay (days) by reason of admission and HIV status.

Reason for admission n, mean	Overall		HIV status					
			Positive		Negative		Unknown	
HIV and related OI*	21	13.2	21	13.2	.	.	.	.
Cancer*	21	12.5	10	8.2	5	23.4	6	10.7
Renal disease*	24	11.3	6	17.8	10	10.0	8	8.0
Other*	3	10.3	2	9.0	1	13.0	.	.
TB and other mycobacterial infections*	186	10.0	163	9.9	17	11.8	6	5.7
Unknown	81	8.5	29	12.3	20	6.6	32	6.3
Viral infections*	24	8.2	9	8.2	9	10.3	6	4.8
Hematologic disorder	25	7.8	16	9.3	3	6.3	6	4.7
Cardiovascular disorder*	127	7.4	20	9.9	35	7.1	72	6.8
Bacterial infection	121	7.3	79	7.9	20	6.8	22	5.7
Gastro-intestinal disease*	23	7.3	5	14.8	3	4.0	15	5.4
Trauma*	3	7.0	.	.	.	.	3	7.0
Parasitic infection	12	6.9	5	10.0	5	4.2	2	6.0
Pulmonary disease	73	6.6	29	7.1	23	6.6	21	5.8
Dermatologic condition	4	5.8	2	9.5	2	2.0	.	.
Diabetes	45	5.6	3	9.0	8	5.8	34	5.3
Endocrine and metabolic disease*	5	5.6	1	13.0	2	4.5	2	3.0
Diarrheal disease	38	5.4	29	6.0	1	2.0	8	3.5
Nervous system disorder*	51	5.4	12	3.3	16	3.8	23	7.5
Drug adverse event*	22	5.0	5	13.8	4	4.5	13	1.8
Hypertension	56	4.9	1	1.0	8	5.9	47	4.8
Psychiatric	39	4.6	8	7.1	4	7.0	27	3.5
Musculo-skeletal	9	4.2	2	11.5	5	2.2	2	2.0
Obstetrics and gynecology	2	1.0	2	1.0	.	.	.	.
Total	***1015***	***7.6***	***459***	***9.3***	***201***	***7.3***	***355***	***5.6***

* These were the top 5 unique reasons by HIV status and used in summary Supplementary Table 5

Supplementary Table 5. Summary length of stay (days) by HIV status and reason for admission.

Reason	Overall				Positive		Negative		Difference (Neg-Pos)			Unknown	
	N	Mean	95% CI		N	Mean	N	Mean	Mean	95% CI		N	Mean
HIV and related OI	21	13.2	(8.9,	17.3)	21	13.2	-	-	-	-	-	-	-
Cancer	21	12.5	(7.4,	17.6)	10	8.2	5	23.4	15	(-1.7,	32.1)	6	10.7
Renal disease	24	11.3	(8.2,	14.3)	6	17.8	10	10.0	-7.8	(19.9,	2.2)	8	8.0
TB and other mycobacterial infections	186	10.0	(8.8,	11.0)	163	9.9	17	11.8	1.9	(-2.5,	6.4)	6	5.7
Viral infections	24	8.2	(5.6,	10.7)	9	8.2	9	10.3	2.1	(-5.8,	10.1)	6	4.8
Cardiovascular disorder	127	7.4	(6.4,	8.3)	20	9.9	35	7.1	-2.7	(-7.3,	1.9)	72	6.8
Gastro-intestinal disease	23	7.3	(4.2,	10.2)	5	14.8	3	4.0	-10.8	(-32.5,	10.9)	15	5.4
Trauma	3	7.0	(5.1,	19.1)	-	-	-	-	-	-	-	3	7.0
Endocrine and metabolic disease	5	5.6	(1.0,	10.1)	1	13.0	2	4.5	-8.5	(-63.5,	46.5)	2	3.0
Nervous system disorder	51	5.4	(4.1,	6.5)	12	3.3	16	3.8	0.4	(-2.1,	3.1)	23	7.5
Drug adverse event	22	5.0	(2.7,	7.3)	5	13.8	4	4.5	-9.3	(-19.5,	0.9)	13	1.8
Other*	508	6.6	(6.0,	7.0)	207	8.3	100	6.1	-2.1	(-3.9,	-0.3)	201	5.1
Total*	***1015***	***7.6***	***(7.2,***	***8.0)***	***459***	***9.3***	***201***	***7.3***				***355***	***5.6***

* Includes all other reasons which were not the amongst the top 5 most frequent reasons

** All admissions where the outcome is unknown are excluded, as they do not have a discharge date

Supplementary Table 6. Distribution of bed days by reason for admission.

Reason for admission Total bed days (%)	Overall		HIV status					
			Positive		Negative		Unknown	
TB and other mycobacterial infections*	1852	(18.3)	1617	(35.5)	201	(8.5)	34	(1.7)
Cardiovascular disorder*	936	(12.5)	197	(4.4)	249	(17.4)	490	(20.3)
Bacterial infection*	887	(11.9)	625	(17.2)	136	(10.0)	126	(6.2)
Unknown*	687	(8.0)	356	(6.3)	131	(10.0)	200	(9.0)
Pulmonary disease*	480	(7.2)	207	(6.3)	151	(11.4)	122	(5.9)
HIV and related OI	277	(2.1)	277	(4.6)	0	0	0	0
Nervous system disorder	273	(5.0)	40	(2.6)	61	(8.0)	172	(6.5)
Hypertension*	273	(5.5)	1	(0.2)	47	(4.0)	225	(13.2)
Renal disease	271	(2.4)	107	(1.3)	100	(5.0)	64	(2.3)
Cancer	263	(2.1)	82	(2.2)	117	(2.5)	64	(1.7)
Diabetes*	253	(4.4)	27	(0.7)	46	(4.0)	180	(9.6)
Diarrheal disease*	205	(3.7)	175	(6.3)	2	(0.5)	28	(2.3)
Viral infections	196	(2.4)	74	(2.0)	93	(4.5)	29	(1.7)
Hematologic disorder	196	(2.5)	149	(3.5)	19	(1.5)	28	(1.7)
Psychiatric*	180	(3.8)	57	(1.7)	28	(2.0)	95	(7.6)
Gastro-intestinal disease	167	(2.3)	74	(1.1)	12	(1.5)	81	(4.2)
Drug adverse event	111	(2.2)	69	(1.1)	18	(2.0)	24	(3.7)
Parasitic infection	83	(1.2)	50	(1.1)	21	(2.5)	12	(0.6)
Musculo-skeletal	38	(0.9)	23	(0.4)	11	(2.5)	4	(0.6)
Other	31	(0.3)	18	(0.4)	13	(0.5)	0	0
Endocrine and metabolic disease	28	(0.5)	13	(0.2)	9	(1.0)	6	(0.6)
Dermatologic condition	23	(0.4)	19	(0.4)	4	(1.0)	0	0
Trauma	21	(0.3)	0	0	0	0	21	(0.8)
Obstetrics and gynecology	2	(0.2)	2	(0.4)	0	0	0	0
Total	***7733***	***(100.0)***	***4259***	***(100.0)***	***1469***	***(100.0)***	***2005***	***(100.0)***

* These were the top 5 unique reasons by HIV status and used in summary Supplementary Table 5

Supplementary Table 7. Mean cost per admission (HIV-positive only) , by cost category in USD.

Reason for Admission	N	Total	Fixed	Event	Lab	Drug+ ARV	Fluid
Renal disease	6	3,944	1,241	1,459	372	110	762
Drug adverse event	5	2,576	961	1,129	234	21	232
Endocrine and metabolic disease	1	2,472	905	1,063	363	140	1
HIV and related OI	21	2,435	918	1,079	218	83	137
Gastro-intestinal disease	5	2,394	1,030	1,211	132	20	2
Unknown	29	2,350	652	766	219	69	198
Hematologic disorder	16	2,038	648	762	241	52	336
Parasitic infection	5	1,927	696	818	189	98	126
TB and other mycobacterial infections	163	1,922	686	806	198	66	165
Musculo-skeletal	2	1,880	800	941	93	44	3
Other	2	1,807	626	736	196	59	189
Cardiovascular disorder	20	1,784	686	806	223	32	37
Viral infections	9	1,783	572	673	167	120	250
Cancer	10	1,621	571	671	176	63	140
Diabetes	3	1,586	626	736	174	40	9
Dermatologic condition	2	1,580	661	777	137	4	1
Bacterial infection	79	1,470	551	647	147	71	53
Psychiatric	8	1,413	496	583	212	15	107
Pulmonary disease	29	1,355	497	584	173	52	49
Diarrheal disease	29	1,151	420	494	147	21	69
Nervous system disorder	12	683	232	273	118	23	37
Hypertension	1	282	70	82	131	0	-
Obstetrics and gynecology	2	280	70	82	125	3	1
All	***459***	***1,783***	***632***	***743***	***188***	***61***	***134***

APPENDIX D: Paper 4 – Submitted format

Long LC, Evans DH, Rosen SB, Sauls C, Brennan A, Sanne IM, Fox M. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. ***Submitted to JIAS.*** *Under review.*

Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV

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Abstract

Introduction: South Africa has one the largest HIV treatment programs, which should be associated with an increase in life expectancy and a reduction in HIV-related mortality. There are a number of discrepancies between the various reported South African HIV-related mortality estimates. A complementary approach to monitoring changes in HIV-related mortality may be to use inpatient care records to examine trends in causes of death and HIV status over time. We investigated the natural mortality experienced in the medical ward of a hospital during 2010 to estimate the contribution of HIV to mortality.

Methods: We conducted a cross-sectional study of inpatient mortality at a regional, hospital in Johannesburg, South Africa. The study population included all adult deaths due to natural causes amongst medical ward inpatients. Cause of death was recorded from the mortuary register. HIV status was ascertained directly from the mortuary register or from laboratory tests specific for HIV diagnosis or monitoring. Resource utilization and cost were based on length of stay in hospital and a reported patient day equivalent cost.

Results: 1,167 inpatient deaths were included in the study, the majority of which were HIV positive (58%). HIV prevalence amongst the males (55%) was slightly lower than that amongst the females (61%) and HIV positive patients were younger (40 years old) than those HIV negative (56 yo) and of unknown HIV status (68 yo). "Infections and parasites" was the most common cause of natural deaths (29%). On average HIV positive patients were admitted for slightly longer (10.5 days) than HIV negative (9.6 days) and HIV status unknown (8.9 days), yet HIV positive inpatient deaths accounted for the majority (62%) of the total bed days. The mean cost per admission was USD 1,976 (95% CI: USD 1,877–USD 2,096).

Conclusions: Even with widespread access to ART, the majority of inpatient natural deaths at a large public sector hospital in 2010 were among HIV positive patients and were likely related to HIV. In view of the importance of accurate data on causes of death, both for HIV

30 interventions and to track other diseases, large-scale expansion of this approach over a
31 longer period is needed.
32
33 **Word Limit: 350 words (349 excluding headings currently)**

Introduction

South Africa has a large generalized HIV epidemic, with over 6 million HIV positive citizens, and one the world's largest HIV treatment programs, with an estimated 2.6 million patients on treatment [1]. Key indicators used to measure the success of this program include an increase in life expectancy and a reduction in HIV-related mortality for antiretroviral therapy (ART) patients. Tracking changes in the contribution of HIV to overall mortality over time is thus an important component of evaluating the national HIV treatment program.

Mortality reporting in South Africa is managed by the Department of Home Affairs and governed by the Births and Deaths Registration Act 1992 (Act No 51 of 1992) [2]. In 2013 Statistics South Africa (StatsSA) reported that 90% of all deaths were due to natural causes and 44% of all deaths occurred in hospitals [3]. In 2011 they reported the percentage of mortality attributable to HIV to be 3.4% and showed this percentage increasing between 2011 and 2013 [3]. This is in contrast to the results of the Thembisa model, an integrated demographic and epidemiologic model of the South African HIV/AIDS epidemic, which shows a decreasing percentage of deaths attributable to AIDS since 2005 with the introduction of antiretroviral treatment [4]. Thembisa estimates that in 2011 there were 169,000 AIDS deaths, which would put the percentage of mortality attributable to HIV to be almost 10 times that estimated in the StatsSA report (169,000/514,480=32%) [3, 4]. Bradshaw and colleagues estimated that fewer than 10% (20,012/207,685) of deaths due to HIV/AIDS in 2010 were registered with HIV as the primary cause of death [5], which supports the discrepancy between the results of StatsSA and modeled estimates. The inconsistency between Deaths Registry data, as reported by StatsSA; modeling estimates of HIV-attributable mortality; and analyses of the registration data suggests that other sources of information are needed to understand the role of HIV in mortality as ART access expands [6].

Data on the contribution of HIV to total mortality from other sources than the Deaths Registry are scarce. The majority of mortality with a known place of death occurs within

hospitals. In 2010 and 2013, 52% and 57% of mortality with a known place of death occurred in hospitals, respectively [3, 7]. A complementary approach to monitoring changes in HIV-related mortality may be to use the relatively detailed information available from inpatient care records to examine trends in causes of death and HIV status over time. We investigated the natural mortality experienced in the medical ward of a large, urban, public sector hospital during 2010 to estimate the contribution of HIV to mortality.

Methods

Study Population and Data

We conducted a retrospective, cross-sectional study of inpatient mortality at a regional, Gauteng Province Department of Health hospital in Johannesburg, South Africa. The hospital serves an urban population of both formal and informal settlements and has 11 inpatient medical wards with 347 beds.

The study population included all adult (≥18 years old) deaths due to natural causes (attributed to illness or an internal malfunction of the body) amongst patients admitted to a medical ward between January 1 and August 31, 2010, an 8-month period intended to capture seasonal variation. Deaths from other (non-natural) causes (e.g. motor vehicle accident) or which occurred during admission to specialist wards (e.g. casualty, surgery) were excluded. Inpatient deaths, which were missing the data required to determine study eligibility, such as date of admission, were excluded. Deaths among pregnant women were also excluded because pregnant women requiring admission were routinely referred to another hospital.

Cause of Death and HIV Status

All persons who die in hospital are taken to the hospital mortuary where the details of death are recorded in the mortuary register. This register includes date of death, gender, age, date of admission, hospital ward, and primary cause of death. In some instances, additional information about co-morbid conditions potentially related to the cause of death

is also recorded. South Africa classifies and codes deaths according to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [7, 8]. We assigned a three character ICD-10 code to each primary cause of death. If the cause of death was classified as code R00-R99 ("symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified"), other co-morbid conditions were examined and if available coded as the primary cause of death. Patients whose final primary cause of death is classified as signs or symptoms (R00-R99), heart failure, unspecified renal failure or malignant neoplasms of ill-defined sites are often not reported on individually and classified as 'ill defined' causes of death. We include these deaths and report these codes to allow for full comparison with other publications.

HIV status was determined independently of the listed cause of death and co-morbid conditions. Patients were classified as HIV-positive if a positive HIV status was noted in the mortuary register or if laboratory test results specific for HIV diagnosis or monitoring (e.g. HIV test, CD4 count, or viral load test) could be retrieved from National Health Laboratory Services (NHLS) records. Patients were classified as HIV-negative if a negative HIV test was recorded in the mortuary register, during the current admission or in the month prior to admission. Patients for whom HIV status could not be definitively determined (i.e. no positive HIV test, no HIV monitoring tests, no negative HIV test during the admission or within the month prior to admission) were classified as having an unknown HIV status.

Resource Utilization and Costs

To estimate resource utilization and cost of care, we first captured length of stay (date of admission to date of death), an accepted proxy for inpatient resource usage. The total bed day utilization (sum of all admission lengths) by patients in the data set was divided by the total available at the facility (number of beds x number of days in the follow up period) to estimate the burden of HIV-related deaths on facility capacity. We then used the published patient day equivalent (PDE) cost to translate the length of stay and total bed days into an average cost per admission and total cost by cause of death. The patient day equivalent (PDE) cost for hospitalization in Gauteng for 2013/2014 was ZAR 2,164 (South African

Rand) [9]. This was converted into United States dollars (USD) using the average 2014 USD:ZAR weekly exchange rate of 10.84.

The study received ethical approval from the Institutional Review Boards of the University of Witwatersrand and Boston University.

Results

Baseline description

Baseline characteristics of the study population are presented in Table 1. Over the 8-month period 1,201 natural inpatient deaths met study inclusion criteria. Of these, 34 had a missing admission date and were excluded. The final analytic cohort included 1,167 inpatient deaths, an average of 145 deaths per month. The majority of inpatient deaths were HIV positive (n=682, 58%), less than a third had an unknown HIV status (n=343, 29%) and just over a tenth were confirmed HIV negative (n=142, 12%).

Table 1. Baseline characteristics of inpatient mortality

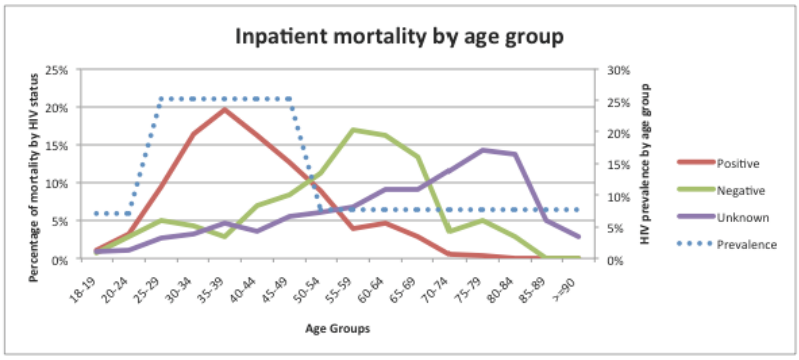
	Overall N=1,167		HIV status					
			Positive n=682		Negative n=142		Unknown n=343	
Gender, n (%)								
Male	595	(51.0)	331	(48.5)	99	(69.7)	165	(48.1)
Female	571	(48.9)	350	(51.3)	43	(30.3)	178	(51.9)
Missing	1	(0.1)	1	(0.1)	0	0	0	0
Age in years, n (%)								
18-19	11	(0.9)	7	(1.0)	1	(0.7)	3	(0.9)
20-24	30	(2.6)	22	(3.2)	4	(2.8)	4	(1.2)
25-29	81	(6.9)	65	(9.5)	7	(4.9)	9	(2.6)
30-34	129	(11.1)	112	(16.4)	6	(4.2)	11	(3.2)
35-39	154	(13.2)	134	(19.6)	4	(2.8)	16	(4.7)
40-44	133	(11.4)	111	(16.3)	10	(7.0)	12	(3.5)
45-49	117	(10.0)	86	(12.6)	12	(8.5)	19	(5.5)
50-54	98	(8.4)	61	(8.9)	16	(11.3)	21	(6.1)
55-59	74	(6.3)	27	(4.0)	24	(16.9)	23	(6.7)
60-64	86	(7.4)	32	(4.7)	23	(16.2)	31	(9.0)
65-69	69	(5.9)	19	(2.8)	19	(13.4)	31	(9.0)
70-74	49	(4.2)	4	(0.6)	5	(3.5)	40	(11.7)
75-79	58	(5.0)	2	(0.3)	7	(4.9)	49	(14.3)
80-84	51	(4.4)	0	0	4	(2.8)	47	(13.7)
85-89	17	(1.5)	0	0	0	0	17	(5.0)
>=90	10	(0.9)	0	0	0	0	10	(2.9)
Age, median (IQR)	46	(36, 62)	39.5	(33, 48)	56	(46, 64)	68	(53, 79)
Length of stay in days, n (%)								
1	103	(8.8)	48	(7.0)	11	(7.7)	44	(12.8)
2-5	452	(38.7)	254	(37.2)	66	(46.5)	132	(38.5)
6-10	240	(20.6)	159	(23.3)	20	(14.1)	61	(17.8)
11-15	133	(11.4)	75	(11.0)	13	(9.2)	45	(13.1)
>=16	239	(20.5)	146	(21.4)	32	(22.5)	61	(17.8)
Length of stay, mean (95% CI)	9.9	(9.4-10.5)	10.5	(9.8-11.3)	9.6	(8.1-11.1)	8.9	(8.1-9.6)

Month of death, n (%)								
January	92	(7.9)	53	(7.8)	16	(17.4)	23	(6.7)
February	119	(10.2)	79	(11.6)	20	(16.8)	20	(5.8)
March	142	(12.2)	94	(13.8)	16	(11.3)	32	(9.3)
April	168	(14.4)	105	(15.4)	25	(14.9)	38	(11.1)
May	147	(12.6)	102	(15.0)	21	(14.3)	24	(7.0)
June	145	(12.4)	94	(13.8)	26	(17.9)	25	(7.3)
July	183	(15.7)	77	(11.3)	10	(5.5)	96	(28.0)
August	171	(14.7)	78	(11.4)	8	(4.7)	85	(24.8)

There were a similar number of males and females in the sample, but the HIV prevalence amongst the males (55%, 331/595) was slightly lower than that amongst the females (61%, 350/571), which reflects what is seen in the general population. The median (inter-quartile range) age of the cohort was 46 (36-62) years, with HIV positive patients younger (40, IQR: 33-48) than those HIV negative (56, IQR: 46-64) and of unknown HIV status (68, IQR: 53-79).

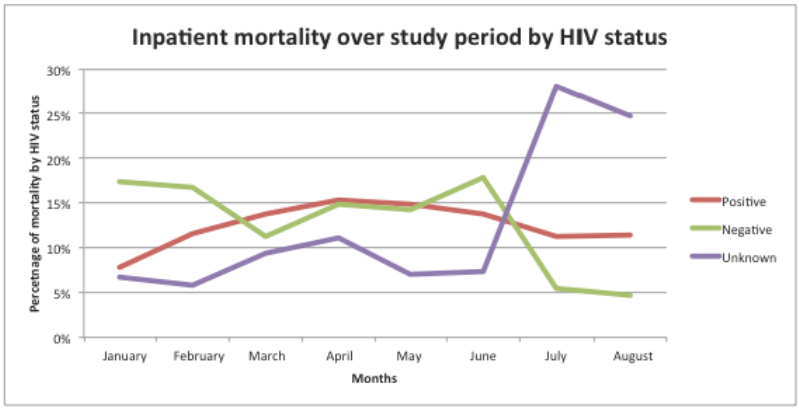
Figure 1 plots inpatient mortality by age group as well as national HIV prevalence estimates by age group [10]. Mortality occurred at much younger ages in HIV-positive patients than in those of negative or unknown status, as illustrated in Figure 1. The percentage of subjects with a confirmed HIV status (HIV-positive + HIV-negative / Total patients) fell rapidly by age group, with 89% of 18-49 year-olds having a confirmed status and only 24% of those who are 65 years and older. In other words, patients of unknown HIV status were older. Similarly, known HIV prevalence (confirmed HIV-positive /total patients) in the cohort fell from 82% amongst 18-49 year-olds to 10% amongst those who are 65 years and older.

Figure 1. Inpatient mortality by HIV status and age group



Patients who have compromised immune systems (such as those with HIV and the elderly) may be more likely to be admitted and die during months when infectious diseases like influenza are more prevalent. To explore this, mortality is plotted by calendar month of death and HIV status in Figure 2. The peak of the annual severe acute respiratory illness (influenza) infections in 2010 occurred in July and August [11], coincident with the peak of mortality in the HIV unknown group (elderly). Mortality due to influenza, acute lower respiratory infections and chronic respiratory infections showed raised rates during the months of July and August (Data not presented). Mortality in the HIV negative and HIV positive groups, in contrast, showed no clear seasonal patterns.

Figure 2. Inpatient mortality by calendar month of death



Description of causes of death

Table 2 describes the major causes of death using ICD-10 code chapters by HIV status as well as the top 3 specific causes of death by ICD 10 block for each HIV status group. "Infections and parasites" was the most common cause of natural deaths (29%), followed by "Respiratory" (21%) and "Circulatory" (17%) conditions. HIV positive patients accounted for nearly 9 out of every 10 deaths related to infections and parasites (294/334), despite comprising just 58% of all deaths.

Table 2: Cause of death by HIV status. The top 3 specific causes of death (ICD10 blocks) for each HIV status group are shown as subsets of the chapters they form part of and are shown in *italics*. The top 3 specific causes of death for each HIV status group are marked with an asterisk.

Cause of death (ICD10 chapter / block) n (%)	Overall N=1,167		HIV status: Positive n=682		HIV status: Negative n=142		HIV status: Positive n=343	
Infections & parasites (I: A00-B99)	334	(28.6)	294	(43.1)	9	(6.3)	31	(9.0)
Tuberculosis (A15-A19)	*224*	*(19.2)*	*204*	*(29.9)**	*4*	*(2.82)*	*16*	*(4.7)*
Respiratory (X: J00-J99)	241	(20.7)	132	(19.4)	28	(19.7)	81	(23.6)
Influenza and pneumonia (J09-J18)	*97*	*(8.3)*	*67*	*(9.8)**	*7*	*(4.9)*	*23*	*(6.7)*
Other acute lower respiratory tract infections (J20-J22)	*80*	*(6.9)*	*44*	*(5.0)**	*9*	*(6.3)**	*27*	*(7.9)**
Chronic lower respiratory diseases (J40-J47)	*42*	*(3.6)*	*9*	*(1.3)*	*7*	*(4.9)*	*26*	*(7.6)**
Circulatory (IX: I00-I99)	202	(17.3)	40	(5.9)	45	(31.7)	117	(34.1)
Other forms of heart disease (I30-I52)	*112*	*(9.6)*	*19*	*(2.8)*	*25*	*(17.6)**	*68*	*(19.9)**
Cerebrovascular diseases (I60-I69)	*39*	*(3.3)*	*6*	*(0.9)*	*7*	*(4.9)*	*26*	*(7.6)**
Signs & symptoms (XVIII: R00-R99)	77	(6.6)	30	(4.4)	15	(10.6)	32	(9.3)
Nervous system (VI: G00-G99)	61	(5.2)	45	(6.6)	7	(4.9)	9	(2.6)
Genitourinary system (XIV: N00-N99)	55	(4.7)	33	(4.8)	11	(7.7)	11	(3.2)
Renal failure (N17-N19)	*53*	*(4.5)*	*32*	*(4.7)*	*10*	*(7.0)**	*11*	*(3.2)*
Endocrine, nutritional & metabolic (IV: E00-E99)	55	(4.7)	23	(3.4)	10	(7.0)	22	(6.4)
Hematological & immune mechanism (III: D50-D89)	48	(4.1)	40	(5.9)	2	(1.4)	6	(1.7)
Neoplasms (II: C00-D48)	42	(3.6)	16	(2.3)	8	(5.6)	18	(5.2)
Digestive system (XI: K00-K93)	34	(2.9)	20	(2.9)	5	(3.5)	9	(2.6)
Mental & behavioral (V: F00-F99)	11	(0.9)	5	(0.7)	2	(1.4)	4	(1.2)
Skin and subcutaneous tissue (XII: L00-L99)	4	(0.3)	2	(0.3)	0	(0.0)	2	(0.6)
Congenital & chromosomal (XVII: Q00-Q99)	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.3)
Factors influencing health status (XXI: Z00-Z99)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)
Musculoskeletal & connective tissue (XIII: M00-M99)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)
Total	***1167***	***(100.0)***	***682***	***(100.0)***	***142***	***(100.0)***	***343***	***(100.0)***

*Top 3 specific causes of death in that HIV category

Despite infections and parasites accounting for 43% of deaths among HIV-positive patients, only one patient had HIV listed as the primary cause of death. The most common infectious disease across all groups was tuberculosis, responsible for 19% of deaths overall and nearly a third (30%) of deaths amongst HIV positive patients. Heart disease, in contrast, was the leading cause of death amongst HIV negative (18%) and unknown patients (20%). Further details on cause of death by age group are reported in Table 3.

199 **Table 3.** Specific cause of death by broad age category

Cause of death (based on ICD-10 block)	18-49 n = 655 HIV+ = 82%			50-64 n = 258 HIV+ = 47%			65+ n = 254 HIV+ = 10%		
	Rank	n	%	Rank	n	%	Rank	n	%
Tuberculosis (A15-A19)*	1	191	29%	1	29	11%			
Influenza and pneumonia (J09-J18)	2	54	8%	3	25	10%	4	18	7%
Human immunodeficiency virus disease (B20-B24)									
Intestinal infectious diseases (A00-A09)	6	29	4%	7	11	4%			
Other viral diseases (B25-B34)									
Certain disorders involving the immune mechanism (D80-D89)									
Other forms of heart disease (I30-I52)	7	26	4%	1	29	11%	1	57	22%
Inflammatory diseases of the central nervous system (G00-G09)	5	32	5%						
Other acute lower respiratory infections (J20-J22)	3	51	8%	7	11	4%	4	18	7%
Aplastic and other anaemias (D60-D64)	4	34	5%						
Cerebrovascular diseases (I60-I69)	11	10	2%	9	10	4%	3	19	7%
Diabetes mellitus (E10-E14)				10	9	3%	8	11	4%
Hypertensive diseases (I10-I15)				5	15	6%	6	14	6%
Chronic lower respiratory diseases (J40-J47)				4	18	7%	2	22	9%
Ischaemic heart diseases (I20-I25)									
Malignant neoplasm of digestive organs (C15-C26)									
Renal failure (N17-N19)	7	26	4%	5	15	6%	7	12	5%
Protozoal diseases (B50-B64)	9	23	4%						
Metabolic disorders (E70-E90)	10	17	3%				10	6	2%
Abnormal findings on examination of blood, without diagnosis (R70-R79)							9	8	3%
Other natural causes		162	25%		86	33%		69	27%
All natural causes		***655***	***100%***		***258***	***100%***		***254***	***100%***

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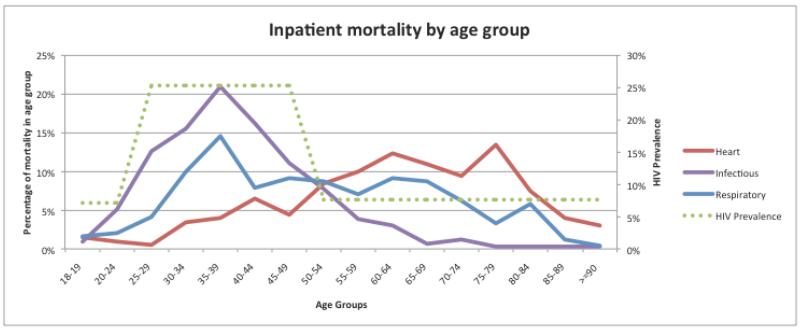
Figure 3. Heart disease compared to infectious disease by age group



In Figure 3, distribution of mortality by major cause is illustrated across age g revealing a distinct pattern of mortality by age and cause, which would be expect population with a high HIV prevalence. Infectious diseases follow the same m profile as that of the HIV positive group shown in Figure 1, with the peak in the mort the younger age groups. Bradshaw et al dub this type of characteristic age s mortality profile the 'AIDS signature' [5]. Diseases of the circulatory system, which directly related to HIV, show steadily increasing mortality with increasing age. Resp disease appears more evenly spread among HIV positives, HIV negatives, and thos unknown HIV status (Figure 3).

Bed days and cost of admissions

On average, patients in the sample were admitted for 9.9 days prior to death. HIV p patients were admitted for slightly longer (mean 10.5 days, 95% confidence interv 11.3 days) than HIV negative (9.6, 95% CI: 8.1-11.1) and HIV status unknown (8.9, 9 8.1-9.6) patients. However, because HIV positive inpatient deaths were more comm positive inpatient deaths accounted for the majority (62%) of the bed days associated with inpatient deaths (Total HIV-positive bed days / Total bed days), cor to HIV negative and HIV status unknown inpatient deaths (12% and 26% respectivel

"Infections and parasites," which accounted for the majority of deaths, had a mean length of stay in HIV positive patients that was almost double (11.2, 95% CI: 9.97 -12.33) that of the negatives (5.9, 95% CI: 2.28 - 9.50) and unknowns (6.9, 95% CI: 4.51-9.29). Overall the disease categories "infections and parasites" (31%), "respiratory" (16%) and "cardiovascular" (13%) accounted for more than half (60%) of all the bed days associated with inpatient deaths.

Applying a bed day equivalent cost of USD 200 (ZAR 2,164), the mean cost per admission was USD 1,976 (95% CI: USD 1,877 – USD 2,096).

Discussion

In 2010 South Africa's national ART program was 5 years old, and more than 1.2 million people were estimated to be on ART. This equated to ART coverage of over 60% at the prevailing eligibility threshold of a CD4 count <200 cells/ul [12]. Despite relatively high levels of access to care, however, the results of this study suggest that HIV-positive inpatient medical mortality remained high in 2010, accounting for at least 58% of all deaths during the 8-month study period.

The role of HIV in inpatient mortality in 2010 can be compared to results of a similar study at the same study site covering the years just preceding the national rollout of ART in South Africa (2000-2003) [13]. That study examined all 2,138 inpatient deaths occurring over three months of each year over a four-year period. A large majority (94%) were natural-cause deaths, and most (75%) were from the medical wards, making them comparable to the sample in our study. The numbers of deaths per month and the gender and age distribution were similar between the two studies. The proportion of patients known to be HIV positive more than doubled from 20% in 2000-2003 to 58% in 2010. This is likely due in part to poor ascertainment of HIV status prior to 2004, but the large increase in HIV positives could also suggest a real increase in the proportion of HIV positive deaths over this time period.

Statistics South Africa (StatsSA) reported that there were 28,660 natural deaths in the City of Johannesburg Metropolitan Municipality in 2010 [7]. Our sample of 1,167 thus covers 4% (1,167/28,660) of the natural deaths in Johannesburg that year [7] (Appendix Table A.3). The StatsSA report also notes that in Gauteng Province, where Johannesburg is located, HIV disease [ICD10 B20-B24] was the 7th leading cause of natural death, accounting for 3.4% of all natural deaths. This is equivalent to only 15% of the 21,548 deaths classified as "Infections and parasites (A00 – B99)" [3]. Our study, in contrast, found that 88% of all deaths classified as "Infections and parasites (A00 – B99)" were among HIV positive patients. If we very conservatively assume that only those HIV positive deaths classified as "Infections & parasites" can be directly attributed to HIV (that is, we assume that 56% of deaths among HIV positive patients are not caused by HIV), then 25% of all natural deaths in our study would be directly attributable to HIV, a seven-fold increase over the StatsSA estimate for the province. While deaths due to HIV may be over-represented in hospital admissions compared to the population at large the largest contributor to this difference is likely the under reporting of HIV as a cause of death, even when the HIV status of patients is known.

StatsSA reported that in 2010 44% of all deaths occurred in hospitals, which translates into approximately 91,381 AIDS deaths in hospitals [5, 7]. The mean hospital cost associated with an inpatient related death was USD 1,976 in our cohort, therefore these deaths equate to a cost of approximately USD 180 million. While it is impossible to remove inpatient AIDS deaths completely it is reasonable to assume that this can be reduced substantially with earlier ART initiation and better treatment adherence. If the cost of ART for a year costs USD 358 [14] then for every inpatient AIDS death averted a patient could receive just over 5.5 years of treatment.

Limitations

Our study had several limitations. As noted above, the mortality reported here accounts for only 4% of natural cause mortality in the City of Johannesburg Metropolitan Municipality in 2010. When compared with national mortality statistics, however, the distribution by

major causes of death is similar, which suggests that the findings have relevance beyond a single site. Of more concerns is that only 70% of the sample had a verified HIV status, and older patients were more likely to be of unknown HIV status. The mortality attributed to HIV here should thus be regarded as a lower boundary on true HIV-related mortality, as it is likely that at least a few patients of unknown status were in fact HIV-positive. Finally, while every attempt was made to match methods for assigning cause of death to those used by Statistics South Africa and we believe that the chance of misclassification is low, it is possible that patients may have been assigned the wrong cause of death.

Conclusions

In conclusion, we found that even with widespread access to ART, the majority of inpatient natural deaths at a large public sector hospital in 2010 were among HIV positive patients and were likely related to HIV. Our results provide support to the contention that HIV related mortality is dramatically under-reported [5, 6] in national statistics. A solution to this problem may be the introduction of an electronic mortuary register would allow for rapid, real time identification of any trends observed in the mortality of patients, both HIV positive and negative. In view of the importance of accurate data on causes of death, both for HIV interventions and to track other diseases, research on this or other solutions is needed.

Competing interests

The authors declare that they have no competing interest.

Acknowledgements

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Disclaimer: The author's views expressed in this publication do not necessarily reflect the views of the United States Agency for International Development or the United States Government.

Authors' contributions

L.L. was the principal investigator and was primarily responsible for designing and coordinating the study, preparing and cleaning the analytic dataset and analyzing the data. M.F., D.E. and A.B. provided assistance with statistical analysis and supervision. C.S. assisted with coordinating field study activities, data collection and data cleaning. S.R. contributed to the original design of the study, provided assistance with the costing component and provided supervision. I.S. provided supervision and support on the clinical aspects of the analysis. L.L. did the analysis and prepared the first draft of the manuscript. All authors reviewed and approved the final draft of the manuscript.

List of abbreviations

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CI	confidence interval
HIV	human immunodeficiency syndrome
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	interquartile range
PDE	patient day equivalent
StatsSA	Statistics South Africa
yo	years old

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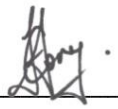
APPENDIX E: Student declaration for published papers

As per the University of Witwatersrand requirements for dissertations that include published work a student declaration is included.

Student Declaration – Lawrence Long

Declaration: Student's contribution to articles

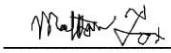
I, **Lawrence Camdon Long**, student number 0601332H, declare that this Thesis is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis.

Signature of Student 

Lawrence Long

Date 7 November 2016

Name of Primary Supervisor Professor Matthew Fox

Signature of Primary Supervisor 

Matthew Fox

Date 7 November 2016

APPENDIX F: Co-author declaration for published papers

As per the University of Witwatersrand requirements for dissertations that include published work a declaration from each co-author is included.

The co-authors for the publications include (in alphabetical order):

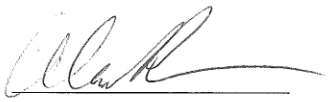
Alana Brennan
Denise Evans
Matthew Fox
Imogen Jaffray
Shakes Modi
Faith Moyo
Buyiswa Ndibongo
Sydney Rosen
Ian Sanne

Co-author Declaration - Alana Brennan

Co-authors agreement for the use of published articles

By signing this declaration, the co-author listed below agrees to the use of the article by the student, Lawrence Long, as part of his Thesis.

Co-author name: Alana Brennan

Co-author signature: 

Alana Brennan

Co-authored articles:

1. Long L, **Brennan A**, Fox MP, Ndibongo B, Jaffray I, Sanne I, Rosen S. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med. 2011;8(7):e1001055.

2. Long LC, Rosen SB, **Brennan A**, Moyo F, Sauls C, Evans D, Modi SL, Sanne I, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

3. Long LC, Evans DH, Rosen SB, Sauls C, **Brennan A**, Sanne IM, Fox M. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. *Under review.*

Co-author Declaration - Denise Evans

Co-authors agreement for the use of published articles

By signing this declaration, the co-author listed below agrees to the use of the article by the student, Lawrence Long, as part of his Thesis.

Co-author name: Denise Evans

Co-author signature: 

Denise Evans

Co-authored articles:

1. Long LC, Fox MP, Sauls C, **Evans D**, Sanne I, Rosen SB. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. PLoS One. 2016;11(2):e0148546.

2. Long LC, Rosen SB, Brennan A, Moyo F, Sauls C, **Evans D**, Modi SL, Sanne I, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

3. Long LC, **Evans DH**, Rosen SB, Sauls C, Brennan A, Sanne IM, Fox M. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. *Under review.*

Co-author Declaration - Matthew Fox

Co-authors agreement for the use of published articles

By signing this declaration, the co-author listed below agrees to the use of the article by the student, Lawrence Long, as part of his Thesis.

Co-author name: Matthew Fox

Co-author signature: _____

Matthew Fox

Co-authored articles:

1. Long L, Brennan A, **Fox MP**, Ndibongo B, Jaffray I, Sanne I, Rosen S. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med. 2011;8(7):e1001055.

2. Long LC, **Fox MP**, Sauls C, Evans D, Sanne I, Rosen SB. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. PLoS One. 2016;11(2):e0148546.

3. Long LC, Rosen SB, Brennan A, Moyo F, Sauls C, Evans D, Modi SL, Sanne I, **Fox MP**. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

4. Long LC, Evans DH, Rosen SB, Sauls C, Brennan A, Sanne IM, **Fox M**. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. *Under review.*

Co-author Declaration - Imogen Jaffray

Co-authors agreement for the use of published articles

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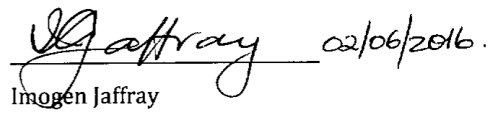
Co-author signature:  02/06/2016.

Imogen Jaffray

Co-authored articles:

1. Long L, Brennan A, Fox MP, Ndibongo B, **Jaffray I**, Sanne I, Rosen S. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med. 2011;8(7):e1001055.

Co-author Declaration - Shakes Modi

Co-authors agreement for the use of published articles

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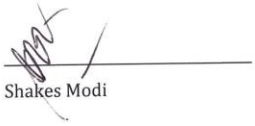
Co-author name: Shakes Modi

Co-author signature: 

Shakes Modi

Co-authored articles:

1. Long LC, Rosen SB, Brennan A, Moyo F, Sauls C, Evans D, **Modi SL**, Sanne I, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

Co-author Declaration - Faith Moyo

Co-authors agreement for the use of published articles

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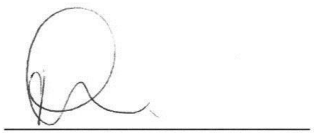
Co-author name: Faith Moyo

Co-author signature: 

Faith Moyo

Co-authored articles:

1. Long LC, Rosen SB, Brennan A, **Moyo F**, Sauls C, Evans D, Modi SL, Sanne I, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

Co-author Declaration - Buyiswa Ndibongo

Co-authors agreement for the use of published articles

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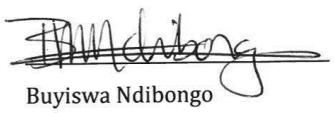
Co-author name: Buyiswa Ndibongo

Co-author signature: 

Buyiswa Ndibongo

Co-authored articles:

1. Long L, Brennan A, Fox MP, **Ndibongo B**, Jaffray I, Sanne I, Rosen S. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med. 2011;8(7):e1001055.

Co-author Declaration - Sydney Rosen

Co-authors agreement for the use of published articles

By signing this declaration, the co-author listed below agrees to the use of the article by the student, Lawrence Long, as part of his Thesis.

Co-author name: Sydney Rosen

Co-author signature: 

Sydney Rosen

Co-authored articles:

1. Long L, Brennan A, Fox MP, Ndibongo B, Jaffray I, Sanne I, **Rosen S**. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med. 2011;8(7):e1001055.

2. Long LC, Fox MP, Sauls C, Evans D, Sanne I, **Rosen S**. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. PLoS One. 2016;11(2):e0148546.

3. Long LC, **Rosen S**, Brennan A, Moyo F, Sauls C, Evans D, Modi SL, Sanne I, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

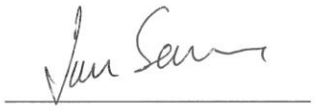
4. Long LC, Evans DH, **Rosen S**, Sauls C, Brennan A, Sanne IM, Fox M. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. *Under review.*

Co-author Declaration - Ian Sanne

Co-authors agreement for the use of published articles

By signing this declaration, the co-author listed below agrees to the use of the article by the student, Lawrence Long, as part of his Thesis.

Co-author name: Ian Sanne

Co-author signature: 

Ian Sanne

Co-authored articles:

1. Long L, Brennan A, Fox MP, Ndibongo B, Jaffray I, **Sanne I**, Rosen S. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med. 2011;8(7):e1001055.

2. Long LC, Fox MP, Sauls C, Evans D, **Sanne I**, Rosen SB. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. PLoS One. 2016;11(2):e0148546.

3. Long LC, Rosen SB, Brennan A, Moyo F, Sauls C, Evans D, Modi SL, **Sanne I**, Fox MP. Treatment outcomes and costs of providing antiretroviral therapy at a primary health clinic versus a hospital-based HIV clinic in South Africa. *Under review.*

4. Long LC, Evans DH, Rosen SB, Sauls C, Brennan A, **Sanne IM**, Fox M. Inpatient mortality profile at an urban hospital in South Africa: The burden of HIV. *Under review.*

APPENDIX G: Ethical clearance

The work presented in this thesis is the product of three independent study protocols, each of which received its own ethics approval. This was necessary because the study populations, study designs and objectives were different and could not be incorporated into a single study protocol. Two studies deal specifically with the outpatient component (Chapters 7 and 8, Papers 1 and 2 respectively) and one study deals with the inpatient component (Chapters 9 and 10, Papers 3 and 4 respectively).

Primary ethics approval was sought from the Human Research Ethics Committee (Medical) of the University of Witwatersrand, Johannesburg, South Africa. The ethical clearance certificate numbers for the respective papers are listed below:

Paper 1:	M10221
Paper 2:	M120541
Paper 3:	M101011
Paper 4:	M101011

Secondary ethics approval was also sought by co-authors at their respective academic institutions if required.

Paper 1 – Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Professor Sydney Rosen

CLEARANCE CERTIFICATE	**M10221**
PROJECT	A Retrospective Cost-Effectiveness analysis of Antiretroviral Treatment Maintenance Using a Down Referral Model for HIV/AIDS in SA
INVESTIGATORS	Professor Sydney Rosen.
DEPARTMENT	HERO/Centre for Global Health andDevelopment
DATE CONSIDERED	26/02/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 26/02/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Paper 2 – Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Prof S Rosen/Mr L Long

CLEARANCE CERTIFICATE	**M120541**
PROJECT	Retrospective Cost-Effectiveness Analysis of Nurse-Initiated and Management Antiretroviral Treatment for HIV/AIDS in South Africa
INVESTIGATORS	Prof S Rosen/Mr L Long.
DEPARTMENT	Health Economic & Epidemiology
DATE CONSIDERED	25/05/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 01/10/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the

Paper 3 and 4 – Ethics Approval

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)

Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

29 July 2012

Mr Lawrence Long
Deputy Division Head
Health Economic &
Epidemiology Research Office
Themba Lethu Clinic
Helen Joseph Hospital
University

Sent by e-mail: llong@heroza.org

Dear Mr Long

RE: Protocol M101011: "Analysis of the cost of HIV-Related Inpatient Care Using Un-linked Retrospective Data"
Protocol amendment

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has reviewed and approved the following amendments on the abovementioned protocol as detailed in your letter dated 13 June 2012:

- Use of output for PhD
- Extension of follow-up period and increase in sample size

Thank you for keeping us informed and updated.

Yours sincerely,

Anisa Keshav
Secretary
Human Research Ethics Committee (Medical)

APPENDIX H: Originality report

As per the University of Witwatersrand requirements this thesis (excluding journal articles) has been submitted to Turnitin. Proof of submission to Turnitin, a copy of the report cover page and approval from the supervisors is included.

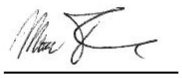
SUPERVISORS APPROVAL OF TURNITIN REPORT

Student Name:	LAWRENCE CAMDON LONG
Student Number:	0601332H
Title of paper:	The impact of a large scale treatment program on HIV treatment delivery in a resource limited setting

We have reviewed the Turnitin originality report (see attached) and approve the thesis for submission for external evaluation.

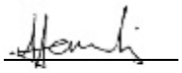
Supervisor 1

Supervisor Name: MATTHEW FOX

Supervisor Signature: 

Supervisor 2

Supervisor Name: DENISE EVANS

Supervisor Signature: 

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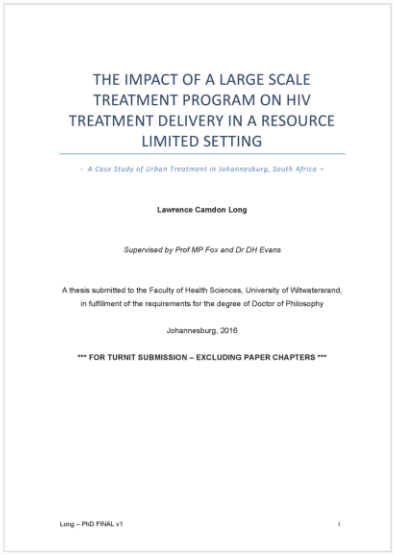

THE IMPACT OF A LARGE SCALE TREATMENT PROGRAM ON HIV TREATMENT DELIVERY IN A RESOURCE LIMITED SETTING

– A Case Study of Urban Treatment in Johannesburg, South Africa –

Lawrence Camdon Long

Supervised by Prof MP Fox and Dr DH Evans

A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, in fulfillment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 2016

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APPENDIX I: Literature review summaries

The articles included in the Literature Review (Section 1) for inpatient and outpatient treatment are listed and described in Supplementary Tables 8 and 9, respectively.

Supplementary Table 8. Inpatient literature review summary.

Number	Title	Authors	Year Published	Comparator	Population			Sites		Outcome	Cost perspective & Year
					Included, n	Year	Data time period	Type	Num. study sites		
INPX_1	HIV infection among woman admitted to the gynecology service of a district hospital in South Africa	Wilkinson D, Wilkinson NF, Connolly C	1999	HIV status	Adult women, gynecology ward; 196	1997	3 mo	District, Rural	1	Mortality	No cost
INPX_2	The costs and perceived quality of care for people living with HIV/AIDS in the Western Cape Province in South Africa	Govender V, McIntyre D, Grimwood A, Maartens G	2000	None	Adult, HIV positive; 350	1999-2000	Not specified	Primary & Secondary, Urban	6	No outcome	Provider & Patient, 2000
INPX_3	HIV/AIDS: Impact on maternal mortality at the Johannesburg Hospital, South Africa, 1995-2001	Kruger AM, Bhagwanjee S	2003	HIV status	Adult women, maternal deaths; 55	1996 & 2001	18 mo	Tertiary, Urban	1	Mortality	No cost
INPX_4	Impact of HIV on admissions and deaths in a tuberculosis hospital - recommendations for admission and discharge criteria	Thanassi Q, Post F, Bekker L, Maartens G	2003	HIV status	Adult, TB hospital admission; 4724	1998-2001	4 yrs	Specialist - TB, Urban	1	Mortality	No cost
INPX_5	Cost of inpatient care for HIV positive patients at Red Cross Children's Hospital, Cape Town	Yengopal V, Naidoo S	2004	HIV status	Pediatric admissions; 154	2001	2 mo	Tertiary, Urban	1	Mortality	Provider, 2001
INPX_6	Tuberculosis at Chris Hani Baragwaneth Hospital: numbers of patients diagnosed and outcomes of referrals to district hospitals	Edginton M, Wong M, Mahlaba D, Hodkison H	2005	HIV status	Adult and pediatric, TB admissions; 1291	2001	8 wks	Tertiary, Urban	1	Mortality, not by HIV status	No cost
INPX_7	Trends in adult medical admissions in a rural South African hospital between 1991 and 2002	Reid A, Dedicoat M, Lalloo D, Gilks C	2005	Time periods	Adult, medical ward admissions; 1907	1991-2002	2 mo per yr	District, Rural	1	Mortality	No cost
INPX_8	The impact of HIV on the profile of paediatric admissions and deaths at Pelonomi Hospital, Bloemfontein, South Africa	van Deventer JD, Carter CL, Schoeman CJ, Joubert G	2005	Time periods	Paediatric, HIV positive admissions; 4087	1991 & 2001	24 mo	Regional, Urban	1	Mortality	No cost
INPX_9	Cost-effectiveness of HAART Therapy in South Africa	Badri M, Maartens G,	2006	Treatment status	Adult, HIV positive	1995-2000	Not specified	Tertiary, Urban	Multiple - not	Life years gained	Provider, 2004

		Mandalia S, Bekker L, Penrod JR, Platt R, Wood R, Beck E			admissions; 1630				specifie d		
INPX_10	The cost effectiveness of antiretroviral treatment in Khayelitsha, South Africa - a primary data analysis	Cleary S, McIntyre D, Boulle A	2006	Treatment status	Adult, HIV positive admissions; 61	2002	0.6 yrs pre ART 1.03 yrs ART	Tertiary, secondary, district, Urban	3	Mortality - modeled	No cost
INPX_11	Deaths at Red Cross Children's Hospital, Cape Town 1999-2003 - a study of death notification forms	Grandin W, Westwood T, Lagerdien K, King M	2006	Age group, Year of admission	Pediatric deaths; 1978	1999-2003	5 yrs	Tertiary, Urban	1	Mortality	No cost
INPX_12	Prevalence of HIV status and CD4 counts in a surgical cohort: their relationship to clinical outcome	Cacala S, Mafana E, Thomson S, Smith A	2006	HIV status	Adult, surgical admissions; 350	Not specif ied	6 wks	Not specified, Not specified	1	Mortality	No cost
INPX_13	Healthcare utilization of patients accessing an African national treatment program	Harling G, Orrel C, Wood R	2007	Treatment status	Adult, HIV positive on treatment; 212	2005	48 wks	Tertiary, secondary, specialist, Urban	Multiple - not specifie d	No outcome	No cost
INPX_14	Evolving cost of antiretroviral care in South Africa	Harling G	2007	None	Adult, HIV positive admissions; 211	2002-2004	max 112 wks on tx	Outpatient clinic, Urban	1	No outcome	Provider, 2004
INPX_15	Comparative costs of inpatient care for HIV-infected and uninfected children and adults in Soweto, South Africa	Thomas L, Manning A, Holmes C, Naidoo S, van der Linde F, Gray G, Martinson N	2007	HIV status	Adult and pediatric, medical ward admissions; 1091	2005	1.5 mo	Tertiary, Urban	1	Mortality	Provider, 2005
INPX_16	Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study	Martinson N, Karstaedt A, Venter W, Omar T, King P, Mbengo T, Marais E, McIntyre J, Chaisson R,	2007	HIV status	Adult, TB deaths; 50	2003-2005	16 mo	Tertiary & low care, medium term specialist, Urban	2	Mortality	No cost

		Hale M									
INPX_17	High rates of HIV in surgical patients in Soweto, South Africa: impact on resource utilization and recommendations for HIV testing	Martinson N, Omar T, Gray G, Vermaak J, Badicel M, Degiannis E, Steyn J, McIntyre J, Smith M	2007	HIV status	Adult, surgical admissions; 1000	2003-2004	9 mo	Tertiary, Urban	1	Mortality, Additional surgery	No cost
INPX_18	Children with Human Immunodeficiency Virus infection admitted to a pediatric intensive care unit in South Africa	Rabie H, de Boer A, van den Bos S, Cotton MF, Kling S, Goussard P.	2007	HIV status	Pediatric, ICU admissions; 465	2003	12 mo	Tertiary, Urban	1	Mortality	No cost
INPX_19	HIV-associated maternal mortality - primary causes of death at King Edward VIII Hospital, Durban	Ramogale M, Moodley J, Sebitloane M	2007	HIV status	Adult, maternal deaths; 378	1998-2004	7 yrs	Tertiary, Urban	1	No outcome	No cost
INPX_20	Adverse drug reactions in adult medical inpatient in a South African hospital serving a community with a high HIV/AIDS prevalence	Mehta U, Durrheim D, Blockman M, Kredo T, Gounden R, Barnes K	2008	Adverse drug reaction status	Adult, medical admissions; 665	2005	3 mo	Secondary, Urban	1	Mortality, ADR	No cost
INPX_21	Quality of cause of death certification at an academic hospital in Cape Town, South Africa	Nojilana B, Groenewald P, Bradshaw D, Reagon G	2009	None	Adult, deaths; 983	2004	12 mo	Tertiary, Urban	1	None	No cost
INPX_22	Early severe morbidity and resource utilization in South African adults on antiretroviral therapy	Smith de Cherif T, Schoeman JH, Cleary S, Meintjes GA, Rebe K, Maartens G	2009	Treatment status	Adult, HIV positive admissions; 106	2004	9 mo	Secondary, Urban	1	Mortality	Provider, 2003
INPX_23	Clinical and financial burdens of secondary level care in a public sector antiretroviral roll-out setting (G F Jooste Hospital)	Kevany S, Meinthies G, Rebe K, Maartens G, Cleary S	2009	Outpatients	Adult, HIV positive admissions; 25	2005	1 mo	Secondary, Urban	1	Mortality	Provider, 2005

INPX_24	Early and later direct costs in a southern African antiretroviral treatment programme: A retrospective cohort analysis	Leisegang R, Cleary S, Hislop M, Davidse A, Regensburg L, Little F, Maartens G	2009	None	Adults, HIV positive private patients; 10735	1998-2007	9 yrs	All levels - private, Mixed	Multiple - not specified	No outcome	Provider, 2007
INPX_25	The clinical spectrum and cost implications of hospitalized HIV-infected children at Karl Bremer Hospital, Cape Town, South Africa	Schoeman CS, Pather MK,	2009	HIV status	Pediatric, admissions; 46	2001	6 mo	District, Urban	1	Mortality, Discharge, Transfer	Provider, 2001
INPX_26	Postmortem findings in HIV/AIDS patients in a tertiary care hospital in rural South Africa	Garcia-Jardon M, Bhat VG, Blanco-Blanco E, Stepian A.	2010	None	HIV positive deaths, age not stated; 86	2000-2008	n/a	Tertiary, Rural	1	No outcome	No cost
INPX_27	Acute hospitalization needs of adults admitted to public facilities in Cape Town Metro district	de Vries E, Raubenheimer P, Kies B, Burch V	2011	None	Adult, medical admissions; 767	2008	4 mo	All levels, Urban	11	No outcome	No cost
INPX_28	High prevalence of comorbidity and need for up-referral among inpatient at a district-level hospital with specialist tuberculosis services in South Africa - the need for specialist support	van der Plas H, Mendelson M	2011	Drug sensitive vs. drug resistant	Adult, admissions; 244	2008	4 days	Specialist - TB, Urban	1	No outcome	No cost
INPX_29	Cost and resource use of patients on antiretroviral therapy in urban and semi urban public sectors of South Africa	Meyer-Rath G, Miners A, Santos A, Variava E, Venter W	2012	Other site	Adult, HIV positive on treatment admissions; 38	2008	15 mo	Tertiary & Secondary, Mixed	2	No outcome	Provider, 2011
INPX_30	Comparison of in-hospital morbidity and mortality in HIV-infected and uninfected children after surgery	Karpelowsky J, Millar A, van der Graaf N, Bogerijen G, Zar H	2012	HIV status	Pediatric, surgical admissions; 327	2004-2008	48 mo	Tertiary, Urban	1	Mortality	No cost
INPX_31	Changes in pediatric HIV-related hospital admissions and	Meyers T, Dramowski	2012	HIV status	Pediatric, medical	1996-2011	Varied	Tertiary, Urban	1	Mortality	No cost

	mortality in Soweto, South Africa 1996-2011: light at the end of the tunnel?	A, Schneider H, Gardiner N, Kuhn L, Moore D			admissions; 3063						
INPX_32	Twelve-month outcomes of patients admitted to the acute general medical service at Groote Schuur Hospital	Stuart-Clark H, Vorajee N, Zuma S, van Niekerk L, Burch V, Raubenheimer P, Peter J	2012	Mortality	Adult, medical admissions; 415	2009	9 wks	Tertiary, Urban	1	Mortality	No cost
INPX_33	Operationalizing early antiretroviral therapy in HIV-infected in-patients with opportunistic infections including tuberculosis	Sunpath H, Edwin C, Chelin N, Nadesan S, Maharaj R, Moosa Y, Smeaton L, Court R, Knight S, Gwyther E, Murphy R	2012	Treatment status	Adult, HIV positive with OI; 382	2006 -2007	10 mo	Secondary, Not specified	1	Mortality, VL suppression	No cost
INPX_34	Causes of death on antiretroviral therapy: A post mortem study from South Africa	Wong E, Omar T, Setlhako G, Osih R, Feldman C, Murdoch D, Martinson N, Bangsberg D, Venter W	2012	AIDS stages	Adult, HIV positive deaths; 39	2009	12 mo	Tertiary, Urban	1	No outcome	No cost
INPX_35	Rates and cost of hospitalization before and after initiation of antiretroviral therapy in urban and rural settings in South Africa	Meyer-Rath G, Brennan A, Fox M, Modisenyane T, Tshabangu N, Mohapi L, Rosen S, Martinson N	2013	Treatment status	Adult, HIV positive admissions; 3906	2003-2010	7 yr 4 mo	Tertiary & District, Mixed	2	No outcome	Provider, 2009
INPX_36	Complications of antiretroviral therapy initiation in hospitalized	van der Pla H, Meintjies	2013	None	Adult, HIV positive initiating	2009-2011	24 mo	Specialist - TB, Urban	1	Mortality, Morbidity	No cost

	patients with HIV-associated tuberculosis	G, Schutz C, Goliath R, Myer L, Baatjie D, Wilkinson R, Maartens G, Mendelson M			TB treatment; 112						
INPX_37	HIV-related medical admissions to a South African district hospital remain frequent despite effective antiretroviral therapy scale up	Meintjies G, Kerkhoff A, Burton R, Schutz C, Boulle A, Van Wyk G, Blumenthal L, Nicol M, Lawn S	2015	Treatment status	Adult, HIV positive medical admissions; 609	2012-2013	15 mo	District, Urban	1	Mortality	No cost
INPX_38	TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and metanalysis	Ford N, Matteelli A, Schubber Z, Hermans S, Meintjies G, B Grinszteijn, Waldrop G, Kranser K, Doherty M, Getahun H	2016	None	Adult and pediatric, HIV positive TB admissions; 38637	2015	1 mo	All levels, Mixed	Multiple - not specified	Mortality	No cost

Supplementary Table 9. Outpatient literature review summary.

Number	Title	Authors	Year Published	Intervention	Comparator	Population		Sites	Follow-up	Outcomes	Cost perspective & Year
						Included, n	Data time period	Number & Location (Urban/Rural)			
Outpx_1	Implementing antiretroviral therapy in rural communities: The Lusikisiki model of decentralized HIV/AIDS care	Bedelu M, Ford N, Hilderbrand K, Reuter H	2007	Nurse initiation and management at PHC	Doctor initiation and management at HIV clinic	ART initiates, age not specified. N = 1,025	2004-2006	12, Rural	12 mo	Retention Mortality Lost to follow-up CD4 count Viral load	No cost
Outpx_2	Using a file audit to evaluate retention in care and patient outcomes in a programme to decentralize antiretroviral treatment to primary health care facilities in a high prevalence setting in Kwazulu-Natal, South Africa	Searle C, Ramkissoon A, Govender T	2010	Doctor initiation at HIV clinic and nurse management at PHC	None	Stable ART px down referred, age not specified. N = 2071	2006-2008	33, Mixed	Majority 0-5 mo	Retention Lost to follow-up CD4 count Viral load	No cost
Outpx_3	Nurse versus doctor management of HIV infected patients receiving antiretroviral therapy (CIPRA-SA): a randomized non-inferiority	Sanne I, Orrell C, MP Fox, Conradie F, Ive P et. al.	2010	Doctor initiation at PHC and nurse management at PHC	Doctor initiation and management at PHC	Adult ART initiates. N = 812	2005-2009	2, Urban	30 mo	Retention Mortality Lost to follow-up Viral load Toxicity	No cost

	trial										
Outpx_4	Exploring task shifting practices in antiretroviral treatment facilities in the Free State Province, South Africa	de Wet K, Wouters E, Engelbrecht M	2011	Task shifting of HIV care and treatment related activities from nurse to CHW	None	Nurse / CHW on duty at PHC. N = 65 nurses 37 CHWs	2009	12, Not specified	None	No outcomes	No cost
Outpx_5	As study of patient attitudes towards decentralization of HIV care in an urban clinic in South Africa	Mukora E, Charalambous S, Dahab M, Hamilton R, Karstaedt A	2011	Doctor initiation at HIV clinic and nurse management at PHC	None	Adult ART px on treatment > 3 mo. N = 76	2008	1, Urban	None	No outcomes	No cost
Outpx_6	Outcomes of stable HIV-positive patients down-referred from a doctor-managed antiretroviral therapy clinic to a nurse-managed primary health clinic for monitoring and treatment	Brennan A, Long L, Maskew M, Sanne I, Jaffray I, MacPhail P, Fox MP	2011	Doctor initiation at HIV clinic and nurse management at PHC	Doctor initiation and management at HIV clinic	Adult, stable ART px. N = 2772	2008-2009	2, Urban	12 mo	Retention Mortality Lost to follow-up CD4 count Viral load	No cost
Outpx_7	Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: An observational	Long L, Brennan A, Fox MP, Ndibongo B, Jaffray I, Sanne I, Rosen S	2011	Doctor initiation at HIV clinic and nurse management at PHC	Doctor initiation and management at HIV clinic	Adult, stable ART px. N = 2848	2008-2009	2, Urban	12 mo	Retention Mortality Lost to follow-up CD4 count Viral load	Provider, 2009

	cohort									
Outpx_8	Does accessibility to antiretroviral care improve after down-referral of patients from hospitals to health centres in rural South Africa	Moshabela M, Schneider H, Cleary SM, Pronyk PM, Eyles J	2011	Initiation at HIV clinic and management at PHC / HCW not specified	Initiation at HIV clinic and management at HIV clinic / HCW not specified	Adults. N = 329	2008	2, Rural	min 6 mo	Access Utilisation	No cost
Outpx_9	Loss to follow-up of stable antiretroviral therapy patients in a decentralized down referral model of care in Johannesburg, South Africa	O'Connor C, Osih R, Jaffer A	2011	Doctor initiation at HIV clinic and nurse management at PHC	None	Adult, stable ART px. N = 3361	2007-2009	7, Urban	mean 6 mo	Retention Lost to follow-up	No cost
Outpx_10	Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomized trial	Fairall L, Bachman M, Lombard C, Timmerman V, Uebel K, Zwarenstein M, et al	2012	Nurse initiation and management at PHC	Doctor initiation and management at HIV clinic	Adults with CD4 count < 350 cells/ul not on treatment. N = 9252	2008-2010	31, Mixed	12-18 mo	Retention Mortality Lost to follow-up CD4 count Viral load Hospital admissions	No cost
Outpx_11	Electronic decision protocols for ART patient triaging to expand access to HIV treatment in South Africa: A	Mitchell M, Hedt B, Eshun Wilson I, Fraser H, John M, Menezes C, Grobusch M Jackson J, Taljaard J, Lesh N	2012	Counselor triaging of ART px	Doctor triaging of ART px	Adults on ART regimen > 3 mo. N = 1189	2007-2008	2, Urban	None	Correctly screened	No cost

	cross sectional study for development and validation										
Outpx_12	TB/HIV-related training, knowledge and attitudes of community health workers in the Free State province, South Africa	Heunis C, Wouters E, Kogozi G, Janse van Resnburg-Bonthuysen, Jacobs N	2013	Use of CHW for HIV/TB related services	None	CHW at PHC serving in TB/HIV program. N = 206	2012	28, Mixed	None	No outcomes	No cost
Outpx_13	Cost effectiveness of nurse-led versus doctor-led antiretroviral treatment in South Africa: pragmatic cluster randomized trial	Barton G, Fairall L, Bachman M, Uebel K, Timmerman V, Lombard C, Zwarenstein M	2013	Nurse initiation and management at PHC	Doctor initiation and management at HIV clinic	Adults with CD4 count < 350 cells/ul not on treatment. N = 9252	2008-2010	31, Mixed	12 mo	Mortality	Provider, 2009
Outpx_14	NIMART rollout to primary healthcare facilities increases access to antiretrovirals in Johannesburg: An interrupted time series analysis	Nyasulu J, Muchiri E, Mazwi S, Ratshefola M	2013	Initiation at PHC / HCW not specified	Initiation at HIV clinic / HCW not specified	All ART initiates. N = 20,535	2009-2012	17, Urban	30 mo	Number of patients initiating ART	No cost
Outpx_15	Outcomes of a nurse-managed service for stable HIV-positive patients in a large South African public sector	Grimsrud A, Kaplan R, Bekker L, Myer L	2014	Doctor initiation at HIV clinic and nurse management at down referral site	Doctor initiation and management at HIV clinic	Adult, stable ART px. N = 5,746	2002-2012	2, Urban	60 mo	Retention Mortality Lost to follow-up Viral load	No cost

	antiretroviral therapy program										
Outpx_16	Clinical mentorship of nurse initiated antiretroviral therapy in Khayelitsha, South Africa: A quality of care assessment	Green A, de Azevedo V, Patten G, Davies MA, Ibeto M, Cox V	2014	Clinical mentorship of NIMART nurses	Prior to clinical mentorship of NIMART nurses	Adults. N = 229 px 8 nurses	2011-2012	8, Urban	None	Number of ART initiations ART management indicators	No cost
Outpx_17	Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa	Grimsrud A, Sharp J, Kalombo C, Bekker LG, Myer L	2015	CHW management in community	None	Adult, stable ART px. N = 2,133	2012-2013	74, Peri-urban	None	Retention Mortality Lost to follow-up Viral Load	No cost
Outpx_18	Successful tuberculosis treatment outcomes among HIV/TB coinfected patients down-referred from a district hospital to primary health clinics in rural South Africa	Jacobson K, Moll A, Friedland G, Shenoi S	2015	HIV/TB coinfected initiated on TB treatment at HIV clinic and managed at PHC	HIV/TB coinfected initiated and managed on TB treatment at HIV clinic	All. N = 657	2012-2013	17, Rural	Not specified	TB outcomes: Treatment completed Cure Lost to follow-up Mortality	No cost

APPENDIX J: Summary of research implications

Thesis Chapter	Implication
	PRACTICAL / POLICY
Chapter 7	Treatment of antiretroviral patients should be shifted from specialist HIV treatment centres managed by doctors to primary health clinics managed by nurses. (This work supported the shift of standard of care in South Africa to nurse initiation and management of antiretroviral treatment, known as NIMART.)
Chapter 8	Under NIMART patients should be triaged with complicated HIV patients referred for treatment to specialist HIV clinic (normally hospital based outpatient clinics) where there is access to higher level clinical staff and services. Uncomplicated patients should be treated at primary health clinics.
Chapter 9	Screening for and successful treatment of tuberculosis needs to be invested in and scaled up substantially to support the HIV program. Early identification and treatment of HIV positive patients who are not accessing the primary public health system will be critical to reducing the burden on inpatient facilities. HIV prevalence amongst medical inpatients at public health facilities should be used as an indicator of the success of the national HIV program.
Chapter 10	Morgue registers should be electronic and used to calibrate the national mortality estimates which substantially under report HIV related mortality.
	METHODOLOGICAL
Chapters 7-10	It is possible to conduct rigorous economic evaluations based on routine patient level

	data in the public health system in South Africa.
Chapters 7&8	Defining treatment outcome algorithms ensures that each patient can be assigned an outcome even in the absence of perfect timing and data around standard treatment outcome indicators.
Chapter 9	The patient day equivalent (PDE) cost method is an accurate estimate of HIV related inpatient cost provided the reasons for admission are similar to those seen in this cohort.

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