

PATIENT RETENTION AT KEY MILESTONES AFTER HIV DIAGNOSIS AT A PRIMARY
HEALTHCARE CLINIC OFFERING EARLY ANTIRETROVIRAL THERAPY INITIATION
IN JOHANNESBURG, SOUTH AFRICA

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in
partial fulfillment of the requirements for the degree of Doctor of Philosophy in the
Department of Epidemiology.

Chapel Hill
2012

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ABSTRACT

KATE CLOUSE: Patient retention at key milestones after HIV diagnosis at a primary healthcare clinic offering early antiretroviral therapy initiation in Johannesburg, South Africa
(Under the direction of Audrey Pettifor)

A significant challenge to the impact of South Africa's national ART program is poor patient retention. We report retention in early HIV care among patients at Witkoppen Health and Welfare Centre in Johannesburg, South Africa, using data obtained via file review and electronically. We look first at multiple stages of early HIV care among newly-diagnosed, non-pregnant adults (N=842). Retention from HIV testing to CD4 staging was 69.8% (95%CI 66.7-72.9%). For patients initially ART-ineligible (n=221), 57.4% (95%CI 49.5-65.0%) returned for a repeat CD4 within 12 months. Among those ART-eligible (n=589), 73.5% (95%CI 69.0-77.6%) were retained between CD4 staging and ART initiation. Retention increased with time on ART, from 80.2% (95%CI 75.3-84.5%) at 6 months to 95.3% (95%CI 91.7-97.6%) between 6-12 months. Cumulative retention from HIV diagnosis to 12 months on ART was 36.9% (95%CI 33.0-41.1%) for those ART-eligible and 43.0% (95%CI 36.4-49.8%) from diagnosis to repeat CD4 testing within one year among those ART-ineligible.

We examined loss to follow-up (LTFU) before and after delivery among pregnant women newly-diagnosed with HIV (N=273). Of 139 (51.3%) ART-eligible patients, 66.9% (95%CI 58.8-74.3%) initiated ART prior to delivery and overall, 40.5% (32.3-49.0%) were cumulative retained through six months on ART. Of those ART-ineligible at HIV diagnosis, only 21.1% (95%CI 14.6-29.0%) were retained through a repeat CD4 test after delivery.

LTFU (≥ 1 month late) before delivery was 20.5% (95%CI 16.0-25.6%) and, among those still in care, 47.9% (95%CI 41.2-54.6%) within six months after delivery.

The study clinic has offered ART initiation at CD4 ≤ 350 cells/ μ l since 2010. We compared 12-month patient outcomes for those who presented and initiated ART at baseline CD4 values ≤ 200 versus 201-350 cells/ μ l (N=1430). Among men and non-pregnant women, initiating at 201-350 cells/ μ l was associated with 26-42% reduced LTFU (≥ 3 months late) compared to those initiating at ≤ 200 . We found no CD4 effect among pregnant women.

As countries expand HIV testing and ART programs, success will depend on linkage to and retention in care, especially during the period prior to ART initiation. Our findings highlight the additional challenge of continuity of care among HIV-positive pregnant women and adults ineligible for ART.

ACKNOWLEDGEMENTS

I am deeply indebted to my dissertation committee for sharing their time, guidance and support throughout this process. Audrey Pettifor deserves special recognition for guiding me through the past four years with unwavering dedication. Her assistance, honesty, and inspiration have been invaluable to me personally and professionally. I would like to thank my friends and fellow students in the Department of Epidemiology, particularly Nora Rosenberg, Christine Tucker, Jen Deese and Christina Mack, for always being forthcoming with advice, ideas and encouragement. Nancy Colvin has been so wise and helpful throughout my four years in the department. This research would not have been possible without the generous cooperation of Dr. Jean Bassett and her staff, who offer an amazing public service at Witkoppen Health and Welfare Centre. Also at Witkoppen, I'd like to recognize Dr. Heather Dansey for expanding my clinical knowledge in the most fun way possible. I would like to thank Annelies Van Rie for introducing me to Witkoppen, as well as to TB research. My colleagues at HE²RO in Johannesburg have helped me to reach this step, and I am grateful for their support, particularly Matt Fox for his patience and commitment, as well as his guidance and leadership. Mhairi Maskew has been an unfailing advocate for me, as well as an amazing teacher; I appreciate her support tremendously. None of this would be possible without the love of my family, who have supported me at every step of my career, even if it means that I am far away from them.

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ANC	Antenatal care
ART	Antiretroviral therapy
AZT	Zidovudine
CD4	Cluster of differentiation 4
CI	Confidence interval
HIV	Human immunodeficiency virus
HR	Hazard ratio
IQR	Intra-quartile range
LTFU	Loss to follow-up or lost to follow-up
PHC	Primary healthcare clinic
PMTCT	Prevention of mother-to-child transmission of HIV
RR	Risk ratio
WHO	World Health Organization

CHAPTER 1

INTRODUCTION AND REVIEW OF THE LITERATURE

Sub-Saharan Africa is the region of the world hardest hit by the HIV/AIDS pandemic. Of the 33.3 million people living with HIV/AIDS in 2009, 22.5 million (68%) are in sub-Saharan Africa, and the region is home to 72% of the world's HIV/AIDS deaths.¹ South Africa's epidemic remains the world's largest with 5.6 million people living with HIV in 2009, adult HIV prevalence estimated at 16.9%, and 410,000 estimated new infections in 2010.¹⁻³

South Africa also has the largest antiretroviral therapy (ART) program in the world.¹ The national ART program started in 2004 and has quickly grown in size with over 1.7 million adults and children enrolled over the first seven years.⁴ This advancement has dramatically altered the health and quality of life of people living with HIV/AIDS. UNAIDS estimates that over 700,000 adult life-years were gained as a result of ART in South Africa through 2009.¹ At the same time, the rapid scale-up of the national ART program has put tremendous pressure on the limited resources of a public health sector that is struggling to meet the immense need. It is estimated that only 52% of patients eligible for ART are currently on treatment.⁴ Despite the fact that 300,000 patients enroll in the South African ART program each year,⁵ an estimated 280,000 people died of AIDS in 2010, representing 43% of the country's total deaths.³ Moving forward, South Africa will need to expand its national ART program to meet the needs of more patients within a context of limited resources, while ensuring quality, sustainable care.

An enormous challenge to the existing South African ART program and current attempts to expand its impact is the large number of patients who either do not access care, or who leave care. Numerous barriers to initiating and remaining in care exist for HIV-positive individuals, including psychological and social factors such as denial of disease status and severity,⁶ distrust of the healthcare system in terms of quality care and confidentiality,⁷⁻⁹ and disease stigma.^{2,6,7,9,10}

The “necessity-concerns” conceptual framework, which has been utilized in medication adherence research across a span of diseases,^{11,12} may accurately describe the considerations an individual faces when seeking HIV care and adhering to ART.¹³ This framework describes how patients’ perceived need for ART may be at odds with the clinical necessity, and explains how pre-existing beliefs about ART, such as fear of side effects, may dissuade eligible patients from accessing treatment. Similarly, low perceived need for ART among patients eligible for ART may predict both failure to initiate and adherence to ART.¹³ While this framework, to our knowledge, has not been used among southern African populations, other researchers in the region have noted that patients who did not feel sick were less likely to access care or continue treatment.^{6,9} Others may prefer traditional medicine and healers to ART and clinics.^{6,8,9,14}

In addition to numerous psychological and social obstacles to accessing and remaining in care, structural barriers also may prevent patients from initiating or continuing care. At the healthcare facilities, these may include complex, disjointed systems of healthcare,¹⁰ lengthy queues,^{6,8} and limited operating hours that conflict with employment commitments.⁸ Furthermore, poverty and an inability to pay for transit fares and clinic fees limits individuals’ ability to access care.^{7-10,14} Lacking food to eat while taking ART also has been mentioned as a barrier in Southern Africa.⁹ Frequent migration and housing instability among low-income, highly-mobile populations in South Africa also may lead to interruptions in care.^{14,15} While the majority of research focuses on barriers to care, community

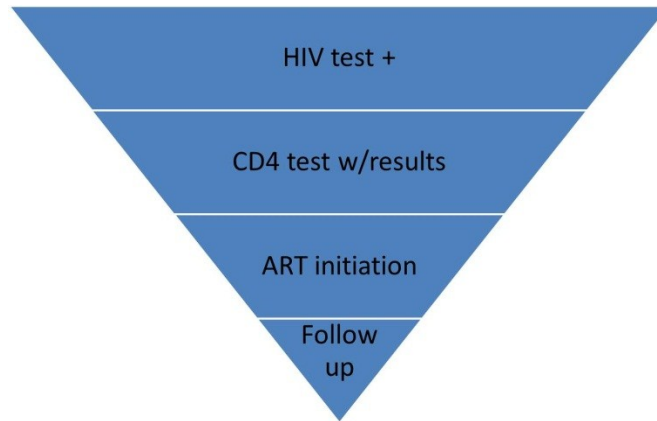
involvement, faith-based initiatives, and active tracing and home visits have been noted as facilitators of retention in care.^{16,17}

As a result of these barriers, HIV-positive patients in South Africa and other resource-limited countries are more likely to have advanced immunosuppression (i.e. lower CD4 counts) when starting ART, thus, are more likely to be at increased risk of mortality, underscoring the urgency of initiating and retaining patients in care.^{18,19} Continuous engagement in care is particularly important for HIV patients since HIV requires lifelong treatment with high adherence as patients who stop and restart treatment increase their risk of drug resistance, treatment failure and ultimately, death.^{20,21} Two South Africa-based studies linked to the national death registry have estimated mortality among patients lost to care at 31% after one year and 36-44% after two years.^{22,23} Even patients who remain in care but missed multiple ART appointments within the first six months of initiation are at increased risk of poor CD4 responses and failure to achieve viral suppression.²⁴

Patient attrition refers to loss to care, which includes both patients who die and patients who are lost to follow-up (LTFU) (i.e. those who do not return to the clinic after a defined period of time). Patients can leave care at any point in their care, so dividing care up into meaningful periods over which to assess retention is necessary. Focusing specifically on the first year of HIV care (a time of high attrition), it is helpful to characterize retention in relation to key events in care. For those who test HIV-positive, blood must be collected and (in most cases) sent to an outside lab for CD4 testing, then the patient must return for results at a later visit, typically the visit following HIV diagnosis. For ART-eligible patients, adherence counseling is often required prior to treatment initiation. Patients who are ineligible for ART are to be enrolled in a wellness program with follow-up visits every six months for CD4 monitoring. Since there are multiple points in the process where patients may be lost to care, there are fewer patients at each step of the process, as shown in Figure

1. This loss of patients through consecutive time points is sometimes referred to as the “HIV treatment cascade.”²⁵

Figure 1. HIV-positive patient loss to care over time



In recent years, quantifying the problem of patient attrition in care among HIV-positive patients worldwide as well as within the public-sector in South Africa has begun to receive attention. Following the introduction of ART in the public-sector in South Africa in 2004, research primarily focused on patient retention in care after treatment initiation. These studies now provide many years of data about patient retention in care following initiation (see Table A.1). A large (N=44,177) collaborative analysis of eight cohorts initiating ART across South Africa found that patient attrition increased with duration on treatment, and by 36 months, 29% were LTFU.²⁶ A review of 33 publications of cohorts in sub-Saharan African countries (N=226,307) found that ART programs lose about 25% of their patients within two years.²⁷ In both analyses, younger patients and those who initiated with very low CD4 counts were significantly more likely to be LTFU.

Results of this research on program retention suggest that rates of LTFU and mortality are highest in the first year of HIV care.²⁷⁻²⁹ Thus, loss of patients during the earliest phases of HIV care – immediately after diagnosis and prior to ART initiation – is gaining research attention (see Table A.2) and several studies have described pre-ART loss within South Africa. Studies in Durban, Johannesburg and Cape Town have found that only

about half (45-63%) of newly-diagnosed patients complete CD4 staging (including results notification) within eight weeks to six months after testing HIV-positive.³⁰⁻³² One study noted that CD4 testing was lowest (15%) among patients with a CD4 count >200 cells/ μ l.³³

Patients who are ineligible for ART based on CD4 testing must return for regular CD4 monitoring and eligibility assessment for ART. This is a particularly difficult period in which to retain patients, for patients with higher CD4 values may feel well and may not seek care, and facilities may prioritize sicker patients over the routine care of patients with higher CD4 counts. It is also difficult to measure retention among patients ineligible for ART because the defined end point – becoming eligible for ART based on CD4 testing – is unique to each individual patient and there is no time period for eligibility that is appropriate for all patients. Thus, studies on retention among ART-ineligible patients are few but indicate poor rates of repeat testing. In a Cape Town study, 46.3% of patients with CD4 >200 cells/ μ l returned for repeat CD4 testing during the four-year study period,³² and in Johannesburg, only 26% of patients with CD4 \geq 350 cells/ μ l returned for a pre-ART wellness visit within one year.³⁴

Once a patient has been identified as eligible for initiating ART, it is essential that treatment is started promptly. However, only 39% of ART-eligible patients in a Durban cohort initiated treatment and another 20% died within 12 months of eligibility determination.³⁵ A Cape Town-based study found that only two-thirds (67%) of eligible patients accessed ART within six months of testing,³² and a large study from the Free State found that 26% died prior to initiating ART.³⁶

A 2011 systematic review of patient attrition after HIV diagnosis and prior to ART initiation in sub-Saharan African cohorts found high overall attrition. The median proportion retained at each time period was 59% from HIV diagnosis to CD4 staging, 46% from pre-ART care to ART eligibility (for those ineligible based on CD4 count), and 68% from eligibility to ART initiation. While none of the 28 studies reported cumulative retention through all of

the stages of pre-ART care, the product of the median proportions of patients retained at each time point suggested only 18% of patients were continuously retained in care through all three stages.³⁷

As the above summary describes, the recent awareness of the importance of pre-ART retention has encouraged research quantifying patient attrition at specific time points in early HIV care – CD4 staging, pre-ART care for ART-ineligible patients, ART initiation – but very few studies have followed patient outcomes from the time of testing HIV-positive beyond ART initiation to report patient attrition. One previous study in rural Uganda from the early days of ART availability (2005-2007) reported retention from initial CD4 testing through ART initiation, but does not report on retention following ART initiation. The authors found rather high rates of return for early visits: 88% of patients eligible for ART returned for their CD4 staging visit, and 74% of eligible patients attended a third visit and started ART.³⁸ Another study from rural Malawi investigated attrition among patients with WHO stage 1 and 2 disease through the first six months of HIV care (starting after CD4 testing), but without providing clear results for attrition by stage.³⁹ They report that 89.7% of those who initiated ART were in care six months later, compared to 23.5% who did not initiate, but do not clearly differentiate attrition by ART eligibility status or account for the impact of differing visit schedules. The authors note that 95% of LTFU occurred between CD4 collection and results notification. This study also focused on a rural community, with markedly different facilities and services for patients on ART (dedicated clinics) and those not yet initiated (general outpatient services).

A recent review of 28 pre-ART studies in sub-Saharan Africa concluded, “Offering a definitive answer to our core question—what proportion of patients who test positive for HIV are staged, enroll and remain in pre-ART care until ART eligibility, and initiate ART—is not possible...no study provides all the information needed to answer this question, even for a single setting.”³⁷ To our knowledge, only one study from southern Africa has reported patient

retention at multiple time points from the time of testing HIV-positive beyond ART initiation. A study in Mozambique looked at five periods in early ART care: HIV testing, CD4 staging, enrollment at a separate ART facility, ART initiation and ART adherence at six months.²⁵ The study's data were from the first year of the country's ART program (2004-2005), when ART initiation sites were limited and separate from HIV testing sites. They found that among 7,005 HIV-positive patients, 56.5% enrolled at the ART facility within 30 days of testing, 77.1% of whom completed CD4 staging within 30 days of enrollment. Half (49.4%) of these patients were ART-eligible of whom 31.3% initiated ART within 90 days of CD4 testing. Using pharmacy data, the authors found that 83.0% of these patients were adherent to ART six months post-initiation. Attrition was highest between testing HIV positive and enrolling for ART care (43.5%) and between CD4 testing and ART initiation (within 90 days) for those ART-eligible (68.7%). However, this study does not report a cumulative measure of patient attrition from the time of testing HIV positive through ART retention, nor does it discuss attrition among patients ineligible for ART.

In addition to incomplete and disjointed analyses of patient attrition, the definitions of patient attrition and LTFU vary widely among studies. As shown in the appendix, LTFU definitions vary, usually indicating an absence of from one to six months from a health facility, some requiring follow-up by clinic staff. Similarly, the time periods permissible for completion of key stages of early HIV care, such as CD4 staging and ART initiation differ significantly by study. The lack of a standardized definition for patient LTFU and time periods of care is a serious impediment to aggregating or generalizing results. In an attempt to overcome this heterogeneity of definitions, recommendations for standardized definitions for retention in pre-ART care have recently been proposed, allowing for estimates that can be compared across programs and countries.³³ The recommendations are as follows:

- Pre-ART stage 1: The proportion of patients who complete CD4 staging (including results notification) within three months of HIV testing.

- Pre-ART stage 2: For patients ineligible for ART, the proportion completing a repeat CD4 test within 12 months of first CD4 staging date.
- Pre-ART stage 3: The proportion initiating ART within three months of determining ART eligibility.

In addition to measuring the scope of the problem, investigations of patient attrition from early HIV care can identify groups who may be most at risk of dropping out of care. While the data above demonstrate that patient retention in HIV care is known to be an important challenge in the public sector throughout southern Africa, a few studies have suggested that pregnant women may have LTFU rates that exceed that of men and non-pregnant women.^{40,41} A study from a community clinic in the North West Province of South Africa found that among 925 patients initiating ART, pregnant women had the highest cumulative probability of LTFU after six months, and pregnant women with a baseline CD4 value ≤ 200 cells/ μ l were at six times the risk of LTFU than any other group (RR 6.06, 95%CI 2.30, 16.71).⁴¹ Another study from outside Cape Town found higher LTFU in both the pre-ART and post-ART periods among pregnant women, compared to non-pregnant women.⁴⁰ The largest study to date to explore LTFU among pregnant women, an analysis of nearly 30,000 women initiating ART within five cohorts in South Africa, found that LTFU was 54% higher in pregnant women than in non-pregnant (aHR 1.54; 95%CI 1.38-1.72), despite less immunosuppression and decreased mortality.⁴²

Another sub-population that may be at increased risk of LTFU is that of patients initiating ART at less advanced immunosuppression indicated by higher CD4 values. In late 2009, the WHO revised their HIV treatment guidelines to expand eligibility criteria for ART to anyone with a CD4 count ≤ 350 cells/ μ l in order to treat patients before they develop advanced immunosuppression.^{43,44} Struggling to enroll and retain patients within their previous guidelines (eligibility at CD4 counts < 200 cells/ μ l), South Africa revised its national ART guidelines in 2010 to expand eligibility to pregnant women and TB patients with CD4

counts ≤ 350 cells/ μ l, but did not immediately adopt WHO's recommendations for early initiation for all.⁴⁵ In August 2011, South Africa announced a revised policy of ART initiation for all adults with CD4 counts < 350 cells/ μ l in response to recent developments in HIV research and international recommendations⁴⁶ based on consensus that patients who initiate ART with a CD4 > 200 cells/ μ l are at reduced risk of death and serious opportunistic infections, such as tuberculosis.⁴⁷⁻⁵⁰ There is already strong evidence that initiating at higher CD4 values also contributes to HIV prevention. The results of a large clinical trial demonstrated early treatment (CD4 counts 350-550 versus 250 cells/ μ l) reduced HIV transmission by 96%.⁵¹ Others advocate for a "test-and-treat" approach where all HIV-positive patients start ART at the time of diagnosis regardless of CD4 count.⁵²

Given the recent policy change in South Africa, there are few studies that have explored LTFU among those initiating ART at CD4 counts 200-350 cells/ μ l versus < 200 cells/ μ l in southern Africa, and none in routine settings (see Table A.3). While initiating ART at higher CD4 values is known to be associated with improved clinical outcomes,^{48,50} it remains to be seen whether these gains will be overshadowed by increased LTFU. As part of a randomized controlled trial, a study in Johannesburg (N=812) found slightly higher LTFU among those initiating with a baseline CD4 > 200 cells/ μ l (14%) than ≤ 200 (10%), suggesting that patients with higher CD4 counts may be more slightly likely to be lost from care.⁴⁸ By comparison, Lesotho, a rural nation completely surrounded by South Africa, adopted an early initiation (< 350 cells/ μ l) policy in 2007, and a study (N=1177) of patient outcomes under routine clinic settings showed that patients initiating ART with CD4 counts above 200 cells/ μ l were 39% less likely to be LTFU after nearly two years on treatment.⁴⁷ Given that South Africa's national ART program recently raised its initiation threshold, it is essential that we evaluate the impact of early initiation on LTFU and other patient outcomes within a routine clinic setting.

To summarize, the body of research investigating patient attrition has increased substantially in the past decade, particularly in South Africa. However, notable areas for improvement and contribution remain. No study has followed a cohort from the time of HIV diagnosis through ART care to report on cumulative loss through consecutive stages of care. Additionally, no study has followed patients ineligible for ART long-term to understand retention in HIV care prior to ART initiation. Study generalizability is hampered by differing and often conflicting definitions of time periods of care and attrition and/or LTFU. Lastly, exploring the nuances of attrition among different sub-populations is an emerging topic, with early research suggesting that pregnant women have higher rates of LTFU than men or non-pregnant women after a period of follow-up, and no study reporting on the influence of higher CD4 values at ART initiation on LTFU within the setting of routine care in South Africa. In the context of this research environment, the present research study has been completed and three manuscripts describe the study findings.

CHAPTER 2

STATEMENT OF SPECIFIC AIMS

Specific Aim 1: Compare retention among recently-diagnosed HIV-positive patients over multiple stages in the early HIV care process within a single clinic.

In Chapter 4, *Patient retention from HIV diagnosis through one year on antiretroviral therapy at a primary healthcare clinic in Johannesburg, South Africa*, we compare the proportion of recently-diagnosed HIV-positive non-pregnant adult patients (N=842) retained in care through three stages of pre-ART and two stages of post-ART retention. We also report cumulative retention from the time of testing HIV-positive to 12 months on ART for those ART-eligible at testing, and from HIV testing to a repeat CD4 count for those ineligible for ART.

Hypothesis

Aim 1 is an descriptive analysis, so we are primarily concerned with investigating the proportions lost at each stage and cumulative retention. The research questions that motivate this aim are, “What is patient retention at each stage? At which stage is attrition highest?” We hypothesize that attrition will be highest prior to the initiation of ART.

Rationale

Patients who initiate ART have already successfully been retained for multiple visits and, thus, may be more inclined to continue in care. Studies that investigate patient retention starting at the time of ART initiation are missing pre-ART loss, which may be the period of highest attrition.

In Chapter 5 *Loss to follow-up before and after delivery among women testing HIV-positive during pregnancy in Johannesburg, South Africa*, we investigate retention before and after delivery among women testing HIV-positive during pregnancy (N=273).

Hypothesis

Aim 1 is an descriptive analysis, so we are primarily concerned with investigating the proportions lost at each stage and cumulative retention. The research question that motivates this aim is, “Are pregnant women who test positive for HIV more likely to drop-out of care after delivery than before?” We hypothesize that patient loss will be higher after delivery than before delivery.

Rationale

In South Africa, most deliveries occur at hospitals, while antenatal and postnatal visits occur at the primary healthcare level. This disjointed system of healthcare is a barrier to continuous retention in care. In addition, travel around the time of birth may contribute to patient attrition in the postpartum period.

Specific Aim 2: Measure the impact of initiating patients who present with CD4 counts 200-350 cells/ μ l on patient loss to follow-up in a routine clinic setting.

In Chapter 6, *Initiating ART when presenting with higher CD4 counts results in reduced loss to follow-up under South Africa’s 2010 revised antiretroviral therapy guidelines*, we evaluate the 12-month hazard of LTFU among patients initiating ART (N=1430) by baseline CD4 count to explore if LTFU is greater among patients with higher CD4 counts (200-350 cells/ μ l) than patients presenting with more advanced immunosuppression (CD4 <200 cells/ μ l).

Hypothesis

We hypothesize that patients initiating ART with higher CD4 counts may be more likely to be LTFU.

Rationale

Patients with less immunosuppression often feel healthier than patients who are sicker. Thus, the imperative of remaining in HIV care may be less obvious.

CHAPTER 3

RESEARCH METHODS

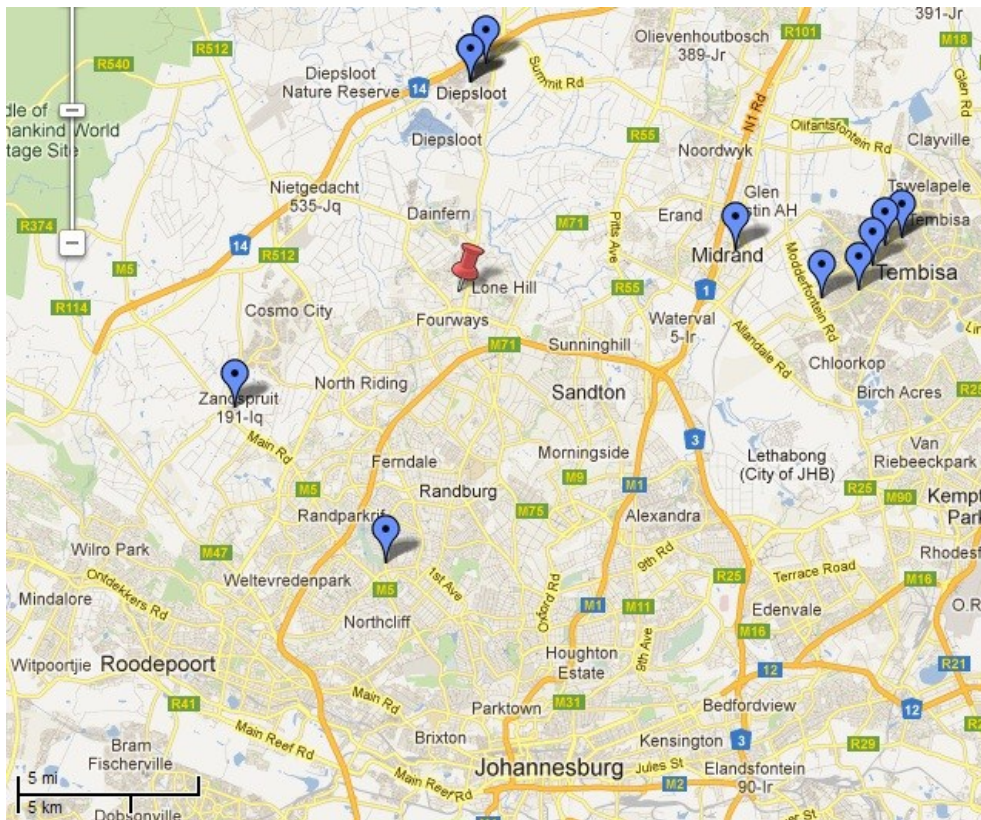
Study setting and population

Witkoppen Health and Welfare Centre (Witkoppen) is a high-volume primary health clinic in Johannesburg, South Africa. Witkoppen sees about 8,500 patients a month, of whom about 40% are HIV-positive and a substantial proportion are recent immigrants from neighboring countries, predominately Zimbabwe. This high patient volume makes Witkoppen a well-suited setting for studies of HIV care and treatment. The clinic provides HIV/AIDS services (including the initiation and follow-up of ART), integrated HIV/TB services, family planning, pre-/post-natal care, pediatric services, chronic care, mental health services and social welfare assistance. Patient visits cost R40 (approximately US\$5), but most patients' visits are fully subsidized by the clinic due to patients' inability to pay. Witkoppen is operated by a non-governmental organization and receives financial support from the Gauteng Department of Health, the President's Emergency Plan for AIDS Relief (PEPFAR) through a South African NGO called Right to Care, and other public and private support. At Witkoppen, physicians and nurses with a primary healthcare nurse (PHCN) designation (similar in training and education to the nurse practitioner level in the US) may initiate patients onto ART as is called for under South Africa's current ART recommendations. In general, patients at Witkoppen are treated according to the South African National Treatment Guidelines,⁴⁵ with an important exception. In early 2010, Witkoppen began initiating all HIV-positive patients

with a CD4 count ≤ 350 cells/ μ l, over one year before South Africa adopted this policy nationwide.⁵³

Witkoppen primarily serves a vast community of formal and informal settlements in Northern Johannesburg, such as Diepsloot, Cosmo City and Zandspruit, communities burdened with high unemployment, poverty and crime. The area is under-resourced in terms of public healthcare facilities and staff. Figure 2 shows Witkoppen as the red push-pin; blue markers indicate all public clinics within the same municipal district (City of Johannesburg Region A), as well as two additional clinics (Zandspruit Clinic and Windsor Clinic) from areas in which Witkoppen patients reside. Of the clinics shown, Witkoppen is one of the largest, both in terms of patient loads and personnel.

Figure 2. Map of Witkoppen Health and Welfare Centre and surrounding public clinics.



Map courtesy of Google Maps

The setting of the proposed study provides a unique opportunity to examine LTFU at higher CD4 values under routine clinical care. Since Witkoppen is one of the few clinics in South Africa that has operated under a policy of initiation ≤ 350 cells/ μ l since 2010, we can examine the effects of implementing the WHO guidelines in a routine clinical setting using available data. LTFU here can be measured in the context of a highly integrated clinic: all relevant services – HIV counseling and testing, phlebotomy, ART initiation, antenatal care, as well as other clinic services – are available within the same facility, reducing the impact of having to access and wait at multiple facilities. Also, while slow time to initiation is often cited as a barrier to care and a factor contributing to LTFU, Witkoppen has a demonstrated ability to initiate patients onto ART promptly. Previous linkage to care studies in South Africa performed at government facilities found a median time from HIV diagnosis to ART initiation (among eligible patients) ranging from 95 days to 6.6 months.^{35,36} In contrast, a 2011 study of TB suspects at Witkoppen indicated that the median time from HIV diagnosis to ART initiation was 26.5 days with 70% of patients eligible for ART initiated.⁵⁴ Before ART initiation, patients must receive necessary ART counseling, but appointments are scheduled with an understanding of the need for prompt initiation, particularly for patients presenting with advanced immunosuppression. This means that we can measure LTFU within the setting of a clinic that has already worked to reduce some of the known barriers to retention, including multiple facilities and deferred care. We would expect that other clinics that have not implemented such integration measures may experience higher patient attrition.

Ethical considerations

Ethical approval for this analysis was granted from the Public Health-Nursing IRB at the Office of Human Research Ethics at the University of North Carolina at Chapel Hill and the Human Research Ethics Committee of the University of the Witwatersrand. This analysis

was conducted using routine data collected in patient files as standard clinical procedure and did not require individual patient consent.

Data collection

For Aim 1, we conducted a retrospective observational cohort (N=1144) study through patient files review. To determine patient outcomes, records were reviewed a minimum of 12 months (median 16.5 months, IQR: 14.8-18.1) from the time of testing HIV-positive. For patients whose CD4 count at the time of HIV testing made them eligible for ART who went on to begin ART, files were reviewed a minimum of one year post-ART initiation. Data were single-entered into a Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) spreadsheet by KC and analyzed using SAS, version 9.2 (SAS Institute, Cary, NC). The files of 18 patients (1.6%) could not be retrieved after multiple attempts, so data were obtained from the clinic's electronic medical records system. Of these patients, six were pregnant and contributed to Chapter 5. Because the policy of using a higher ART initiation threshold was new at Witkoppen in 2010, individual eligibility for ART was assessed for each patient during the file review, which led clinician decision to deem 23 patients with CD4 values 200-350 being ineligible for ART and three patients with CD4 >350 cells/ μ l eligible.

For Aim 2, we also used a retrospective cohort (N=1430), but used data electronically captured at Witkoppen using TherapyEdge-HIV™ Patient Management System (Associated Biological Systems, South Africa). Data are captured at the clinic by data capturers and clinicians, and are regularly quality-checked by a data manager. Data were exported from TherapyEdge-HIV™ and analyzed using SAS, version 9.2.

Eligibility and exclusion criteria

For Aim 1, our inclusion criteria were adult patients (18 years and older) who tested HIV-positive for the first time at Witkoppen from 1 January – 30 June 2010. We started with a roster from the clinic data manager of all 1612 patients who likely met the inclusion criteria, listing only clinic file number and date of testing. Of these, 23 (1.4%) patients less than 18 years old and 320 (19.9%) patients who tested HIV-positive elsewhere and already knew their HIV status were removed for failure to meet inclusion criteria. This left 1270 patients on the roster, from which we excluded the following groups:

- Invalid clinic file numbers (seven digits instead of six) (n=3, 0.2%)
- Patients who could not be identified using the file number provided: a paper file could not be located after at least three separate attempts and the file number was not found in TherapyEdge-HIV™ (n=122, 9.6%). While it is possible for paper files to go missing, it is unlikely for a patient who tests HIV-positive to be missing a paper file and also not be found in TherapyEdge-HIV™. For this reason, we believe that the file numbers provided to us by the data manager for these 122 patients were erroneous.

This left 1144 individuals for analysis for Aim 1. Of these, 844 were not pregnant and were analyzed in Chapter 4. The remaining 300 were pregnant at the time of testing HIV-positive and were analyzed in Chapter 5.

For Aim 2, our inclusion criteria were adult patients who initiated ART for the first time at Witkoppen between April and December 2010. We exported TherapyEdge-HIV™ data on 1699 patients from Witkoppen's server on May 6, 2012 who were likely eligible. After removing 67 (3.9%) patients less than 18 years old and 118 (6.9%) patients who were not ART-naïve, we were left with 1514 patients. From this total, we excluded the following:

- Patients missing a baseline CD4 value (n=29, 1.9%)

- Patients with a baseline CD4 value >350 cells/μl (n=55, 3.6%)

This left 1430 individuals in our analysis dataset for Aim 2.

Pre- and post-initiation clinic visit schedule

Patients with CD4 values ≤350 cells/μl or those with WHO clinical stage 3 or 4 disease are eligible to start ART at Witkoppen. For ART-eligible patients, South African treatment guidelines stipulate initiation of ART at the third patient visit, following clinical assessments and adherence counseling. However, patients with CD4 counts <100 cells/μl, those with MDR/XDR-TB, stage IV disease, or pregnant patients eligible for ART are designated to be fast-tracked to begin ART within two weeks of diagnosis. Patients ineligible for ART are to be enrolled in a “wellness program,” which are poorly defined in national guidelines, apart from providing routine HIV care with CD4 monitoring every six months. At Witkoppen, wellness services also include TB screening at every visit, ongoing HIV counseling, family planning and Pap smears.⁴⁵

While actual visit schedules vary based on patient and clinic availability, the general schedule of visits at Witkoppen is as follows.

Visit 1: Diagnosis visit. HIV testing begins with pre-test counseling, typically administered in small groups. Patients then go individually to a separate room for HIV testing via finger pricking. Witkoppen utilizes two simultaneous dried blood spot rapid tests (First Response, Premier Medical Corp., Ltd., Kachigam, India), packaged individually, with HIV testing results available within 5-20 minutes. All patients receive immediate individual post-test counseling. If the patient tests positive, after examination by a nurse, he or she is sent for blood collection for CD4 count testing, still on the same date as diagnosis. Patients are given a scheduled date to return for CD4 results, usually one to four weeks after Visit 1.

Visit 2 (1-4 weeks after Visit 1): CD4 staging visit. At the second visit, the patient receives his or her CD4 count results, followed by a full clinical assessment by a physician. At

Witkoppen, counselors provide CD4 results, along with a thorough explanation of the meaning of the result. If the patient is eligible to initiate ART, a first adherence counseling session is provided concurrently. Counseling messages regarding adherence are not known to have been revised or improved during the study period. If the patient is not eligible for ART, he or she will be scheduled to return six months later for repeat CD4 testing and clinical follow-up.

Visit 3 (1-4 weeks after Visit 2): ART initiation visit. If the patient is eligible to initiate ART, a second adherence counseling session is commenced at this visit. Following successful completion of two adherence sessions, the clinician initiates ART. If the patient has been designated for fast-track initiation based on CD4 value, the first three visits are recommended to occur within two weeks.

Visit 4 (1 month after Visit 3): First post-ART visit. Following ART initiation, the first post-initiation follow-up clinical visit is scheduled for approximately one month after initiation.

Visits 5+. Subsequent medical visits and counseling are scheduled for one- or two-month intervals, depending on the patient's clinical condition. Typically, patients on ART return on a monthly basis until they are considered stable and adherent (usually 5-6 months after initiation), at which time they may be given multi-month ART prescriptions, or may be transferred out to other clinics for care. For patients who remain at the clinic, CD4 and viral load testing is repeated six and 12 months after initiation and annually thereafter.

Antenatal visits: For pregnant women, South Africa's maternal health guidelines recommend antenatal clinic (ANC) visits start as early as possible in pregnancy, and the basic antenatal schedule for women includes five visits prior to delivery, regardless of HIV status, scheduled at 14, 20, 26, 32 and 38 weeks gestation.⁵⁵ The national guidelines stipulate a maternal prevention of mother to child transmission (PMTCT) regimen for all HIV-infected women with twice-daily zidovudine (AZT) beginning at 14 weeks gestation; intrapartum single-dose nevirapine and three-hourly AZT; and postpartum single-dose tenofovir and emtracitabine.⁵⁶

Additionally, for pregnant women with a CD4 value ≤ 350 cells/ μ l, lifelong ART should be initiated as soon as possible.⁴⁵ For HIV-positive women, there are no guidelines for combining ANC and HIV visits, so clinics are expected to dovetail HIV activities (CD4 results notification, ART initiation, etc.) with ANC visits.

Statistical analysis

Outcome: Chapter 4

The primary outcome for the first manuscript is the proportion of adult, non-pregnant, recently-diagnosed HIV-positive patients retained in care at Witkoppen during each of the following stages of early HIV care:

- Pre-ART stage 1: HIV diagnosis to CD4 results notification
- Pre-ART stage 2: For those not eligible for ART at staging (CD4 > 350 cells/ μ l) from CD4 results notification to eligible for ART
- Pre-ART stage 3: ART eligibility at staging to ART initiation
- Post-ART 0-6 months: ART initiation to six months after ART initiation
- Post-ART 6-12 months: Six months to 12 months after ART initiation

Completing each stage is defined as the proportion of patients who achieve each of the following milestones of early HIV care within each time period described above:

- Pre-ART stage 1: CD4 staging (including results notification) completed within three months of HIV diagnosis
- Pre-ART stage 2: For patients ineligible for ART, repeat CD4 test completed within 12 months of first CD4 staging date
- Pre-ART stage 3: ART initiated within three months of ART eligibility determination
- Post-ART 0-6 months: Retained in care for up to six months after ART initiation
- Post-ART 6-12 months: Retained in care for up to 12 months following six months on ART

We define patient retention as being alive and in care and not transferred and patient attrition as either patient drop-out or death. For participants for whom South African ID numbers are available, mortality outcomes were identified and confirmed by using the National Population Registry (death registry) of the South African Department of Home

Affairs in October 2011, at the end of follow-up.²² Patients who requested a transfer to another clinic are noted and removed from the analysis at the start of the stage in which they transferred.

Cumulative retention among ART-eligible patients is defined as completing pre-ART stages 1 and 3, and remaining on ART for at least 12 months. For those who were ART-ineligible at the time of testing HIV-positive, cumulative retention is defined as completing pre-ART stages 1 and 2.

Exposure: Chapter 4

As aim 1 is a descriptive analysis, we are primarily concerned with investigating the proportion retained at each stage. However, we also investigate the effect of baseline characteristics as independent predictors of attrition in the any pre-ART and post-ART (0-12 months) time period.

Covariates: Chapter 4

We explore the following patient characteristics as independent predictors of attrition at any pre-ART stage and post-ART (0-12 months): sex, age, CD4 count at the time of HIV testing, nationality, employment status, HIV positive at first visit to the clinic, and TB treatment at time of HIV diagnosis.

Analytic methods: Chapter 4

Baseline patient characteristics are summarized using counts and proportions for categorical variables and interquartile ranges (IQRs) for continuous variables. We report retention at the three stages of pre-ART care and two post-ART time points as counts and proportions with 95% confidence intervals (95%CI). Cumulative retention is reported using proportions and 95%CI and excludes patients who transfer at any point during the analysis. We identified predictors of any pre-ART or post-ART attrition by estimating adjusted risk ratios and 95%CI obtained by log-binomial regression analysis.

Outcome: Chapter 5

The primary outcome for the second manuscript is the proportion of recently-diagnosed HIV-positive pregnant patients retained in care at Witkoppen during the antenatal and postnatal periods. These periods are described in greater detail in the “analytic methods” section below.

Exposure: Chapter 5

As above, Aim 1 is a descriptive analysis, so we are primarily concerned with measuring the proportions lost at each stage. However, we also investigate the effect of baseline characteristics as independent predictors of LTFU before and after delivery.

Covariates: Chapter 5

We explore the following patient characteristics as independent predictors of attrition before and after delivery: age, CD4 count at the time of HIV testing, nationality and timing of first ANC visit.

Analytic methods: Chapter 5

Patient characteristics are described using proportions and 95%CI for categorical variables, and medians and IQR for continuous variables. We examine retention among pregnant women in two ways. Firstly, we report retention through several stages of pre- and post-ART care within the antenatal and postnatal periods using counts and proportions with 95%CI. The activities of early HIV in the stages used in Chapter 5 are similar to those in Chapter 4 (i.e., CD4 staging, ART initiation, etc.) but the timing of the events relates to before and after delivery. The first stage for all patients is completing CD4 staging, including results notification, prior to delivery. For those ART-eligible, subsequent stages include ART initiation prior to or after delivery, completing a clinic visit after delivery, and six months retention on ART. ART initiation prior to delivery is a key component of South Africa’s PMTCT program⁵⁶ and maximal effectiveness of ART for PMTCT has been shown to be reached around 13-15 weeks prior to birth.^{57,58} For ART-ineligible patients, subsequent

stages are returning for a clinic visit after delivery and receiving a repeat CD4 test after delivery. A diagram of these stages is presented in Figure 6 in Chapter 5. Retention is defined as completing each stage and is determined using clinic visit data. Patients who transfer are noted and removed from the analysis at the start of the stage in which they transferred.

Cumulative retention among ART-eligible women is defined as receiving CD4 results and initiating ART before delivery and remaining on ART for at least six months. Among those ART-ineligible, cumulative retention is defined as receiving CD4 results before delivery and returning for a repeat CD4 test after delivery. Cumulative retention analyses exclude patients who transferred during the antenatal (n=6) and postnatal (n=11) periods.

Secondly, we use time-to-event analysis to assess LTFU before and after delivery by estimating person-time in the antenatal and postnatal periods. LTFU, the outcome for this part of the analysis, is defined as not returning to the clinic within one month after the last scheduled visit. A one-month definition of LTFU is shorter than used in many studies, but pregnant women in antenatal care have more repeat visits within a short time period leading up to birth, thus one month after the last scheduled visit indicates that the patient is likely well off the clinic schedule. The one-month definition also allowed us to determine loss to follow-up in the antenatal period despite late presentation for the first ANC visit. For the antenatal period, person-time began accruing at testing HIV-positive and ended at the first of the following three events: 1) delivery, 2) loss to follow-up or 3) transfer to another facility prior to delivery. For women remaining in care during the postnatal period, person-time began accruing at delivery and ended at the first of 1) six months after delivery, 2) loss to follow-up or 3) transfer after delivery. No deaths were reported during the antenatal and postnatal time periods studied, so these represent all possible outcomes. After confirming the assumption of proportional hazards using the martingale residuals method (ASSESS statement in SAS), we examined predictors of overall loss within the antenatal and postnatal

periods using Cox proportional hazard regression and report adjusted hazard ratios and 95%CI. In the visual display of these results (Table 5), we also include LTFU rates (proportion LTFU/person-time) for each category presented.

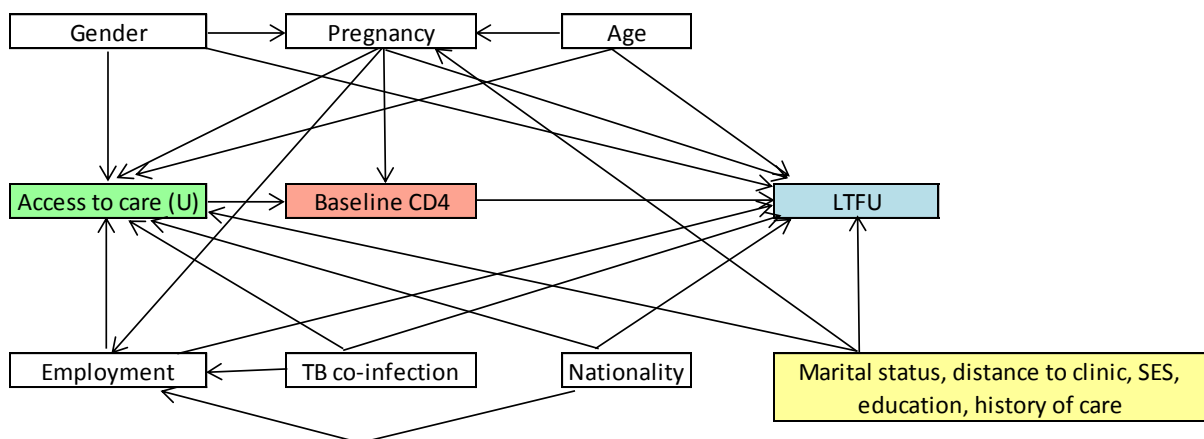
Outcome: Chapter 6

In Chapter 6, the primary outcome is LTFU, defined as not returning to the clinic within three months after the last scheduled visit. Secondary outcomes are mortality, which is obtained from the clinic file and from data linkage with the National Population Registry (South African Department of Home Affairs) and incident tuberculosis, defined using ICD-10 codes for any diagnosis of pulmonary *M. tuberculosis* infection after ART initiation date.

Exposure: Chapter 6

As shown in pink in Figure 3, baseline CD4 value at the time of initiating ART is the primary exposure in Chapter 6. Baseline CD4 is defined as the CD4 value closest to ART initiation, during a window six months prior to ART initiation to seven days post-initiation, and is categorized into ≤ 200 cells/ μ l and 201-350 cells/ μ l.

Figure 3. Directed acyclic graph (DAG) for potential confounders of the association between baseline CD4 value and loss to follow-up.



Covariates: Chapter 6

Covariates considered in Chapter 6 are shown in white in Figure 3 and are described in detail below.

- Age is categorized 18-29, 30-39, ≥40 years and will be examined as a potential confounder. Two dummy variables were created for age 18-29 and ≥40 years, with 30-39 years as the referent group. Age may affect CD4 and LTFU if health-seeking behaviors differ by age. We hypothesize that patients in the younger age groups are more likely to be LTFU.
- Pregnant at ART initiation and gender. Prevalent pregnancy was first explored as a potential effect measure modifier. Pregnant HIV-positive women at Witkoppen often have higher baseline CD4 values than the general clinic population due to routine ANC testing. In terms of LTFU, pregnant women receive more frequent care from different clinicians at a separate clinic within Witkoppen and also may be traced more aggressively by the clinic upon missing a visit. We assessed for relative effect measure modification by including an interaction (pregnancy*CD4) variable in the model, and found that when including the interaction term our estimate of CD4 on LTFU was substantially affected. Thus, we concluded that the estimate of baseline CD4 on LTFU was modified by pregnancy and we present results stratified by a three-level gender variable (non-pregnant female, male, pregnant female) at each of the two CD4 categories. This allows us to compare the effect of presenting for care and initiating at higher and lower CD4 groups by both gender and pregnancy status. Prior research suggests that pregnant women have equal or higher rates of LTFU than other adults,^{40,59,60} thus we hypothesize that they may be more likely to be LTFU.
- Nationality is a binary variable representing South Africa-born or foreign-born and was examined as a potential confounder. Witkoppen serves many recent immigrants to South Africa, and migration may influence retention in care. CD4 count also may be affected if nationality or migration affects access to care. Country of birth is used as a proxy for migration. Most foreign-born patients at Witkoppen are from Zimbabwe, with small numbers of patients from other neighboring countries, so we will group all foreign-

born patients into one category. We hypothesize that patients born outside of South Africa are more likely to be LTFU due to instability and frequent migration.

- Employment status may influence a patient's ability to access to care, thus CD4 values and LTFU. Witkoppen offers free services to patients who cannot pay, but transport costs to the clinic are frequently reported by patients as a financial barrier. Alternatively, patients with regular employment may be unable to take time off work to attend clinic visits. We will investigate employment status as a potential confounder and hypothesize that employed patients are less likely to be LTFU. We do not have data on type of work, so we cannot investigate the effect of different types of jobs or potential heterogeneity among the employed by type of work.
- Prevalent TB at ART initiation is coded as a binary variable and was investigated as a potential confounder. Prevalent TB is defined as any diagnosis of pulmonary *M. tuberculosis* infection with a TherapyEdge-HIV™ start date prior to ART initiation and end date after initiation. TB start date is defined in TherapyEdge-HIV™ as diagnosis start date and end date is defined as the date treatment ends. Patients with TB may be sicker than patients without TB, since TB is an opportunistic infection that affects those with advanced immunosuppression, and TB itself lowers CD4 count. Also, those on TB treatment may see a CD4 increase even prior to initiating ART. Since TB affects both CD4 count and LTFU, we will investigate it as a potential confounder and hypothesize that patients co-infected with TB may be more likely to be LTFU.

Covariates that may affect the association between baseline CD4 value and LTFU, but not included in the analysis, are shown in yellow in Figure 3. We did not include marital status because this is not captured in TherapyEdge-HIV™. Also, the high prevalence of common law/traditional marriages, as well as polygamous marriages in South Africa makes the variable difficult to interpret. We also did not evaluate distance to Witkoppen because the clinic almost exclusively serves a specific nearby geographic region, including the areas

of Diepsloot and Cosmo City, which is 10-15 minutes from the clinic by public transport. Socio-economic status (SES) markers, such as household income or inventory, are not available in TherapyEdge-HIV™. As mentioned earlier, Diepsloot is a very poor informal settlement. Education is poorly captured in TherapyEdge-HIV™ and history of care is not available. A previous study at Witkoppen found that 29% of patients suspected of TB did not attend high school.⁵⁴

Analytic methods: Chapter 6

Continuous variables are described using medians and IQR; categorical variables by counts and proportions. For patients who did not die within 12 months of ART initiation, person-time for the LTFU analysis began accumulating at ART initiation ended at the earliest of: 1) 12 months of follow-up, 2) loss to follow-up or 3) transfer. Patients who died within 12-months of ART initiation were followed from ART initiation to their date of death, even if previously considered lost. For the outcome of incident TB, person-time ended at the first diagnosis of TB within 12 months ART initiation or at death, or if neither of those outcomes, at the earliest of 1, 2 or 3 above.

After confirming the assumption of proportional hazards using the martingale residuals method (ASSESS statement in SAS), we used Cox proportional hazard methods to estimate 12-month loss to follow-up, mortality and incident TB, as well as predictors of these outcomes, and reported these using adjusted hazard ratios and 95%CI. Covariates were included in the model as confounders if they resulted in a meaningful change in estimate ($\geq 10\%$) and/or based on prior knowledge and direct acyclic modeling. We produced crude Kaplan-Meier curves depicting time to loss, mortality and incident TB by CD4 group and compared them using the log-rank test for equality of survivor functions using Stata 12 (StataCorp LP, College Station, TX). To assess for misclassification of death as LTFU among patients without a South African national ID, we conducted a sensitivity analysis restricted only to patients with a valid South African ID number. This sensitivity analysis did

not change the size of our effect or our conclusions. We also accounted for death as a competing risk on our estimate of loss to follow-up by utilizing the Fine and Grey model for competing risks analysis in Stata 12 and reported the subdistribution hazard ratio and 95%CI. This analysis considers our event of interest (LTFU) in the presence of other events (death) that may preclude the primary event from occurring. That is, under standard methods, if a patient dies before meeting our definition of LTFU, then the patient is censored and can no longer develop the outcome of interest. Competing risks analyses are recommended to correct for potential overestimation of the proportion obtaining the event of interest when calculating cause-specific hazard ratios.^{36,61,62}

It is important to note that the available data do not allow us to answer the ideal research question, which is, “What is the effect on loss to follow-up among patients with a CD4 count between 200-350 of initiating ART immediately (at a CD4 count between 200-350) versus deferring treatment until the CD4 count falls below 200?” In order to answer that question, we would need pre-ART data to measure LTFU and deaths prior to ART initiation for those in the deferred arm, but pre-ART data are incomplete and unreliable on TherapyEdge-HIV™. If such data were available, we could use marginal structural modeling techniques, which would allow for time-dependent confounding affected by prior exposure.^{63,64} Given the limitations of our data, the appropriate question to ask is, “Among those who are eligible for ART at the time of testing, what is the effect of baseline CD4 at the time of ART initiation on LTFU?” In this scenario, there is no time-varying confounding because our exposure (baseline CD4) is at one time point only (ART initiation). We are estimating LTFU among patients who survived until ART initiation and as such our results cannot be interpreted as a causal relationship.

Study limitations

The primary limitation of this study is that we cannot know if patients continue care at another facility, except among those patients who request an official transfer. This is a limitation that is shared by many studies investigating LTFU due to unlinked patient records. Transfers are classified as a separate outcome from LTFU, but it is possible that patients seek care elsewhere without requesting a formal transfer. It is also possible that patients test for HIV at Witkoppen but seek a second opinion at a different facility, and continue care there. In this study, LTFU must be understood to mean lost from Witkoppen only. The study setting, Witkoppen, is only one clinic, and one that is particularly well-integrated and comparatively well resourced. Thus, the results may not be generalizable to other clinics throughout South Africa with more limited resources and less integration, where LTFU may be greater than what we found at Witkoppen.

These study data are limited, as other retrospective studies, to those which are routinely collected in the patient file or in TherapyEdge-HIV™. File reviews may be inexact and incomplete if certain information is not recorded by the clinician at the time of the visit. Data on TherapyEdge-HIV™ are more likely to be missing than those from the file review, and data most likely to be missing include co-infection diagnosis (such as TB) and visit dates, particularly for patients prior to ART initiation. Since TherapyEdge-HIV™ data is especially poor for pre-ART patients, pre-ART data is only obtained via the file review. Unlike prospective studies, we are limited to the information at hand and cannot request specific information from clinicians about each patient from past visits. Furthermore, we cannot know the reason why LTFU patients might have dropped out of care with the information provided in the files. However, reviewing patient files retrospectively allows us to evaluate patient retention under real-world conditions and following the clinic's protocol, not a specific research protocol which might limit generalizability if visit scheduling and patient follow-up differed from standard practice.

Another limitation is the short follow-up period. Given that Witkoppen began its early initiation policy in early 2010, we only have data through one year after ART initiation. If we extended the study period, we could examine post-initiation retention, as well as pre-ART retention for those ART-ineligible, for a longer period. However, previous studies have shown that the first year of care is a period of high rates of pre-ART and post-initiation LTFU, so this study period provides the opportunity to look closely at the time periods when patients are lost within the first year of care and when interventions to address patient loss might be most useful. Some of the patients categorized as LTFU could turn out to be temporary care interruptions if they eventually return to care. Temporary interruptions and missed visits will not be addressed by this study. Given a longer study period, we could possibly see an increase in patients once considered LTFU returning to care.

Lastly, Witkoppen cares for a large proportion of patients from outside of South Africa, but deaths can only be confirmed using the South African national death registry using a valid South African ID number. This limits our ability to confirm death and raises the possibility that some patients classified as LTFU may in fact have died, which would overestimate our LTFU result and underestimate our mortality result.

CHAPTER 4

PATIENT RETENTION FROM HIV DIAGNOSIS THROUGH ONE YEAR ON ANTIRETROVIRAL THERAPY AT A PRIMARY HEALTHCARE CLINIC IN JOHANNESBURG, SOUTH AFRICA

Introduction

South Africa's national antiretroviral therapy (ART) program is currently the largest in the world, with over 1.7 million adults and children enrolled in the first seven years.^{1,4} Rapid scale-up has put tremendous pressure on the limited resources of the public health sector. Despite the fact that 300,000 patients enroll in the South African ART program each year,⁵ an estimated 250,000 people died of AIDS in 2010³ and only 52% of those currently ART-eligible are receiving treatment.⁴

An enormous challenge to South Africa's attempts to expand the impact of its program is attrition from HIV care. Uninterrupted retention for HIV patients is critical as patients who stop treatment are at increased risk of drug resistance, morbidity and mortality.^{20,21} Several studies have documented rates of retention on ART in resource-limited settings,^{15,26,27,60,65} and have demonstrated that during the first year on HIV treatment patients are at high risk for attrition (i.e., programmatic loss and mortality).²⁷⁻²⁹ More recent work has documented high rates of attrition among patients not yet on ART from the time of testing positive to completion of CD4 staging,^{30,31} from completing staging to repeat CD4 testing for ART eligibility,^{32,34} and from ART eligibility to ART initiation.^{32,35,36}

While these studies highlight a problem with attrition from HIV care, three major limitations impede conclusions about the extent of the problem. First, progression through the consecutive stages of HIV care (e.g., testing positive, CD4 staging, ART initiation) are

typically studied in isolation among distinct cohorts which prevents a measure of overall program attrition from the time of testing positive through long-term ART. To our knowledge, only one study has examined retention through pre-ART and post-ART stages among patients in Southern Africa. Using data from the first year of the public ART program (2004-2005) in Mozambique, Micek et al. reported data from separate HIV testing and treatment facilities and found retention was lowest at the period of enrollment at the ART sites (56.5%) and for timely ART initiation among ART-eligible (31.3%), but did not report cumulative retention through all stages or describe retention among patients ineligible for ART.²⁵ Second, operational definitions of patient retention differ greatly between studies, limiting comparability. Recommendations for standardized definitions for pre-ART care have recently been proposed,³³ allowing for estimates that can be compared across programs and countries. Third, most national HIV programs do not report retention indicators during pre-ART care, so we currently have no way of quantifying the magnitude of loss to initiation at the country level.

To address the limited longitudinal measures of attrition from HIV care across multiple stages of care, we set out to measure attrition through five stages of early HIV care at a single site in a cohort of patients testing positive using the newly recommended definitions.

Methods

Study setting

Witkoppen Health and Welfare Centre (“Witkoppen”) is a high-volume (8,500 patient visits per month) primary healthcare clinic in Johannesburg, South Africa, operated by a non-governmental organization receiving public and private financial support. Witkoppen provides HIV/AIDS services, integrated TB/HIV care, pre/post-natal care, chronic care, mental health services and social welfare assistance to a primarily low-income population

residing in densely-populated peri-urban formal and informal settlements in northern Johannesburg.

Pre-ART care at Witkoppen begins at the time of testing HIV-positive using two simultaneous rapid dried blood spot tests, with results available in about 20 minutes. Blood for CD4 testing is drawn at the clinic on the same day a patient receives a positive HIV result and is sent to an off-site National Health Laboratory Services (NHLS) facility. Patients are scheduled to return for CD4 results 2-4 weeks after testing positive. At this second visit, ART-eligible patients attend a first adherence counseling session and are examined by a clinician. Blood is collected for additional baseline tests, and they are scheduled to return 2-4 weeks later for a second adherence counseling session and ART initiation. Patients initially ineligible for ART receive counseling about their CD4 result, are examined by a clinician, and are scheduled to return for a follow-up CD4 test within six months. Patients – both pre-ART and on-ART – who miss scheduled appointments are to be phoned by clinic staff for rebooking, and if untraceable, to be referred for community outreach tracing.

ART is initiated on-site by doctors and qualified nurses. Patients at Witkoppen are generally treated according to the South African National Treatment Guidelines,⁴⁵ with an important exception. In 2010, Witkoppen began initiating all HIV-positive patients with a CD4 count ≤ 350 cells/ μ l, a year before South Africa adopted this policy nationwide.⁵³

Study design

We conducted an observational cohort study through retrospective clinical record review of all non-pregnant adult individuals at Witkoppen testing HIV-positive for the first time between 01 January–30 June 2010 (N=969). Starting with a roster of eligible patients sourced from the clinic's monthly HIV testing statistics, we excluded patients whose paper files could not be located after three separate attempts using the clinic number provided and

were unlisted in TherapyEdge-HIV™, the electronic clinic HIV patient database (N=125), suggesting an invalid clinic ID number or erroneous inclusion on the list of eligible patients. We also excluded two patients who transferred facilities immediately after testing HIV-positive. For the 842 patients included in the analysis, we reviewed clinic files after a minimum of 12 months (median 16.5 months, IQR 14.8-18.1) from the time of testing HIV-positive or at least 12 months post-initiation for those who were initially eligible for ART. Data were collected using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA).

Approval for this study was granted by the Human Research Ethics Committee of the University of the Witwatersrand and the Institutional Review Board of the University of North Carolina at Chapel Hill.

Definition of study variables

Retention was defined as remaining alive and in care at Witkoppen and was determined using clinic visit dates. Attrition refers to both loss to follow-up (no clinic attendance ≥ 3 months after last scheduled visit) and death but does not include transfers. Patients who transfer are removed from the analysis at the start of the stage in which they transferred. Missed visits among patients who returned to care and treatment interruptions do not contribute to our definition of retention. We defined three stages of pre-ART care³⁷ using standardized definitions³³ for retention in each stage as defined in Table 1. For pre-ART stage 1, we report the proportion of patients who complete CD4 staging within three months after testing HIV-positive. For pre-ART stage 2, we report the proportion of patients not eligible for ART who received a second CD4 test within one year after the first CD4 staging. Patients eligible for ART at the time of HIV diagnosis skip pre-ART stage 2 and move directly to pre-ART stage 3, where we report the proportion of patients initiating ART within three months after being determined ART-eligible. Eight patients (0.9%) reported

initiating ART at other facilities without transferring out and returned to Witkoppen, so the date initiated elsewhere was used. We report post-ART retention at six and 12 months after ART initiation. Retention within a stage is dependent on successfully completing the prior stage. Cumulative retention analyses exclude patients who transferred during the stages reported (n=59).

Table 1. Definitions of stages of early HIV care.

Stage	Key event	Definition of stage	Definition of retention
Pre-ART stage 1	CD4 staging	Start: testing HIV positive End: Completing CD4 staging, including results notification	Completing CD4 staging within 3 months of HIV diagnosis
Pre-ART stage 2	<i>If ineligible for ART</i> Repeat CD4 testing	<i>If ineligible for ART</i> Start: Results notification of first CD4 test after HIV testing End: Patient eligible for ART per repeat CD4 result	<i>If ineligible for ART</i> Completing a repeat CD4 test within 12 months of first CD4 staging date
Pre-ART stage 3	ART initiation	Start: Results notification of ART-eligible CD4 result End: ART initiation	Initiating ART within 3 months of ART-eligible CD4 result
Post-ART retention: 0-6 months	6 months ART retention	Start: ART initiation End: 6 months on ART	Continuing in care for 6 months following ART initiation
Post-ART retention: 6-12 months	12 months ART retention	Start: 6 months on ART End: 12 months on ART	Continuing in care for 12 months following 6 months on ART

Pre-ART stage definitions per Fox, Larson, Rosen, 2011.³³

We defined initial CD4 count as the value at the time of testing HIV-positive. ART-eligibility at the time of testing HIV-positive was confirmed during the file review and is generally defined as a CD4 count ≤ 350 cells/ μ l; however, 23 patients with CD4 values 200-350 cells/ μ l were considered ineligible for ART due to clinician non-compliance with the clinic's ART guidelines and three patients with CD4 > 350 cells/ μ l were considered eligible at clinician discretion. TB treatment was defined as initiating TB treatment within one year of

testing HIV-positive. For patients with an available South African ID number (33.9% of patients lost to follow-up) mortality was confirmed using the National Population Register of the South African Department of Home Affairs.²²

Statistical analysis

Patient characteristics at the time of testing HIV-positive were summarized using counts and proportions for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. We report retention at the three stages of pre-ART care and two ART time points as counts and proportions with 95% confidence intervals (95%CI). We identified predictors of any pre-ART or post-ART attrition by estimating adjusted risk ratios (aRR) and 95%CI obtained by log-binomial regression analysis.

Results

Characteristics of the 842 eligible patients are summarized in Table 2. Overall, 55.1% were female. Patients were a median (IQR) of 34 years (28-40) and had a median (IQR) initial CD4 count of 212 (92-350) cells/ μ l. Nearly half (41.5%) were born outside South Africa, mostly in Zimbabwe (75.9% of foreign-born), and 72.6% tested HIV-positive on their first visit to Witkoppen. Initial CD4 values were not available for 32 patients (3.8%) due to the patient leaving prior to CD4 testing (n=25) or missing lab results (n=7) and never returning for repeat testing. Of the remainder, 589 (72.7%) were ART-eligible when testing HIV-positive. Nearly 11% of patients initiated TB treatment within a year of HIV testing.

Table 2. Characteristics of the study participants (N=842).

Sex, <i>n (%)</i>	
Female	464 (55.1)
Male	378 (44.9)
Age at HIV testing, <i>median (IQR)</i>	
	34 (28-40)
Age at HIV testing, <i>n (%)</i>	
18-29 years	254 (30.2)
30-39 years	352 (41.8)
40 years and older	236 (28.0)
First CD4 value (cells/ μ l), <i>median (IQR)</i>	
	212 (92-350)
First CD4 value, <i>n (%)</i>	
<50 cells/ μ l	102 (12.1)
50-199 cells/ μ l	282 (33.5)
200-350 cells/ μ l	225 (26.7)
>350 cells/ μ l	201 (23.9)
Missing	32 (3.8)
Nationality, <i>n (%)</i>	
Born in South Africa	468 (55.6)
Born outside of South Africa	349 (41.5)
Missing	25 (3.0)
Employment status, <i>n (%)</i>	
Employed	435 (51.7)
Not employed	386 (45.8)
Missing	21 (2.5)
HIV-positive at first clinic visit, <i>n (%)</i>	
Yes	611 (72.6)
No	229 (27.2)
Missing	2 (0.2)
TB treatment*, <i>n (%)</i>	
Yes	92 (10.9)
No	750 (89.1)

IQR, interquartile range

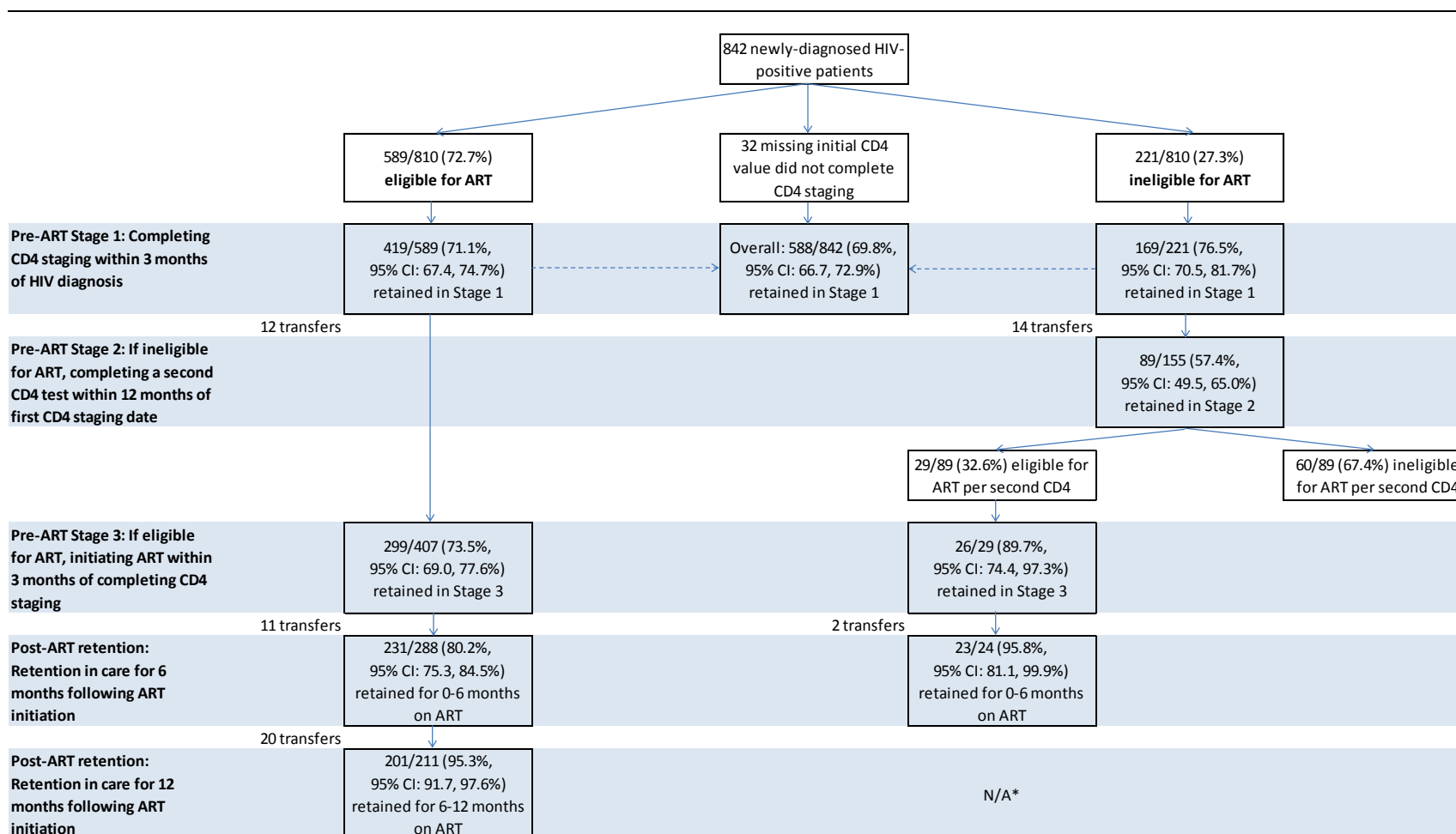
*Initiated TB treatment within one year from the time of testing HIV-positive.

Patient retention by stage

Retention through each of stage of pre- and post-ART care is shown in Figure 1, while Figure 2 shows cumulative continuous retention through all stages of early HIV care. Among patients newly-diagnosed with HIV, the greatest attrition occurred in pre-ART care, with over 25% attrition at each of the three pre-ART stages (Figure 1) among those remaining in care at the beginning of each stage. Overall retention in pre-ART stage 1 was 69.8% (95%CI 66.7%-72.9%) and included 32 subjects with no CD4 count, none of whom completed the stage. When limited to those with a CD4 count, retention was somewhat higher for those ineligible for ART than those eligible when testing HIV positive (76.5% vs. 71.1%, respectively). The lowest proportion retained was in pre-ART stage 2 among those ART-ineligible, with only 57.4% (95%CI 49.5-65.0%) of those who returned for their initial CD4 results returning for a repeat CD4 test within one year. Median (IQR) CD4 value at repeat testing among those previously ineligible for ART was 424 cells/ μ l (337-570) with 32.6% ART-eligible at their second CD4 staging. Retention after ART initiation was higher than during the pre-ART stages at 80.2% (95%CI 75.3-84.5%) between 0-6 months and 95.3% (95%CI 91.7-97.6%) between 6-12 months.

Of 544 patients who were ART-eligible when testing HIV-positive, the cumulative proportion who remained in care through 12 months on ART was only 36.9% (95%CI 33.0-41.1%), and among 207 ART-ineligible patients, 43.0% (95%CI 36.4-49.8%) were retained within one year of initial CD4 staging (Figure 2). While attrition at each stage is substantial, overall attrition steadies over time. Among those completing a stage (or retained for pre-ART stage 2), the median (IQR) time to completing stage 1 (testing to completing staging) was 16 days (9-28), stage 2 (completing staging until a repeat CD4 count) was 162 days (138-186), and stage 3 (ART eligibility to ART initiation) was 23 days (12-36), suggesting most patients who complete a stage do so within the defined time periods.

Figure 4. Study profile of completion of key stages of early HIV care among 842 newly diagnosed HIV-positive patients at an HIV treatment program in South Africa.

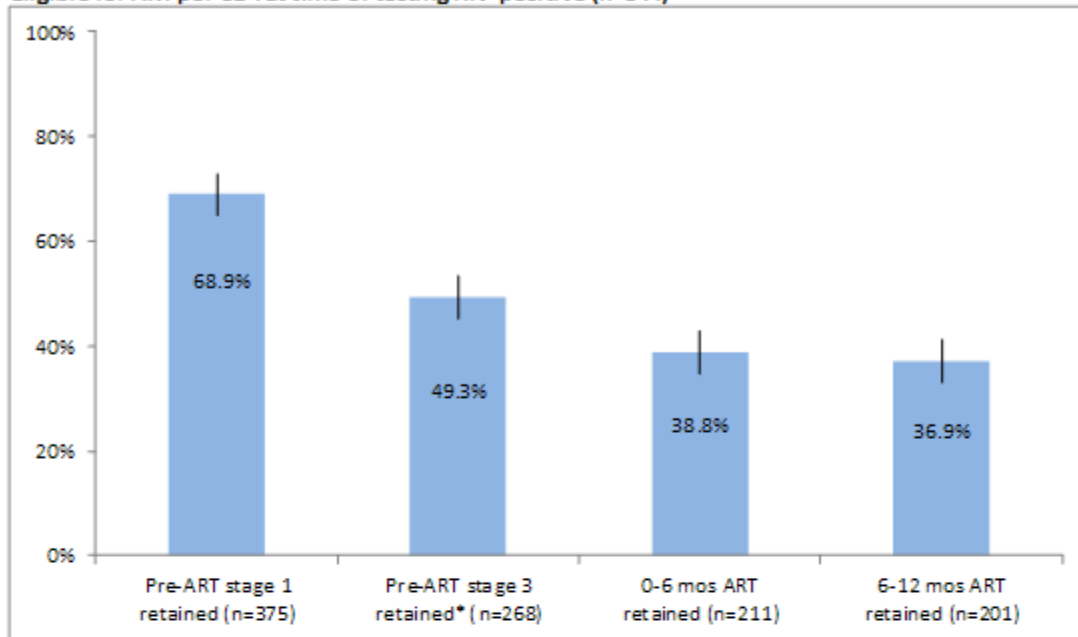


Stage completion is dependent on completing the prior stage in the time period specified. Patients eligible for ART per CD4 value at the time of HIV testing skip Pre-ART Stage 2 and move directly to Pre-ART Stage 3.

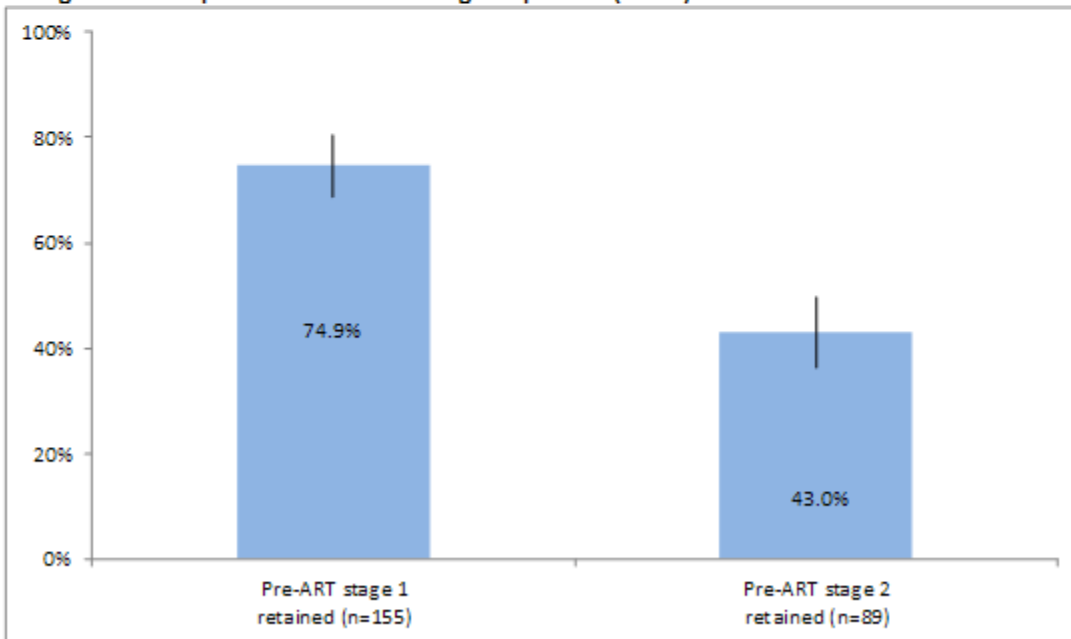
*12 month ART retention data not available by the end of data collection.

Figure 5. Cumulative patient retention from HIV diagnosis through one year on ART for 544 HIV-positive patients eligible for ART, and one year after initial CD4 staging for 207 HIV-positive patients ineligible for ART.

Eligible for ART per CD4 at time of testing HIV-positive (n=544)



Ineligible for ART per CD4 at time of testing HIV-positive (n=207)



Error bars indicate 95% confidence intervals on the proportions.

Stage completion is dependent on completing the prior stage in the time period specified.

*Patients eligible for ART at the time of HIV testing skip pre-ART stage 2 and proceed directly to pre-ART stage 3.

Patients who transferred during the stages shown were excluded from this analysis (n=59).

During the study period, 48 (5.7%, 95%CI 4.3-7.4%) patients died, however when we limit this to the 38.8% (n=327) of the sample with a valid South Africa ID, mortality doubles to 11.9% (95%CI 8.7-15.8%). Initial CD4 results are available for 46 (95.8%) of the deceased patients; of these, 87.0% were eligible for ART. Patients who died had a lower median initial CD4 count (105 cells/ μ l, IQR 49-169) than those who did not (225 cells/ μ l, IQR 101-354), but did not differ from the overall cohort in terms of age, sex or TB treatment. Among ART-eligible patients, 2.5% (95%CI 1.5-4.1%) of patients in pre-ART stage 1 and 3.9% (95%CI 2.4-6.2%) of patients in pre-ART stage 3 died. Following ART initiation, 2.4% (95%CI 1.1-4.8%) of patients died with less than six months on treatment and 1.0% (95%CI 0.2-3.1%) with more than six months on ART. Among patients who were ART-ineligible, none died during pre-ART stage 1 and 2.7% (95%CI 1.1-5.6%) of patients in pre-ART stage 2 died. Overall, 77.5% of ART-eligible patients who died did not initiate ART and the proportion of patients who died declined after ART initiation.

Predictors of pre-ART and post-ART attrition

Younger age (18-29 years) was associated with increased attrition in the pre-ART stages (aRR 1.56, 95%CI 1.21, 2.00), and possibly after ART initiation (aRR 1.27, 95%CI 0.76, 2.13), compared to age 30-39 (Table 3). An initial CD4 <50 cells/ μ l predicted increased attrition before (aRR 1.51, 95%CI 1.08, 2.12) and after ART initiation (aRR 2.30, 95%CI 1.15, 4.63), compared to an initial CD4 200-350 cells/ μ l. Male sex was associated with increased likelihood of attrition before ART (aRR 1.47, 95%CI 1.16, 1.87), but not after ART initiation (aRR 0.76, 95%CI 0.45, 1.28). Patients born outside of South Africa tended to fail to complete 12 months on ART (aRR 1.48, 95%CI 0.92, 2.40) compared to their South African counterparts. TB treatment was strongly associated with decreased attrition in the pre-ART stage (aRR 0.04, 95%CI 0.01, 0.27), but not following ART initiation (aRR 1.42, 95%CI 0.79, 2.53).

Table 3. Multivariate analysis of factors associated with patient attrition prior to ART and within the first 12 months after ART initiation among newly-diagnosed HIV-positive patients at an HIV treatment program in South Africa.

	Any pre-ART stage (n=842)			Any post-ART stage (n=288)*		
	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Age at HIV testing						
18-29 years	96 (37.8)	1.57 (1.26, 1.94)	1.56 (1.21, 2.00)	18 (27.3)	1.55 (0.95, 2.52)	1.27 (0.76, 2.13)
30-39 years	94 (26.7)	1	1	27 (20.0)	1	1
40 years and older	48 (20.3)	0.65 (0.49, 0.86)	0.74 (0.52, 1.04)	12 (13.8)	0.62 (0.34, 1.11)	0.68 (0.36, 1.30)
First CD4 value						
<50 cells/ μ l	32 (31.4)	1.28 (0.93, 1.75)	1.51 (1.08, 2.12)	13 (28.9)	1.60 (0.94, 2.71)	2.30 (1.15, 4.63)
50-199 cells/ μ l	69 (24.5)	0.94 (0.73, 1.21)	1.10 (0.82, 1.48)	31 (21.4)	1.18 (0.74, 1.88)	1.48 (0.81, 2.73)
200-350 cells/ μ l	58 (25.8)	1	1	11 (11.6)	1	1
>350 cells/ μ l	47 (23.4)	0.90 (0.67, 1.19)	0.90 (0.65, 1.26)	NA [†]	NA [†]	NA [†]
Sex						
Female	116 (25.0)	1	1	37 (21.3)	1	1
Male	122 (32.3)	1.29 (1.04, 1.60)	1.47 (1.16, 1.87)	20 (17.5)	0.83 (0.51, 1.35)	0.76 (0.45, 1.28)
Nationality						
Born in South Africa	119 (25.4)	1	1	25 (16.3)	1	1
Born outside of South Africa	115 (33.0)	1.30 (1.04, 1.61)	1.11 (0.88, 1.40)	31 (25.6)	1.57 (0.98, 2.51)	1.48 (0.92, 2.40)
Employed						
Yes	119 (27.4)	1	1	29 (18.5)	1	1
No	113 (29.3)	1.07 (0.86, 1.33)	1.07 (0.84, 1.36)	27 (22.1)	1.20 (0.75, 1.91)	1.13 (0.70, 1.81)
HIV-positive at first clinic visit						
Yes	185 (30.3)	1.31 (1.00, 1.71)	1.16 (0.86, 1.55)	43 (21.1)	1.33 (0.76, 2.34)	1.13 (0.64, 1.99)
No	53 (23.1)	1	1	13 (15.9)	1	1
TB treatment [†]						
Yes	1 (1.1)	0.03 (0.00, 0.24)	0.04 (0.01, 0.27)	14 (25.5)	1.38 (0.81, 2.34)	1.42 (0.79, 2.53)
No	237 (31.6)	1	1	43 (18.5)	1	1

RR, relative risk; CI, confidence interval; n (%) show proportion not retained in each category

Model is adjusted for all variables listed. Patients who transferred out of the clinic are removed from the analysis according to date of transfer.

*Post-ART model includes only patients who were initially eligible for ART and completed pre-ART stage 1 and pre-ART stage 3.

[†]Patients with CD4 values >350 are ineligible for ART.

[†]Initiated TB treatment within one year from the time of testing HIV-positive.

Discussion

Retention in HIV care from the time of testing positive through lifelong ART treatment is critical for getting patients onto treatment promptly and preventing morbidity and mortality associated with disease progression. This study, one of the first to follow a consistent cohort of newly-diagnosed HIV-positive patients over a year through the various stages of pre-ART and early ART care, allowed us to summarize attrition throughout early HIV care. Our findings paint a stark picture—the proportion of patients ART-eligible when testing positive retained continuously in care through one year on ART was under 40%. This suggests that the majority of patients in our study continued to be at high risk of HIV-associated death and opportunistic infections despite knowing their HIV-positive status.

This finding is consistent with a previous review of sub-Saharan African studies that estimated overall retention in pre-ART care to be 33%.³⁷ One critical problem however with summarizing previous studies' results is a lack of consistent definitions of retention and time periods over which retention was measured. Thus while many studies have previously documented high pre-ART^{30-32,34,35} and on-ART attrition^{15,26,27,60,65} at specific stages in care, our finding of substantial patient loss throughout the stages of early HIV care is one of the only studies to document this in a single cohort of ART-eligible and ineligible patients using standardized definitions.³³ Studies that only investigate retention in disjointed cohorts are also unable to comment on the timing of attrition. We found that the pre-ART periods are a time of considerable loss, with over one-quarter of patients still in care lost at each stage.

Our results also document the challenge of retention among patients ineligible for ART at the time of testing positive for HIV. Given that South Africa guidelines call for repeat CD4 testing every six months,⁴⁵ the pre-ART stage 2 definition used gives patients ample time to return. Despite this, we found only 57.4% (95%CI 49.5-65.0%) of ART-ineligible individuals completed a repeat CD4 count within one year. This is true despite the fact that pre-ART services were available at the same clinic where the patient completed HIV testing

and CD4 staging and did not require visiting a separate location. While low, our retention results are higher than other recent studies from South Africa which have shown retention for patients not yet eligible for ART to be between 36.0% and 46.3%,^{32,34} and consistent with a meta-analysis result of 54.2% among ART-ineligible patients in sub-Saharan Africa.⁶⁶

The majority of patients in our study were ART-eligible when testing positive for HIV under the site's threshold of a CD4 count ≤ 350 cells/ μ l. Among these eligible patients, for whom moving from HIV diagnosis to CD4 staging to ART initiation can be completed within two to eight weeks, attrition was greatest in pre-ART care. In just these few first weeks, patient attrition was 28.9% (95%CI 25.3-32.6%) from testing to CD4 staging and 26.5% (95%CI 22.4-31.0%) from ART eligibility to ART initiation. For those who initiated treatment, attrition 0-12 months after ART initiation remained high overall at 25.0% (95%CI 20.1-30.4%), but most attrition occurred during 0-6 months on ART (19.8%, 95%CI 15.5-24.7%) and stabilized between 6-12 months on ART (4.7%, 95%CI 2.4-8.3%). This finding suggests that if patients have the motivation and support to complete the early milestones of CD4 staging and ART initiation, they are likely to remain in care. Given the substantial proportion (28.9%) of ART-eligible patients who did not return for their second clinic visit to receive CD4 results, the challenge is to retain patients within the very first weeks of HIV care: from diagnosis through CD4 staging and ART initiation. Recognition of this challenge has encouraged new efforts to retain these patients, including offering point-of-care CD4 technology and same-day ART initiation.⁶⁷⁻⁶⁹

We identified several important predictors of patient attrition within the first year of HIV care (Table 3). Differing directions of estimates for predictors of pre-ART or post-ART attrition indicate that there may be different drivers of retention within each group at these unique stages that require specific, targeted interventions. For example, males had greater attrition in the pre-ART stages, but no gender difference was observed post-ART. Overall, our findings are consistent with other studies noting poorer retention among males^{27,32,35,36,60}

and younger patients^{27,32,60} and highlight the need for interventions targeted to these specific groups, such as improved male-involvement approaches, youth-friendly services, mobile technology and others. Patients on TB treatment had much less likelihood of attrition during pre-ART stages, which differs from the results of an ART-eligible Durban cohort where newly-diagnosed TB patients experienced 76% greater attrition than TB-free patients.⁷⁰ Our finding likely is due to regular follow-up at the clinic during TB treatment and active tracing of those who default TB treatment. After ART initiation, patients in our study were as likely, or possibly more likely, to drop out of care as those not on TB treatment, highlighting the importance of communicating the need for regular ART care beyond the TB treatment period. Being born outside of South Africa was associated with a nearly 50% increased likelihood of attrition following ART initiation, similar to Bygrave, et al,⁷¹ but in contrast to better retention in care among self-identified foreigners in South Africa found by McCarthy, et al.⁷² Witkoppen has a very high proportion of patients born outside of South Africa, which is becoming increasingly common in Johannesburg public-sector clinics, if not throughout the country.^{68,73} In addition to migration among immigrant patients, clinics should evaluate the potential for short- or long-term migration away from the clinic among immigrant and South African patients, and facilitate links to care and provide sufficient drug supply.

Mortality in our study was low at 5.7%. Even though we used the South Africa Department of Home Affairs National Population Register to verify deaths, which has been shown to be 80% complete for adults with valid ID numbers,⁷⁴ this estimate of overall mortality likely is underestimated as nearly half of our cohort was not South African and when we limited our mortality estimate to only those with a valid South African ID, mortality doubled. It is difficult to compare our mortality estimate to findings of other studies since most focus only on either pre-ART or post-ART mortality. Among patients who died who were eligible for ART, we found that the majority of deaths occurred prior to ART initiation,

further emphasizing the importance of linkage to care during the critical pre-ART period and the need to fast-track patients with severe immunosuppression.

Our results should be interpreted in light of their limitations. First, the generalizability of our results may be limited given that our data represent only one facility. Retention may have been higher than in most settings given the integration of HIV testing and care on-site. Previous studies suggest that moving from facility to facility for CD4 testing, ART initiation, etc., may encourage attrition.^{25,39} Second, retention may be underestimated as some patients considered lost in our analysis may have continued care and initiated treatment elsewhere. We only know of the intention to continue care elsewhere among patients who requested a transfer, a common limitation of studies investigating patient retention. Third, we defined attrition based on visit dates, which does not consider missed visits or treatment interruptions, which may overestimate the true amount of patient engagement in care. Finally, due to high patient drop-out throughout the study period, our sample size was reduced by the post-ART stages, limiting the precision of our regression analysis estimates for this period. Strengths of our study include a comprehensive dataset that allows for retention estimates from the point of testing HIV-positive through ART retention with few missing data. The study was conducted under routine clinical conditions and represents patient retention within a real-world scenario at one clinic.

Our findings help to explicate the problem of attrition from HIV programs throughout the continuum of early HIV care. In our study, patient attrition was highest during the pre-ART period, but our findings suggest that once patients initiate ART, they are more likely to be retained. These findings support the need for retention interventions that target patient loss from the very first visit when a patient learns their HIV-positive diagnosis.

CHAPTER 5

LOSS TO FOLLOW-UP BEFORE AND AFTER DELIVERY AMONG WOMEN TESTING HIV-POSITIVE DURING PREGNANCY IN JOHANNESBURG, SOUTH AFRICA

Introduction

South Africa has a national antenatal HIV prevalence of 30.2%⁷⁵ and more people living with HIV than any other country in the world.¹ In an ongoing effort to improve care for pregnant women with HIV and to prevent mother-to-child transmission (PMTCT), and aligning with concurrent WHO revised PMTCT guidelines,⁷⁶ South Africa's 2010 HIV treatment guidelines called for lifelong ART to be initiated for all pregnant women with a CD4 value ≤ 350 cells/ μ l⁴⁵ and PMTCT guidelines mandated AZT prophylaxis from 14 weeks of pregnancy.⁵⁶ However, implementation of these guidelines remains inadequate, with pregnant women in South Africa commonly presenting for their first ANC visit well into their second trimester or later, delaying HIV diagnosis, AZT prophylaxis and lifelong ART initiation.⁷⁷⁻⁷⁹

In addition to late presentation for ANC services, some studies suggest that pregnant women have poorer retention in HIV care than men and non-pregnant women.^{40,41} Retention in HIV care is paramount, as HIV-positive patients require routine management and daily adherence to ART once initiated,⁸⁰ mortality is high among patients who drop out of ART programs,^{22,28} and HIV/AIDS contributes to nearly half (43.7%) of maternal deaths in South Africa, far overshadowing deaths due to other obstetric complications such as hemorrhage or sepsis.⁸¹ An analysis of nearly 30,000 women initiating antiretroviral therapy (ART) in South Africa found loss was 54% higher in pregnant than in non-pregnant women (aHR 1.54; 95%CI 1.38-1.72), despite decreased mortality.⁴² The reasons for these differences

are still being identified, and may include lower rates of immunosuppression and a lack of perception of need for treatment,^{41,82} increased financial burden,⁴¹ travel or relocation during pregnancy,^{41,78,83} and stigma.^{78,84,85} In South Africa, antenatal coverage is widespread and nearly all births occur in healthcare facilities,⁸⁶ but there is still great difficulty in ensuring an unbroken continuum of HIV care between antenatal care at a primary health clinic (PHC), labor and delivery at a hospital, and postnatal care and ongoing HIV care returning at the PHC.

To date, investigations of retention in HIV care among pregnant women have provided an estimate of loss to follow-up between specific milestones, such as HIV testing to ART initiation,^{40,79,83} or ART initiation to between 6 months and 3 years on treatment,⁴⁰⁻⁴² without evaluating the impact of delivery on loss. While studies from the US demonstrate ART adherence often declines in the postpartum period compared to during pregnancy,⁸⁷⁻⁹⁰ few studies have documented postpartum attendance in HIV care in sub-Saharan Africa in routine clinic settings.⁹¹ We hypothesize loss to follow-up may differ before and after delivery given that women's motivations for seeking care may change during these time periods. This analysis of data from a cohort of newly-diagnosed HIV-positive pregnant women examines loss to follow-up through early stages of HIV care to better understand how loss to follow-up is influenced by delivery.

Methods

This study was conducted at Witkoppen Health and Welfare Centre ("Witkoppen"), a busy facility (8500 clinic visits per month) providing primary healthcare services to formal and informal settlements in northern Johannesburg, South Africa. Between January and June 2010, 300 pregnant women (≥18 years) tested HIV-positive for the first time at their first ANC visit at Witkoppen. We conducted a retrospective cohort study through file review

to assess attrition from pre-ART and on-ART care up to a minimum of 12 months after testing HIV-positive.

HIV Care

At Witkoppen, HIV care is integrated with antenatal care for pregnant women, with assessment for and initiation of ART occurring within ANC. In early 2010, Witkoppen began initiating all adult patients with CD4 ≤ 350 cells/ μ l onto ART, one year prior to national guidelines calling for this approach. We confirmed ART eligibility at the time of HIV testing for each subject through file review. During the time when the study was conducted, CD4 testing was initiated at the same facility immediately following an HIV-positive test result, with a visit scheduled two weeks later to receive the CD4 results. For ART eligible patients, an ART initiation visit was scheduled two to four weeks after receiving the CD4 results.

Antenatal and Postnatal Care

Witkoppen offers antenatal and postnatal care, HIV testing and treatment on-site, as well as other primary healthcare and social welfare services. HIV testing at Witkoppen occurs during a woman's first ANC visit and all HIV-positive pregnant women are given twice-daily zidovudine (AZT) starting as early as 14 weeks gestation, as called for in PMTCT guidelines.⁵⁶ All women who receive antenatal care at Witkoppen are designated to deliver at Hillbrow Hospital in central Johannesburg (32.5 km from Witkoppen) or, if considered high-risk, at Charlotte Maxeke Johannesburg Academic Hospital (28.9 km). At the hospital, women not yet on lifelong ART are given intrapartum single-dose nevirapine and three-hourly AZT, as well as postpartum single-dose tenofovir with emtricitabine for PMTCT. Newborns also start a six-week course of nevirapine syrup from birth.⁵⁶ The hospitals do not routinely report delivery information back to Witkoppen. Following delivery, ANC patients return for postnatal care and HIV treatment services at Witkoppen for ten weeks and then

resume general adult care, all within the same facility and using the same clinic file. Mothers and infants make three postnatal care visits together: 3-7 days after delivery; six weeks after delivery for an infant polymerase chain reaction (PCR) HIV test; and 10 weeks after delivery for infant HIV PCR results. Women previously ineligible for ART should have a repeat CD4 at the six-week postpartum visit.

Timing of delivery

Data on gestational age at HIV testing based on last menstrual period were available in most (88.3%) patient files while date of delivery was available in patient files for 39.7% of women. Thus, we determined a delivery date for 91% of women using either the actual date or an estimation assuming 40 weeks gestation. Women with no calculated delivery date (n=27, 9.0%) were excluded, leaving an analytic sample size of 273.

Statistical Methods

Patient characteristics are described using proportions and 95% confidence intervals (95%CI) for categorical variables, and medians and interquartile ranges (IQR) for continuous variables. We examine retention among pregnant women in two ways. First, we report retention through several stages of pre- and post-ART care within the antenatal and postnatal periods using counts and proportions with 95%CI. The first stage for all patients is completing CD4 staging, including results notification, prior to delivery. For those ART-eligible, subsequent stages include ART initiation prior to or after delivery, completing a clinic visit after delivery, and six months retention on ART. For ART-ineligible patients, subsequent stages include returning for a clinic visit after delivery and receiving a repeat CD4 test after delivery. A diagram of these stages is presented in Figure 1. Retention is defined as completing each stage and is determined using clinic visit data. Patients who transfer are noted and removed from the analysis at the start of the stage in which they

transferred. Cumulative retention analyses exclude patients who transferred during the antenatal (n=6) and postnatal (n=11) periods.

Second, we use time-to-event analysis to assess loss to follow-up before and after delivery by estimating person-time in the antenatal and postnatal periods. Loss to follow-up is defined as not returning to the clinic within a minimum of one month after the last scheduled visit. For the antenatal period, person-time began accruing at testing HIV-positive and ended at the first of the following three events: 1) delivery, 2) loss to follow-up or 3) transfer to another facility prior to delivery. For women remaining in care at the beginning of the postnatal period, person-time began accruing at delivery and ended at the earliest of: 1) six months after delivery; 2) loss to follow-up; or 3) transfer after delivery. No deaths were reported during the antenatal and postnatal time periods studied, so these represent all possible known outcomes. We examined predictors of loss within the antenatal and postnatal periods using Cox proportional hazard regression and report adjusted hazard ratios (aHR) and 95%CI.

Ethical approval for this study was granted by the Human Research Ethics Committee of the University of the Witwatersrand and exemption was given by the Public Health-Nursing IRB at the Office of Human Research Ethics at the University of North Carolina at Chapel Hill.

Results

Clinical and demographic characteristics at HIV testing of the 273 pregnant women are summarized in Table 4. The median (IQR) age at the first ANC visit was 27 years (24-31) and the median CD4 count at the time of HIV testing was 357 cells/ μ l (238-500). Overall, almost half of the cohort (44.7%) was born outside of South Africa, most notably in Zimbabwe (89.3% of those foreign-born).

Table 4. Characteristics of the study participants (N=273).

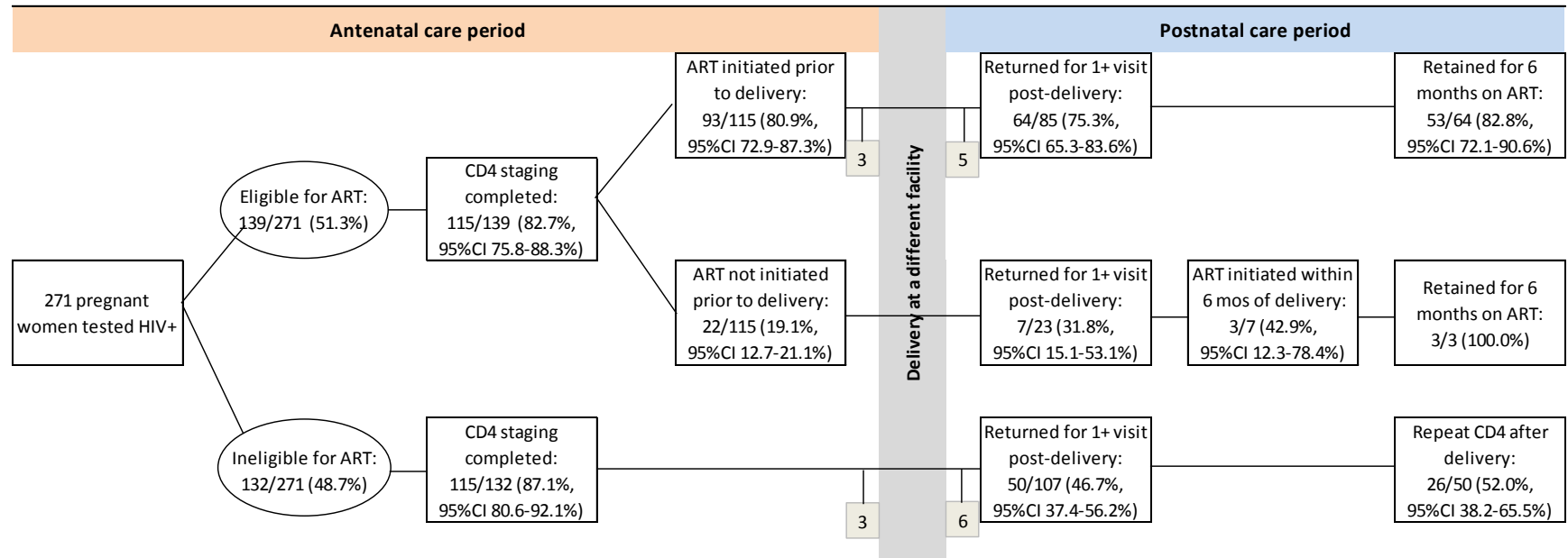
Patient characteristic	
<i>Continuous variables, median (IQR)</i>	
Age at HIV testing	27 (24-31)
First CD4 value (cells/ μ l)	357 (238-500)
Weeks of gestation at first ANC visit	26 (21-30)
<i>Categorical variables, n (%)</i>	
Age at HIV testing	
18-24 years	78 (28.6%)
25-29 years	98 (35.9%)
30 years and older	97 (35.5%)
First CD4 value	
<50 cells/ μ l	4 (1.5%)
50-199 cells/ μ l	48 (17.6%)
200-350 cells/ μ l	83 (30.4%)
>350 cells/ μ l	136 (49.8%)
Missing	2 (0.7%)
Nationality	
Born in South Africa	143 (52.4%)
Born outside of South Africa	122 (44.7%)
Missing	8 (2.9%)
Employment status	
Employed	97 (35.5%)
Not employed	167 (61.2%)
Missing	9 (3.3%)
Gestation at first ANC visit	
\leq 20 weeks	59 (21.6%)
>20 weeks	214 (78.4%)
IQR, interquartile range	

The median (IQR) gestational age at first ANC visit was 26 weeks (21-30) and the median (IQR) time from HIV testing to delivery was 3.1 months (2.1-4.1). AZT monotherapy as part of PMTCT was almost universally implemented. During pregnancy 98.0% received at least one 30-day supply of AZT, all but one of whom (99.7%) started AZT on the day of testing HIV-positive.

Retention during antenatal care

Figure 6 shows retention of pregnant women through early HIV care, contingent on completing earlier stages. Roughly half of all women were ART-eligible at the time of testing; median (IQR) CD4 at HIV testing was 244 cells/ μ l (171-299) among ART-eligible and 500 cells/ μ l (420-599) among ART-ineligible women. Completing CD4 staging prior to delivery was high at 84.9% (95%CI: 80.2-88.8%) overall, and varied little by ART eligibility (87.1% vs. 82.7%). Of those who were ART-eligible and who completed CD4 staging prior to delivery (n=115), most (80.9%; 95%CI: 72.9-87.3%) went on to initiate lifelong ART prior to delivery. These women spent a median (IQR) of 27 days (17-41.5) from HIV testing to ART initiation and a median (IQR) 9.5 weeks (5.1-14.2) on ART prior to delivery. Of the remaining 22 ART-eligible women who completed CD4 staging but did not initiate ART prior to delivery, most (n=18, 81.8%) never returned for ART initiation, one returned but left before initiation, one required further counseling, one refused ART, and one completed the initiation visit but was rescheduled to return for initiation a week later and did not return. Of all 139 ART-eligible women, 66.9% (95%CI: 58.8-74.3%) initiated treatment prior to delivery.

Figure 6. Patient retention before and after delivery among 271 recently-diagnosed HIV-positive ANC patients.



*Two patients with missing initial CD4 values who did not complete CD4 staging were excluded from this figure.

Completion of each stage is dependent on successful completion of the prior stage.

Numbers in small shaded boxes represent the number of patients transferred at that time point.

Retention after delivery

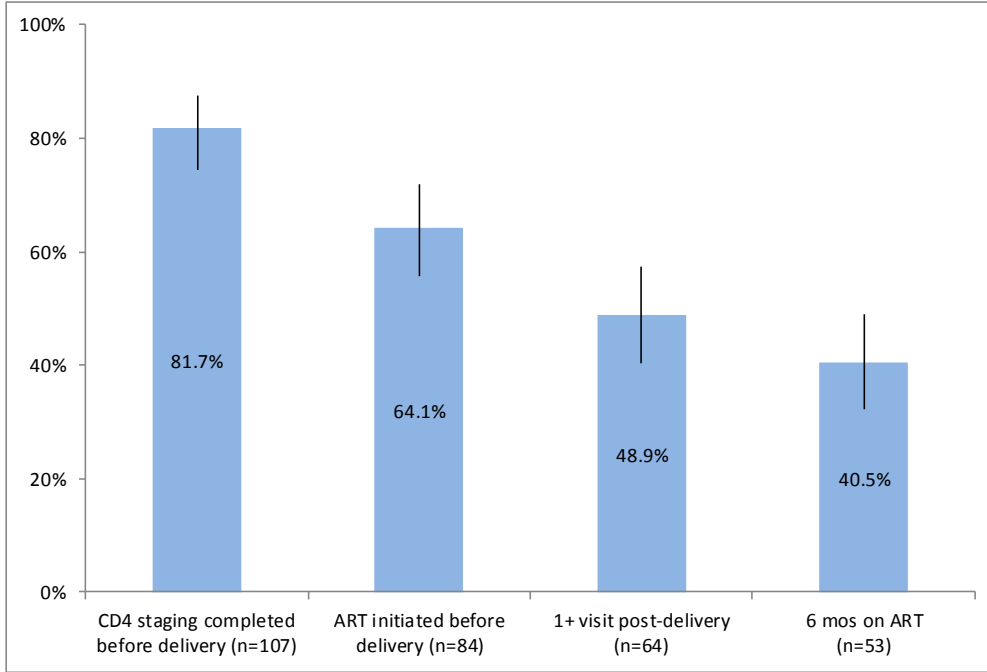
The proportion of patients returning for at least one visit after delivery was highest among those who were eligible for ART and initiated treatment prior to delivery (n=85) at 75.3% (95%CI: 65.3-83.6%) with most of these women (82.8%; 95%CI: 72.1-90.6%) retained in ART care for at least six months. Though the numbers of women who completed CD4 staging and were eligible for but did not initiate ART were small (n=22), only 31.8% (95%CI: 15.1-53.1%) returned at any point after delivery, and less than half of those who did (42.9%; 95%CI: 12.3-78.4%) initiated ART within six months of delivery. The picture was much different for those ineligible for ART at the time of testing positive. Among those ART-ineligible who completed CD4 staging (n=115), less than half (46.7%, 95%CI: 37.4-56.2%) returned for any visits after delivery. Of these 50 women, only half (52.0%, 95%CI: 38.2-65.5%) received a repeat CD4 count after delivery.

Cumulative retention in HIV care

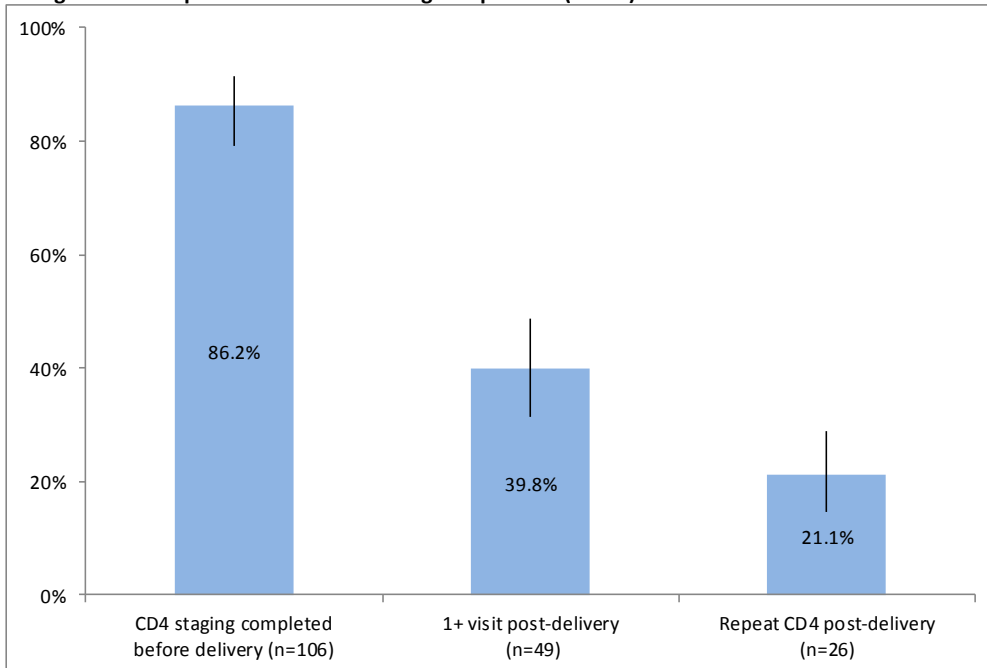
Figure 7 shows cumulative retention for ART-eligible women from HIV testing through delivery and six months on ART as well as for ART-ineligible women through a post-delivery repeat CD4 count. Cumulatively, less than half (40.5%, 95%CI: 32.3-49.0%) of ART-eligible patients who tested HIV-positive during pregnancy completed CD4 staging, initiated ART prior to delivery, returned after delivery and completed six months on ART. Cumulative retention was even lower among those ineligible for ART at the time of HIV testing: only 21.1% (95%CI: 14.6-29.0%) of patients ineligible for ART continued in care to the point of a repeat CD4 count after delivery.

Figure 7. Cumulative patient retention from HIV diagnosis through six months on ART for 131 HIV-positive ANC patients eligible for ART, and through repeat CD4 testing after delivery for 123 HIV-positive ANC patients ineligible for ART.

Eligible for ART per CD4 at time of testing HIV-positive (n=131)



Ineligible for ART per CD4 at time of testing HIV-positive (n=123)



Error bars indicate 95% confidence intervals on the proportions.

Completion of each stage is dependent on successful completion of the prior stage.

Patients who transferred during the ANC period (n=6) and post-delivery period (n=11) were excluded from this figure.

The median (IQR) person-time contributed in the antenatal period was 2.8 months (1.7-3.9) and 4.5 months (1.5-6.0) in the postnatal period. Using time-to-event analysis and analyzing all women regardless of ART eligibility at the time of testing, 20.5% (95%CI: 16.0-25.6%) of women were lost to follow-up prior to delivery. Among women in care at delivery, 47.9% (95%CI: 41.2-54.6%) were lost within six months after delivery, for a cumulative loss to follow-up of 57.5% (95%CI: 51.6-63.3%).

Table 5 presents the results of multivariate analysis of factors associated with loss within the antenatal and postnatal time periods. Presenting late for the first ANC visit (after 20 weeks gestation) was associated with twice the likelihood of loss prior to delivery after adjusting for age, initial CD4 count and nationality (aHR 2.00; 95%CI 1.00, 4.02) but late presentation was not associated with loss during the postnatal period (aHR 1.09; 95%CI 0.65-1.83). ART-ineligibility at the time of HIV testing based on a CD4 count >350 cells/ μ l was strongly associated with loss to follow-up following delivery (aHR 3.30; 95%CI: 1.95-5.58), while pregnant women age 30 years and older were less likely to be lost after delivery (aHR 0.49; 95%CI: 0.30-0.81). Our results suggest that women born outside of South Africa may be more likely to be lost after delivery (aHR 1.36; 95%CI: 0.90-2.06) than women born in South Africa.

Table 5. Multivariate analysis of factors associated with loss to follow-up before and after delivery among 273 newly-diagnosed HIV-positive antenatal patients.

	Antenatal care period (n=273)			Postnatal care period (n=211)		
	n (%)*	Crude HR (95% CI)	Adjusted HR (95% CI)	n (%)*	Crude HR (95% CI)	Adjusted HR (95% CI)
Age at HIV testing						
18-24 years	19 (24.4)	1.26 (0.66, 2.40)	1.25 (0.64, 2.42)	31 (54.4)	0.96 (0.61, 1.52)	0.91 (0.57, 1.43)
25-29 years	18 (18.4)	1	1	45 (57.7)	1	1
30 years and older	19 (19.6)	0.94 (0.54, 1.63)	1.08 (0.55, 2.11)	25 (32.9)	0.50 (0.31, 0.82)	0.49 (0.30, 0.81)
First CD4 value						
<200 cells/mm ³	10 (19.2)	1.12 (0.51, 2.47)	1.24 (0.56, 2.78)	16 (41.0)	1.71 (0.87, 3.36)	1.72 (0.87, 3.42)
200-350 cells/mm ³	16 (19.5)	1	1	18 (27.3)	1	1
>350 cells/mm ³	28 (20.4)	0.95 (0.51, 1.75)	1.03 (0.55, 1.94)	67 (63.2)	3.00 (1.78, 5.05)	3.30 (1.95, 5.58)
Nationality						
Born in South Africa	31 (21.7)	1	1	48 (44.9)	1	1
Born outside of South Africa	25 (20.5)	1.05 (0.62, 1.78)	0.99 (0.57, 1.72)	52 (54.2)	1.33 (0.90, 1.97)	1.36 (0.90, 2.06)
First ANC visit >20 weeks gestation						
No	14 (23.7)	1	1	18 (40.9)	1	1
Yes	42 (19.6)	2.11 (1.07, 4.19)	2.00 (1.00, 4.02)	83 (49.7)	1.29 (0.77, 2.14)	1.09 (0.65, 1.83)

HR, hazard ratio; CI, confidence interval

Loss to follow-up is defined as not returning to the clinic within ≥1 month after the last scheduled visit; antenatal care period is defined as HIV testing date to delivery date; postnatal care period is defined as delivery date to 6 months after delivery.

Adjusted models are adjusted for all variables listed.

* Proportion lost to follow-up during the period for each category listed.

Discussion

Pregnant women diagnosed with HIV during antenatal care require effective care interventions to ensure the prompt initiation of PMTCT and ART, but also must be linked to HIV care that is sustainable beyond the point of delivery. We found that overall loss to follow-up within 13 months of HIV testing among pregnant women recently diagnosed with HIV was staggeringly high at 57.5% (95%CI: 51.6-63.3%). Unlike studies that begin reporting loss to follow-up at ART initiation, our findings span the period from testing HIV-positive through both the pre-ART and early post-ART periods, periods of high attrition. Patients who initiate ART have already successfully been retained through several visits, and thus, may be more inclined to continue in care. Few reports exist of retention of all patients – both ART eligible and ineligible. Our loss to follow-up proportion, which includes this early loss, is much higher than the 12%-32% among pregnant women after six months to three years on ART reported elsewhere which only focuses on the on-treatment period.⁴⁰⁻

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Our analysis also suggests that the focus on cumulative loss to follow-up among pregnant women is missing important trends over time with implications for when to intervene. Loss to follow-up prior to delivery was much lower than after delivery (20.5% vs. 47.9%). The antenatal period is a time of reasonable compliance with HIV care, likely because women are already attending care for another reason for which they have motivation to continue. Our results suggest many women are not returning to the PHC after delivery. Among HIV-positive pregnant women, the challenge is ensuring HIV care extends beyond the period of pregnancy and continues for the lifetime of the mother. In South Africa, infants are to accompany their mothers to the first three postnatal care visits, so failure to attend these visits also suggests a failure to link infants to postnatal care, including PCR testing for HIV.

In addition to a high rate of loss to follow-up, we also found pregnant women presented for their first ANC visit and HIV testing well after the recommended gestational age of 14 weeks for AZT initiation. The median gestational age at HIV testing of 26 weeks in our study matched that found by Stinson et al.,⁷⁹ and represents delayed PMTCT efforts. Half of the pregnant patients in our cohort were ART-eligible at their first ANC visit, yet despite the overall trend of late presentation, 66.9% (95%CI: 58.8-74.3%) of those eligible initiated ART prior to delivery. The median time from first visit to ART initiation of 27 days indicates that patients are being initiated promptly after the first visit, but as the median time on ART is 9.5 weeks, they are not presenting early enough to obtain maximal effectiveness of ART for PMTCT, which is reached around 13-15 weeks duration prior to delivery.^{57,58} The median duration on ART prior to delivery in our study is consistent with findings of 7.6-10.7 weeks in other studies in South Africa.^{77-79,92} Additionally, nearly one-third (31.1%, 95%CI 25.7-41.2%) of ART-eligible women should have initiated before delivery but did not. Recognition of the problem of late presentation to ANC care and its impact on delayed ART initiation, as well as poor linkage to care prior to ART, has spurred interest in rapid or same-day ART initiation among pregnant women using point-of-care CD4 testing.⁹³

South African ANC patients receive a government-mandated ANC card at their first ANC visit, and must present it at the hospital labor ward prior to delivery. There has been speculation that women only attend one ANC visit to get this card but do not return for additional care. Our data do not support this idea. Among pregnant women in our cohort, 15.1% failed to complete CD4 notification (i.e. attended only one clinic visit), which is half the proportion (30.2%) of non-pregnant adults who did not complete CD4 staging during this same period.⁹⁴ Our finding of sufficient linkage to care among pregnant women is consistent with that of Kranzer et al., who found CD4 completion was highest among antenatal care patients in Cape Town when compared to patients of other clinic services.³² This suggests

that many women are making repeat visits while pregnant but then have high rates of loss after delivery.

In our study women who presented late for their first ANC visit (>20 weeks gestation) were twice as likely to be lost prior to delivery (aHR 2.00, 95%CI 1.00-4.02), underscoring the difficulty of retaining patients who are initially slow to seek care. Three South Africa-based studies identified fear of HIV testing/diagnosis, confusion over pregnancy status, transport limitations, lack of perceived benefit, and clinic booking delays as common reasons for late presentation among ANC patients,^{82,95,96} highlighting the multi-level barriers that can prevent timely access to and retention in care among pregnant women. Patients with higher CD4 counts (>350 cells/ μ l) who were ineligible for ART were more likely to be lost postpartum (aHR 3.30; 95%CI 1.95-5.58), emphasizing the importance of retention during pre-ART care. South Africa's PMTCT guidelines call for repeat CD4 testing after delivery, but only 22.6% of ART-ineligible women received a repeat CD4 count. Witkoppen has a very high proportion of patients born outside of South Africa, as is now common in PHCs throughout Johannesburg.^{68,73} These patients may be at greater risk of loss to follow-up after delivery (aHR 1.36; 95%CI 0.90-2.06), likely because of frequent mobility among this group.

Our findings must be considered in light of the study's limitations. First, we do not know why women ceased care at Witkoppen. Under half (45.2%) of the women who were lost received at least one follow-up phone call. We reviewed the files of 84 pregnant patients who were lost to follow-up whom the clinic had made at least one attempt to contact. Over half (52.3%) were unreachable because their cell phone was off or out of service and 20.2% were found to have moved out of the area, usually outside Johannesburg's Gauteng Province. This may indicate that women return to rural homes^{41,78,83} – whether in South Africa or a neighboring country – either immediately prior to or following birth. While migration around delivery is typically short-term, it disrupts the continuity of care, which likely

impairs adherence to ART. We also do not have data on ART adherence, which can affect PMTCT, nor do we have information on the care of the infants.

Second, we do not know if patients who drop out of care at Witkoppen continue in care at other facilities, perhaps in a rural facility or outside South Africa, except for those who request a formal transfer. While this is a limitation shared by most studies of loss to follow-up, it is important to note that loss to follow-up in this study reflects ceasing care at one clinic only, but one that was selected for study due to close integration of antenatal care, postnatal care and HIV services. We also cannot link to hospital data to confirm delivery. More research is needed into ways to improve linkages across treatment sites and ways to improve patient movement between sites (e.g. providing sufficient supply of antiretrovirals).

Finally, our study data, which were collected retrospectively, were limited to those routinely collected in the patient files, but with very few missing data. Our findings regarding timing of first ANC visit and linkage to care among ANC patients are consistent with previously reported studies from other regions of South Africa,^{32,79} suggesting that our results are generalizable to other clinics throughout South Africa.

Our study highlights much room for improvement in the provision of HIV care of pregnant women. We found that pregnant women presented late for their first ANC visit, initiated ART too late to achieve maximal PMTCT effectiveness, and had high rates of drop out around the time of delivery. Pregnant women likely have different motivation for attending healthcare services than non-pregnant adults, and likewise, different reasons why they may become lost. Efforts must be increased to better understand the intentions of pregnant women for seeking healthcare after delivery, understanding their motivations for ceasing HIV care, and improve linkages to care after delivery.

CHAPTER 6

INITIATING ART WHEN PRESENTING WITH HIGHER CD4 COUNTS RESULTS IN REDUCED LOSS TO FOLLOW-UP UNDER SOUTH AFRICA'S 2010 REVISED ANTIRETROVIRAL THERAPY GUIDELINES

Introduction

South Africa's national antiretroviral therapy (ART) program, launched in 2004, is the world's largest,¹ with 1.8 million individuals initiated on ART by mid-2011.⁴ Initially, the threshold for ART eligibility in the national guidelines for adult ART initiation was set at a CD4 cell count below 200 cells/ μ l or a WHO Stage IV clinical condition.⁹⁷ In late 2009, the WHO revised their guidelines by increasing the threshold for eligibility for ART in resource-limited settings to ≤ 350 cells/ μ l.^{43,44} In August 2011, South Africa officially adopted this policy.⁴⁶ It has been estimated that this policy expanded eligibility to an additional 1.06 million (95%CI: 0.88-1.29m) ART-naïve adults with CD4 values 200-349 cells/ μ l.⁴

Patients who initiate ART with a CD4 above 200 cells/ μ l are at reduced risk of death and serious opportunistic infections including tuberculosis, as demonstrated in developed countries,⁹⁸⁻¹⁰⁰ a randomized trial in Haiti,⁵⁰ and observational studies in sub-Saharan Africa.⁴⁷⁻⁴⁹ However, if patients initiate treatment before perceiving the clinical necessity, gains from positive clinical outcomes from earlier treatment may be offset by increases in patient loss to follow-up.¹³ To date, only one study has reported the effect of initiation at higher CD4 counts on loss to follow-up under routine early initiation (≤ 350 cells/ μ l) within sub-Saharan Africa and found 39% reduced loss among those initiating at CD4 cell counts >200 cells/ μ l versus ≤ 200 cells/ μ l (aHR 0.61, 95%CI: 0.43-0.87).⁴⁷

Witkoppen Health and Welfare Centre (Witkoppen) is an NGO-operated clinic serving a primarily poor population from formal and informal settlements in northern Johannesburg, South Africa. In March 2010, a year before the national policy was enacted, Witkoppen began ART initiation for all adult patients at the higher threshold of ≤ 350 cells/ μ l. This provides a unique opportunity to examine the impact of initiating treatment among patients presenting at higher CD4 counts on patient loss to follow-up under routine care.

Methods

We created a retrospective cohort of all adult (≥ 18 years) ART-naïve patients initiating ART at Witkoppen during April-December 2010 who presented with a baseline CD4 value eligible for ART (≤ 350 cells/ μ l). We excluded 29 patients missing a baseline CD4 value, leaving 1430 for analysis. Data were extracted from the clinic's electronic patient record system (TherapyEdge-HIV™) in May 2012, allowing all subjects time to experience a 12-month outcome. Patients who provided a South African ID number ($n=685$, 47.9%) were matched to the National Population Register of the South African Department of Home Affairs in August 2011 to identify deaths.

We sought to estimate the effect of initiating ART with a CD4 count 201-350 versus ≤ 200 cells/ μ l on loss to follow-up (primary outcome) in the first 12 months after ART initiation. We defined loss as not returning to the clinic within 3 months of the patient's last scheduled visit. For loss to follow-up, person-time began accumulating three months after ART initiation (when patients became at risk for loss) and excluded 50 patients who died or transferred in the first three months. Person-time ended at death within 12 months, or the earliest of 12 months of follow-up, loss to follow-up or transfer. We defined baseline CD4 count (≤ 200 and 201-350 cells/ μ l) as the temporally last measure between six months prior and seven days after ART initiation and grouped patients into those who presented and initiated ART with a lower (≤ 200 cells/ μ l) or higher (201-350 cells/ μ l) baseline CD4 value.

We produced crude Kaplan-Meier curves of time to loss by CD4 group. We used Cox proportional hazards regression to estimate the association of CD4 category and 12-month loss to follow-up and report adjusted hazard ratios (aHR) and 95% confidence intervals (95%CI). We also evaluated the impact of death on estimates of loss using a competing risks analysis and report the subdistribution hazard ratio (sHR) and 95%CI.

We identified pregnancy at ART initiation as an effect measure modifier of the relation between CD4 count and loss to follow-up by stratifying estimates of the risk of loss by CD4 group, gender and pregnancy. Based on prior knowledge and change-in-estimate evaluation, we adjusted models for age, nationality, employment and prevalent TB. The study was approved by institutional review boards at the University of North Carolina at Chapel Hill and the University of the Witwatersrand.

Results

Among the 1430 patients, nearly half (48.0%) presented with a CD4 201-350 cells/ μ l at ART initiation (Table 6). Median (IQR) baseline CD4 by group was 105 cells/ μ l (55-154) versus 268 cells/ μ l (239-307). The higher CD4 count group was more likely to be <30 years old (31.7% vs. 24.5%) and female (75.7% vs. 63.4%), partly because there were more pregnant women (19.2% vs. 10.6%) in the higher CD4 group due to routine antenatal HIV testing. The low CD4 count group had more tuberculosis at ART initiation (16.7% vs. 5.7%).

Table 6. Characteristics of the study participants by baseline CD4 group (N=1430).

Patient characteristic	Total (N=1430)	CD4 ≤200 cells/μl (n=743, 52.0%)	CD4 201-350 cells/μl (n=687, 48.0%)
Sex, <i>n (%)</i>			
Female	991 (69.3)	471 (63.4)	520 (75.7)
Male	439 (30.7)	272 (36.6)	167 (24.3)
Age at HIV testing, <i>median (IQR)</i>	34.3 (29.3, 41.2)	35.2 (30.0, 42.2)	33.3 (28.7, 39.9)
Age at HIV testing, <i>n (%)</i>			
18-29 years	400 (28.0)	182 (24.5)	218 (31.7)
30-39 years	625 (43.7)	327 (44.0)	298 (43.4)
40 years and older	405 (28.3)	234 (31.5)	171 (24.9)
First CD4 value (cells/mm ³), <i>median (IQR)</i>	195 (103, 266)	105 (55, 154)	268 (239, 307)
First CD4 value, <i>n (%)</i>			
<50 cells/μl	169 (11.8)	169 (22.8)	0 (0.0)
50-100 cells/μl	182 (12.7)	182 (24.5)	0 (0.0)
101-200 cells/μl	392 (27.4)	392 (52.8)	0 (0.0)
201-350 cells/μl	687 (48.0)	0 (0.0)	687 (100.0)
Nationality, <i>n (%)</i>			
Born in South Africa	969 (67.8)	504 (67.8)	465 (67.7)
Born outside of South Africa	461 (32.2)	239 (32.2)	222 (32.3)
Employment status, <i>n (%)</i>			
Employed	736 (51.5)	391 (52.6)	345 (50.2)
Not employed	694 (48.5)	352 (47.4)	342 (49.8)
TB at ART initiation, <i>n (%)</i>			
No	1267 (88.6)	619 (83.3)	648 (94.3)
Yes	163 (11.4)	124 (16.7)	39 (5.7)
Pregnant at ART initiation, <i>n (%)</i>			
No	1219 (85.2)	664 (89.4)	555 (80.8)
Yes	211 (14.8)	79 (10.6)	132 (19.2)

IQR, interquartile range

Within one year of ART initiation, 15.5% (95%CI: 13.0-18.2%) versus 12.7% (95%CI: 10.3-15.3%) were lost among those in the lower versus the higher CD4 group, respectively (Figure 8). Among non-pregnant females, we found a 42% reduction in loss to follow-up among women initiating ART at higher versus lower CD4 cell counts (aHR 0.58; 95%CI: 0.37-0.91) (Table 7). Males who initiated ART at higher CD4 counts were also at reduced risk of loss to follow-up compared to males who started ART at CD4 count ≤ 200 cells/ μ l (aHR 0.74; 95%CI: 0.44-1.23). However among pregnant women there was no association between CD4 category and loss to follow-up (aHR 0.95; 95%CI: 0.55-1.67). Additionally, younger adults (age 18-29 years) were 38% more likely to become lost to follow-up compared to adults age 30-39 years (aHR 1.38, 95%CI: 1.00-1.92), and unemployed patients were 51% (aHR 1.51, 95%CI: 1.34-2.00) more likely to become lost to follow-up. Estimates differed little when accounting for death as a competing risk. Figure 8 shows the gender variation in loss to follow-up: males were more likely to be lost than non-pregnant females and women pregnant at ART initiation were most likely to be lost.

During the first year of ART care, 29 patients (1.9%; 95%CI: 1.3-2.7%) died and 44 acquired TB (3.1%; 95%CI: 2.3-4.1%). Patients initiating ART at CD4 values 201-350 cells/ μ l were at much lower risk of death (aHR 0.34; 95%CI: 0.13-0.84) and incident TB (aHR 0.44; 95%CI: 0.23-0.85) than those with CD4 ≤ 200 cells/ μ l.

Figure 8. Kaplan-Meier estimates of time to loss to follow-up by baseline CD4 value (top) and by baseline CD4 by gender/pregnancy at ART initiation status (bottom).

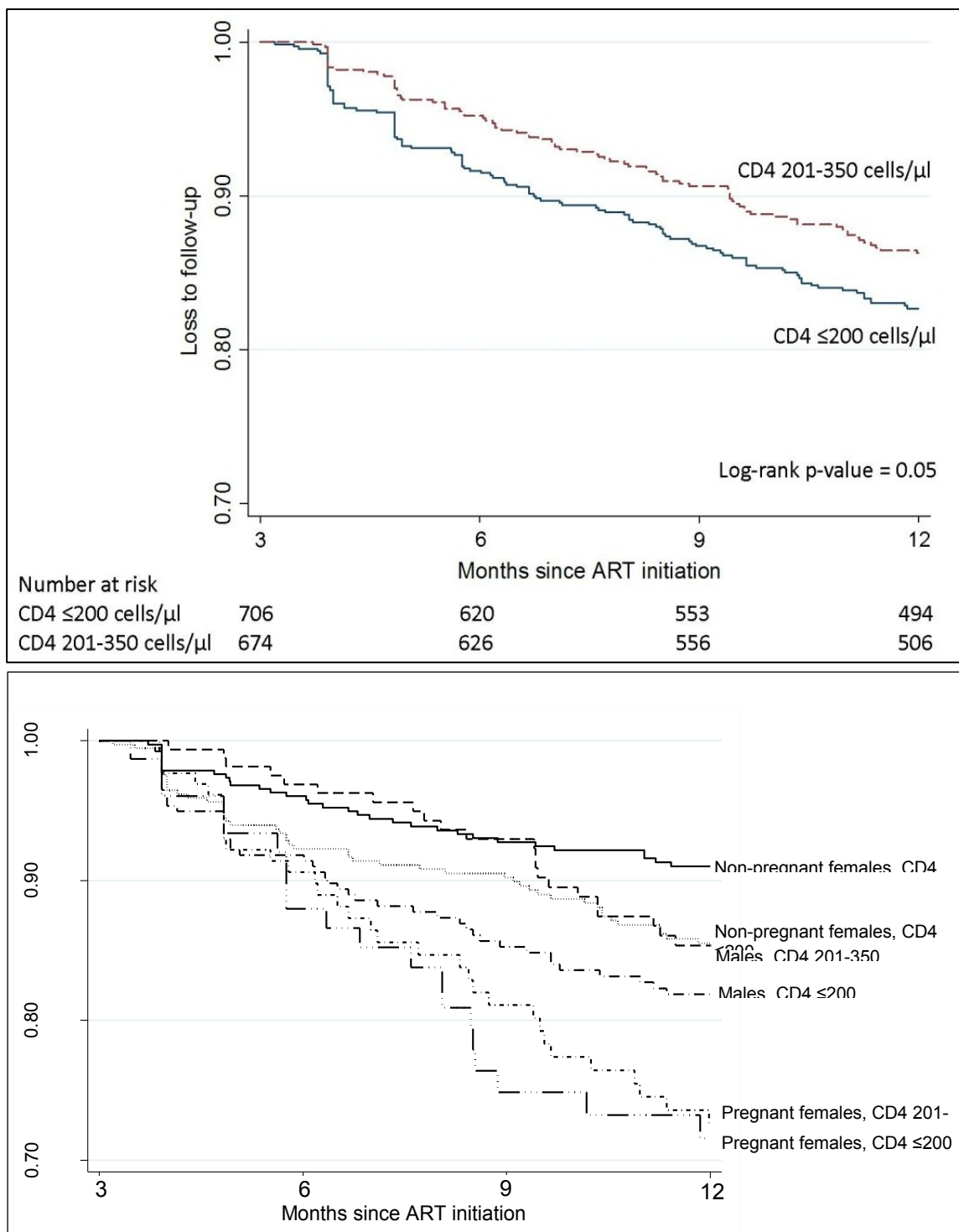


Table 7. Multivariate analysis of factors associated with patient loss to follow-up one year after ART initiation at an HIV treatment program in South Africa (N=1430).

	n (%)	Crude HR (95% CI)	Adjusted HR (95% CI)	Competing risk sHR* (95% CI)
Non-pregnant female, CD4 ≤200 cells/μl	50/369 (13.6)	1	1	1
Non-pregnant female, CD4 201-350 cells/μl	33/380 (8.7)	0.61 (0.39, 0.94)	0.58 (0.37, 0.91)	0.59 (0.38, 0.91)
Male, CD4 ≤200 cells/μl	45/261 (17.2)	1	1	1
Male, CD4 201-350 cells/μl	22/164 (13.4)	0.74 (0.44, 1.23)	0.74 (0.44, 1.23)	0.74 (0.45, 1.24)
Pregnant at ART initiation, CD4 ≤200 cells/μl	20/76 (26.3)	1	1	1
Pregnant at ART initiation, CD4 201-350 cells/μl	32/130 (24.6)	0.93 (0.53, 1.62)	0.95 (0.55, 1.67)	0.96 (0.56, 1.67)
Age at HIV testing				
18-29 years	74/383 (19.3)	1.50 (1.10, 2.06)	1.38 (1.00, 1.92)	1.39 (1.00, 1.91)
30-39 years	83/605 (13.7)	1	1	1
40 years and older	45/392 (11.5)	0.83 (0.58, 1.20)	0.93 (0.64, 1.35)	0.93 (0.64, 1.34)
Nationality				
Born in South Africa	139/931 (14.9)	1	1	1
Born outside of South Africa	63/449 (14.0)	0.95 (0.70, 1.27)	0.82 (0.61, 1.11)	0.83 (0.61, 1.12)
Employment status				
Employed	87/716 (12.2)	1	1	1
Unemployed	115/664 (17.3)	1.50 (1.14, 1.99)	1.51 (1.34, 2.00)	1.50 (1.13, 1.99)
TB at ART initiation				
Yes	22/155 (14.2)	0.97 (0.63, 1.52)	1.01 (0.64, 1.59)	1.00 (0.63, 1.59)
No	180/1225 (14.7)	1	1	1

HR, hazard ratio; CI, confidence interval; n (%) show proportion lost to follow-up in each category

Models are adjusted for all variables listed

Loss to follow-up is defined as not returning ≥3 months after the last scheduled visit; the HR models exclude 50 patients who died or transferred prior to 3 months follow-up (N=1380)

*The competing risk subdistribution hazard ratio (sHR) model includes all 1430 patients and assesses patient loss to follow-up in the presence of the competing risk of death

Discussion

This is the first study from a routine clinical setting in South Africa to demonstrate patients can be initiated on ART at higher CD4 counts without increasing patient attrition. We found 42% (aHR 0.58; 95%CI: 0.37-0.91) reduced risk of loss to follow-up among non-pregnant females and 26% (aHR 0.74; 95%CI: 0.44-1.23) reduced risk among male patients who initiated ART at CD4 counts 201-350 cells/ μ l compared to those \leq 200 cells/ μ l. This result is in concert with a 39% reduced loss among those initiating at CD4 cell counts $>$ 200 cells/ μ l versus \leq 200 in Lesotho.⁴⁷ However our study highlights substantial variation by gender in reduced risk at initiating at higher CD4 cell counts. The association of initiating at higher CD4 counts was greatest among non-pregnant females and males, and null among pregnant women. Patient loss is a major challenge to providing effective HIV care and our results suggest that expanding ART eligibility to patients with higher baseline CD4 values can be done without increasing loss.

We found that loss to follow-up among males of both CD4 groups was substantially higher than non-pregnant females who initiate at CD4 201-350 cells/ μ l (Figure 8), which suggests the need for specific retention interventions targeted to males. Loss to follow-up among women pregnant at ART initiation was the highest of any gender group, but interestingly, baseline CD4 did not substantially affect loss among pregnant women, possibly because loss was already so high. High loss to follow-up among pregnant women recently has been reported in other studies within South Africa,^{41,42,60} and is particularly concerning since HIV is the largest cause of maternal mortality in South Africa.⁸¹

Additionally, our results confirm the considerable reductions in mortality and incident tuberculosis throughout the first year of ART seen among patients who present for care and initiate ART with a higher CD4 count versus those who present with advanced immunosuppression. These findings correspond with those of several studies in resource-limited settings that observed significantly reduced risk of death and opportunistic infections

when initiating treatment at higher CD4 values⁴⁷⁻⁵⁰ and support South Africa's decision to revise its ART guidelines in 2011 to align with WHO recommendations.

Our study has several strengths. The unique study site allowed us to examine the impact of initiating at higher CD4 values within the context of routine, clinical care. Additionally, our analysis assessed the potential for the competing risk of death to bias our associations, but found little evidence of an important influence. We reduced the likelihood of death being misclassified as loss to follow-up by validating deaths using South Africa's national death registry. However, the registry only includes patients with a valid South African ID number (47.9%) and included only deaths through data export in August 2011. We conducted a sensitivity analysis restricted only to patients with a valid South African ID number but this did not change the size of our effect or our conclusions.

Limitations to our analysis include use of data obtained from a single site and therefore findings may not be generalizable to all public-sector settings within South Africa or health care centers in other regions. As with most retention studies, we cannot know if a patient continued care at another facility due to unlinked data at facilities. Thus, loss to follow-up in this study must be understood as lost to the facility where ART was initiated. It is important not to interpret our results as evidence for when to start ART (i.e. a comparison of whether or not to initiate patients when their CD4 count first falls ≤ 350 or defer until CD4 counts reach < 200). Our results only pertain to what happens to patients once they are diagnosed and initiate ART at their initial presentation CD4 value.

Our results show that adult, non-pregnant patients presenting for care and initiating ART at 201-350 cells/ μ l have reduced loss to follow-up than those presenting and initiating ART at ≤ 200 cells/ μ l, with significant variation by gender and pregnancy status. These are the first results to show South Africa's 2011 expansion of ART treatment guidelines can be enacted without increasing attrition among patients initiating at higher CD4 values. As data become available from more sites that adopted the policy of initiating ART at higher CD4 cell

counts, it will be important to perform similar evaluations at other sites in South Africa and other countries. Such information will be invaluable to national HIV/AIDS programs looking for guidance about the implications of earlier ART initiation, and may inform future expansions of the ART treatment criteria in South Africa.

CHAPTER 7

CONCLUSIONS

Summary of findings

To fulfill Aim 1, we produced two manuscripts that investigated retention in care at critical stages of early HIV care among recently-diagnosed patients. In Chapter 4, we found that among non-pregnant adults at Witkoppen, the pre-ART period was the time of highest attrition with over 25% attrition at each pre-ART stage. In Chapter 5, we focused our analysis on pregnant women diagnosed with HIV during antenatal services and found considerable pre-ART loss among those ART-eligible, but notably less than the non-pregnant adults analyzed in Chapter 4. Among ART-eligible non-pregnant adults, 71.1% (95%CI 67.4-74.7%) completed CD4 staging within three months of HIV diagnosis and 73.5% (95%CI 69.0-77.6%) of those initiated ART within three months of CD4 staging. By comparison, among ART-eligible pregnant women, 82.7% (95%CI 75.8-88.3%) completed CD4 staging before delivery and 80.9% (95%CI 72.9-87.3%) of those initiated ART before delivery. However, overall loss to follow-up among pregnant women 13 months after testing HIV-positive was higher at 57.5% (95%CI 51.6-63.3%) compared to 49.6% (95%CI 46.3-53.0%) in non-pregnant adults. Our time-to-event analysis of LTFU prior to and post-delivery showed a marked difference in the periods: 20.5% (95%CI 16.0-25.6%) lost prior to delivery and, among those still in care at delivery, 47.9% (95% CI 41.2-54.6%) after. These results suggest that many pregnant women remain in care during pregnancy but then drop out in great numbers after delivery.

Both manuscripts fulfilling Aim 1 highlighted poor retention among patients ineligible for ART at the time of testing HIV positive. Among non-pregnant adults, 57.4% (95%CI 49.5-

65.0%) completed a second CD4 test within 12 months of testing HIV-positive. Among pregnant women, retention among ART-ineligible patients was even lower: only 46.7% (95%CI 37.4-56.2%) attended at least one clinic visit after delivery and half of those who returned (52.0%, 95%CI 38.2-65.5%) received a repeat CD4 test. Cumulative retention from HIV testing to repeat CD4 testing among non-pregnant adults ineligible for ART was 44.3% (95%CI 37.5-51.2%) and 21.1% (95%CI 14.6-29.0%) among pregnant women ineligible for ART.

In the analysis for Aim 2 (Chapter 6), we found that among adults (non-pregnant and pregnant) initiating ART, LTFU one year post-initiation was 14.6% (95%CI 12.8-16.6%). This is consistent with our results of Chapter 4, which found attrition 0-6 months after ART initiation at 19.8% (95%CI 15.5-24.7%) and 6-12 months at 4.7% (95%CI 2.4-8.3%). Retention was improved after ART initiation, which likely is due to several factors. First, in order to initiate ART, patients must first complete at least one, but usually two, additional visits. A patient who returns for all visits required to initiate ART already has a pattern of clinic attendance and is more likely to remain in care than those who do not. Additionally, ART provides rapid improvements in health, wellbeing and reduces mortality, so by initiating ART, it is possible that these patients' health has improved so that they are more likely to be able to make it to the clinic. By highlighting the difference in pre-ART and post-ART retention as we have through these three manuscripts, we have identified pre-ART as the time of greatest attrition and demonstrated that studies that track adherence from the point of ART initiation are likely to substantially underestimate overall loss.

Furthermore, in Chapter 6, we found reduced LTFU among non-pregnant females and males initiating ART at 201-350 cells/ μ l than those who presented for care and initiated ART at CD4 counts \leq 200 cells/ μ l, after controlling for confounding variables. This is the first paper to report on this outcome within the context of routine ART initiation at CD4 values 201-350 cells/ μ l within a primary healthcare clinic in South Africa. We also reported lower

mortality (aHR 0.34, 95%CI 0.13-0.84) and incident tuberculosis (aHR 0.44, 95%CI 0.23-0.85) among patients initiating at the higher CD4 group, which are consistent with other recent studies.^{47,48,50,101}

Public health significance

Our findings and other studies throughout Southern Africa showing failure to complete early critical milestones of HIV care among patients accessing public sector care suggest that linkages to care between newly-diagnosed HIV-positive patients and long-term, sustainable HIV care are not sufficient and requires intensified efforts and novel approaches.^{30-32,34-37} While patient attrition may not weaken the public healthcare system itself – after all, when patients drop out of care there are fewer to treat – it is a major public health concern. If patients who are considered lost to follow-up at clinics are indeed not seeking HIV care elsewhere, then they are at substantial risk of opportunistic infections and death, and those who have initiated ART but default treatment are also at risk of acquiring drug resistance. If patients do eventually return to care, many will do so with more advanced immunosuppression, requiring additional interventions and/or treatment, greater resource expenditure and substantial healthcare costs, if hospitalized. Thus, patient attrition limits the impact of the national HIV program and its ability to deliver healthy lives to HIV-infected individuals.

On a more positive note, our findings of reduced LTFU, death and incident TB among patients initiating ART at CD4 counts 201-350 cells/ μ l, as compared to \leq 200 cells/ μ l, suggest that the recent expansion of eligibility criteria for ART initiation in South Africa has the potential to translate into substantial clinical benefit for HIV-infected South Africans, if those who have higher CD4 counts seek care before advanced immunosuppression. This, coupled with our finding that patients who initiate ART typically have better retention and patients deemed ineligible for ART have the worst retention, suggest that expanding

treatment guidelines to initiate ART at higher CD4 values may result in improved retention overall. Since this is the first study to report data under routine conditions in South Africa, it will be important to re-evaluate the effect of initiating at higher CD4 values as additional data become available from across the country, and also from other countries as ART eligibility expands.

Throughout these analyses, we have identified some important factors associated with patient attrition at various stages of early HIV care. Compared to non-pregnant females, male sex was associated with attrition in any pre-ART stage in Chapter 4 (aRR 1.47, 95%CI 1.16-1.87) and 12-month LTFU (aHR 1.53, 1.10-2.13) post-initiation in Chapter 6. Younger age (18-29 years vs. 30-39 years) also is a factor associated with attrition in any pre-ART stage (aRR 1.56, 95%CI 1.21-2.00) and 12-month LTFU post-initiation (aHR 1.38, 95%CI 1.00-1.92). We found no significant association with patient nationality and LTFU in any of our analyses.

One of the biggest predictors of attrition that we found is also one of the most concerning. Pregnant women experienced attrition in substantial numbers, as shown in Chapter 5. In the multivariate analysis for Chapter 6, women pregnant at ART initiation were more than three times as likely to be LTFU after 12 months on ART than non-pregnant women initiating at CD4 values 201-350 cells/ μ l. The public health implications of this are profound, including increased risk of death and morbidity for the mother and increased incidence of orphanhood, increased risk of mother-to-child transmission of HIV, and incomplete care for the infant.

Future research directions

While a body of qualitative research on barriers to retention exists, further research that specifically examines pregnant women's reasons for dropping out of care is needed urgently. The phenomenon of pregnant women traveling around the time of delivery is

widely known anecdotally within clinics and among migration experts, and has been suggested in the literature,^{41,78,83} but is not well documented and examined. We must determine whether these suspected travel patterns actually exist and use both quantitative and qualitative research methods to better understand this pregnancy-associated migration and its impact on maternal and infant health. Follow-up studies to confirm linkages to care among new mothers also are missing in the literature. Better data systems that would link patients among all public health facilities would significantly improve researchers' ability to determine if a patient – pregnant or otherwise – is engaged in care elsewhere or lost to follow-up.

Recognition of incomplete linkages to care among recently-diagnosed HIV-positive individuals has led to interventions that aim to reduce the number of visits and days required before a recently-diagnosed patient can begin ART. Such interventions include rapid, point-of-care CD4 testing with same-day results,^{68,69} and faster initiation of ART among pregnant women.⁹³ Two previously-published studies have explored a case management intervention to improve linkages to HIV care, both based in the US,^{102,103} and research on implementation of this type of intervention in the South African setting is needed.

In recent years, programs incorporating the use of mobile phone and text message technology in health promotion, including ART adherence, have appeared throughout the world.¹⁰⁴⁻¹⁰⁶ Such technology also may assist with reducing missed visits and facilitating a link from HIV testing to ART initiation. Lastly, ART initiation and monthly procurement may eventually expand to mobile vans to access hard-to-reach populations in South Africa, but research into the implementation and evaluation of such programs are lacking.¹⁰⁷

Conclusion

Retention among recently-diagnosed HIV-positive patients is a serious concern in South Africa. Our findings help to identify the key time points when patients are most at-risk

of dropping out of care, establishing that the greatest amount of attrition is in the pre-ART period, particularly for patients who are not yet eligible for ART. This study adds to the growing body of literature on early loss to follow-up among HIV-positive individuals. The first year of care is critical for establishing a connection to lifelong care and we must better understand the specific nuances of periods subsequent to HIV diagnosis. We also must measure the impact of broadening ART treatment guidelines so that appropriate policies and interventions can be developed to retain patients across the continuum of care from diagnosis to treatment while expanding treatment options. In summary, the findings not only serve an academic purpose, but also have practical value. Identifying the time periods most associated with LTFU, and the impact of early initiation on LTFU within a routine clinic setting, may impact HIV and ART policy within the public healthcare sector in South Africa and other sub-Saharan African countries. By contributing to the literature of patient retention, we can quicken the transition from estimating and reporting retention to designing and implementing targeted interventions aimed at the groups most likely to be at risk of dropping out during the first year of HIV care.

Table A.1. Summary table of pre-ART retention in HIV care literature

Citation	Year published	Location	Sample size/population	Study design	Follow-up period	LTFU definition	Exposure(s)	Outcome(s)	Statistical methods	Results	Conclusion
1 Bassett IV, Chetty S, Wang B, Mazibuko M, Giddy J, Lu Z, Walensky RP, Freedberg KA, Losina E. Loss to follow-up and mortality among HIV-infected people co-infected with TB at ART initiation in Durban, South Africa. <i>J Acquir Immune Defic Syndr</i> . 2012 Jan 1;59(1):25-30.	2012	Sinikithemba HIV clinic, Durban, South Africa	1034 ART-naïve patients undergoing ART literacy training	Observational cohort	1 year	Missing >3 mos and unable to be reached by phone or confirmed dead after multiple attempts	1) Newly-diagnosed with TB by culture 2) Already on TB treatment at enrollment 3) TB-free	LTFU and mortality	Cox PH regression modeling, adjusted for gender, age, baseline CD4, smoking status, and OI history	aHR for death or LTFU for pts newly-diagnosed with TB vs those TB-free: 1.76 (95% CI: 1.20, 2.60) Trend toward increased death and LTFU among those already on TB tx vs TB-free: HR 1.24, (95% CI: 0.84, 1.82)	Patients newly-diagnosed with TB were 76% more likely to die or be LTFU (all-cause attrition) than those TB-free at enrollment
2 Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South african programme. <i>PLoS One</i> . 2011 May 3;6(5):e19201.	2011	Eastern Cape, South Africa (rural)	1803 adult patients (>19) initiating ART	Observational cohort	Median 13.3 months (IQR: 5.4-25)	No patient contact for >6 months before the end of study period	Age, sex, baseline CD4, baseline viral load, pregnant/inpatient /on TB tx at time of ART initiation	LTFU, death, transfer, alive and on treatment	Cox PH regression modeling, adjusted for competing risks (LTFU or dying)	Overall patient outcomes: 71.5% still in care, 11.1% died, 6.5% LTFU, 10.9% transferred. Higher LTFU (13.6%) for pregnant women and higher death for those initiating ART as inpatients (32.4%) and on TB tx (16.3%). Risk of LTFU was associated with higher CD4 count, younger age, inpatient status and pregnant at ART initiation. Receiving >6 mos pre-ART care was associated with decreased LTFU.	Low LTFU overall, but initiating ART while pregnant or inpatient may require extra counseling to avoid LTFU. Pre-ART care may be protective against ART LTFU.
3 Brennan AT, Maskew M, Sanne I, Fox MP. The importance of clinic attendance in the first six months on antiretroviral treatment: a retrospective analysis at a large public sector HIV clinic in South Africa. <i>J Int AIDS Soc</i> . 2010 Dec 7;13:49.	2010	Johannesburg, South Africa	4476 adult (>18) patients initiating ART	Observational cohort	53 months maximum, 21 months minimum	Not having been to the clinic for at least four months	Missing a scheduled clinic visit by at least 7 days (ARV or medical)	1) mortality, 2) LTFU, 3) immunologic response, 4) virologic suppression	Log-binomial regression (adjusted for age, sex, WHO stage III/IV, BMI, baseline hemoglobin and CD4, and first ART regimen) to estimate RR of missing a visit on CD4 and VL by 6 mos on Art. Cox PH models to estimate HR of mortality and LTFU by missed visit status	Adjusted HR associated with missing ≥3 medical visits: Death: 4.74 (95% CI: 1.39, 16.2) 2.98 (95% CI: 1.10, 8.14)	More missed visits were associated with increased risk of death and LTFU over 12 mos of follow-up. Patients who miss multiple visits in the earliest period of treatment but remain in care are at increased risk of poorer ART outcomes
4 Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. <i>PLoS One</i> . 2009 Jun 4;4(6):e5790.	2009	South Africa, Malawi, Uganda, Zambia, Botswana, Ethiopia, Kenya, Tanzania, Mali and India	6420 adult post-initiation LTFU patients from 17 studies	Systematic review and meta-analysis	Varied	Varied	Study characteristics: urban/rural setting; missed last visit by >3 mos; method of tracing; percentage of patients LTFU included in survey; percentage of patients traced and retrieved during survey	Number of patients who could be traced, number found to be alive and the number who had died	Random-effects meta-analysis on the logit scale; random effects meta-regression for associations between study characteristics and mortality in patients LTFU	Vital status of 63% of patients could be ascertained Combined mortality from random effects meta-analysis: 40% (95% CI: 33%, 48%); if looking only at public ART programs in sub-Saharan Africa: 46% mortality (95% CI: 39%, 54%)	ART programs with high rates of LTFU and poor ascertainment of mortality may underestimate true rates of mortality Mortality in LTFU patients is much higher than mortality usually reported in the first year of ART and mortality was highest in first 6 mos of LTFU
5 Bygrave H, Kranzer K, Hilderbrand K, Whittall J, Jouquet G, Goemaere E, Vlahakis N, Triviño L, Makakole L, Ford N. Trends in loss to follow-up among migrant workers on antiretroviral therapy in a community cohort in Lesotho. <i>PLoS One</i> . 2010 Oct 8;5(10):e13198.	2010	Morija, Lesotho	1185 adult (>18) patients initiating ART	Observational cohort	Minimum 1 year, maximum 2 years	No clinic visit for at least 3 months at the end of the observation period	Migrant status (migrant = crossed into SA for work)	LTFU, death, transfer, study end	K-M estimates of outcomes by migrant status. Poisson regression models of the association between migrant status and LTFU or death, adjusted for age (<40 or >40), sex, baseline CD4 (<200 or >200) and TB at initiation. Poisson model uses Lexis expansion splitting time into 0-3 mos, 3-6 mos, 6-12 mos and >12 mos on ART.	12% of cohort were migrant workers Rates of LTFU were similar for migrants/non-migrants at 3 mos, but much higher for migrants at later points (RR, 95% CI): 3-6 mos: 2.78 (1.15, 6.73) 6-12 mos: 2.36 (1.18, 4.73) >12 mos: 6.69 (3.18, 14.09)	LTFU among migrant workers as time on ART progressed. Theorized that this could be the "health migrant" effect -- returning to work in SA after feeling better on ART.

	Citation	Year published	Location	Sample size/population	Study design	Follow-up period	LTFU definition	Exposure(s)	Outcome(s)	Statistical methods	Results	Conclusion
6	Cornell M, Grimsrud A, Fairall L, Fox MP, van Cutsem G, Giddy J, Wood R, Prozesky H, Mohapi L, Graber C, Egger M, Boule A, Myer L; International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002-2007. <i>AIDS</i> . 2010 Sep 10;24(14):2263-70.	2010	Western Cape, Free State, Gauteng and KZN, South Africa	44,177 adult (≥16) patients initiating ART	Observational cohort	Minimum 1 year, maximum 6 years (median 1.27 years)	Last patient contact was more than 6 months before database closure	Year of ART initiation, baseline CD4 (<50 vs >200, ref.)	Mortality, LTFU and program retention	K-M estimates of time to death, LTFU and overall program retention by year of enrollment. Cox PH regression models, stratified by cohort, adjusted for age, year of enrollment, baseline CD4, WHO stage and VL.	Adjusted HR (CD4 as exposure): Mortality: 5.85 (95% CI: 4.47, 7.65) LTFU: 0.83 (95% CI: 0.76, 0.91) With each successive year of enrollment, risk of mortality decreased. LTFU risk was higher in those with higher baseline CD4, but the association did not persist when WHO staging was added to the model. 6 mo LTFU: 9%; 36 mo LTFU: 30%	High levels of LTFU are a threat to the success of the national ART program.
7	Cornell M, Myer L, Kaplan R, Bekker LG, Wood R. The impact of gender and income on survival and retention in a South African antiretroviral therapy programme. <i>Trop Med Int Health</i> . 2009 Jul;14(7):722-31.	2009	Cape Town, South Africa	2196 adult (≥16) patients initiating ART	Observational cohort	Maximum 4.5 years, median 1 year	Started ART but absent from clinic >3 months	Gender (women = ref.), income (some vs. none, ref.)	Mortality and LTFU	Cox PH regression modeling, adjusted for gender, age, baseline CD4, WHO stage, VL, income	Adjusted HR (income as exposure): LTFU: 0.53 (95% CI: 0.37, 0.77) Men with no income have higher mortality than women with no income: 1.89 (95% CI: 1.25, 2.86) Highest mortality in first year, particularly first 4 month on tx. Significantly higher mortality rate among males did not hold after adjustment. 6% of patients LTFU at 1 year.	Income generation is strongly protective against LTFU and mortality (in men). High mortality in men due to late presentation.
8	Fox MP, Brennan A, Maskew M, MacPhail P, Sanne I. Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa. <i>Trop Med Int Health</i> . 2010 Apr;15(4):405-13.	2010	Johannesburg, South Africa	1037 patients eligible for ART and LTFU	Cross-sectional	---	Missed any clinic appointment by at least 3 months after scheduled visit date	Age, last CD4, last BMI, last Hb, months on ART before being lost	Mortality among LTFU patients	Difference in proportion for mortality before and after vital registration system; K-M estimates of crude predictors of death; Cox PH regression of adjusted predictors of death	Prior to updating mortality using vital registration system, 4.2% of LTFU were known dead; after updating: 10.9%. Strongest predictors of death among LTFU: last CD4 (HR 3.4, 95% CI: 2.3, 5.0) and last BMI <17.5 (HR 2.4, 95% CI: 1.8, 3.1)	High mortality among pts LTFU in South Africa. The probability of death among the LTFU was over 30% at the end of 1 year. Tracing programs still miss a substantial number of deaths among those considered LTFU.
9	Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. <i>Trop Med Int Health</i> . 2010 Jun;15 Suppl 1:1-15.	2010	Sub-Saharan Africa (16 countries)	226,307 patients initiating ART within 39 cohorts	Systematic review and meta-analysis	At least 6 months follow-up required	LTFU varied by study; in meta-analysis, attrition = patients who died or were LTFU; retention = 1 - attrition	Age, gender, baseline CD4, duration of follow-up (≤12 mos vs >12 mos), patient payment required (y/n), sector (public/private/other), year of cohort initiation (<2004 vs ≥2004)	All-cause patient attrition from ART programs	Summarized retention rates from 39 cohorts using random-effects meta-analysis using a Freeman & Tukey arc-sin transformation of the retention proportions and standard errors; presented point estimates of retention and 95% CI; extrapolated retention rates for all studies through 3 years using a best-case, worst-case and midpoint scenario; linear regression modeling to examine predictors of retention	Retention estimated at 86.1% at six months, dropped to 72.3% by 36 months Predictors of lower retention rates at 6 mos: CD4 count <100, median age <36, having <60% females in cohort; predictors of lower retention rates at 12 mos: median age <36, CD4 count <100 and cohort follow-up ≤12 mos	Overall attrition may be slowing as ART programs scale-up and mature Programs with lower median CD4 and fewer females are at higher risk of patient attrition Need to prioritize patient tracking and vital status ascertainment and track patient transfers

Citation	Year published	Location	Sample size/population	Study design	Follow-up period	LTFU definition	Exposure(s)	Outcome(s)	Statistical methods	Results	Conclusion
10 Kaplan R, Orrell C, Zwane E, Bekker LG, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. AIDS. 2008 Aug 20;22(13):1679-81.	2008	Gugulethu, South Africa	1677 women initiating ART, about 15% of whom were pregnant at time of initiation	Observational cohort	3 years	No clinic attendance for 12 or more weeks	Pregnant at the time of ART initiation	LTFU and mortality during the first year of ART	Multivariate analysis; K-M estimates of association between pregnancy and LTFU	Women pregnant at ART initiation were more likely to be LTFU than non-pregnant women (aRR: 2.1, 95% CI: 1.4, 3.1) but mortality was not associated with pregnancy Younger women (<25 yrs) were more likely to be LTFU than women >35 (aRR: 2.2, 95% CI: 1.3, 3.6)	Pregnant women are at higher risk of LTFU during the pre-ART and post-ART periods, despite being at lower risk of mortality during these times. This finding highlights the need for programmatic interventions to address retention in care for this patient population.
11 Myer L, Cornell M, Fox M, Garone D, Wood R, Prozenzsky H, Ndirangu J, Keiser O, Boule A and leDEA-Southern Africa Collaboration. Loss to follow-up and mortality among pregnant women and non-pregnant women initiating ART: South Africa. CROI 2012. Oral abstract #22.	2012	5 South African cohorts (leDEA Collaborative)	29,653 women initiating ART, of whom 1956 (6.6%) were pregnant	Observational cohort	Min 6 months, maximum 7 years	Unclear	Pregnant at the time of ART initiation	LTFU and mortality during the first year of ART	Product-limit estimations of proportion alive or LTFU during the first year of ART; Cox PH regression modeling	Women pregnant at ART initiation were much likely to be LTFU than non-pregnant women (19% vs 11%; aHR: 1.54, 95% CI: 1.38, 1.72) Pregnant women less likely to die in the first year of treatment than non-pregnant women (3% vs 9%)	Women who start ART during pregnancy have lower mortality but much greater LTFU than non-pregnant women. Interventions must promote retention of women initiating ART during pregnancy.
12 Sanne IM, Westreich D, Macphail AP, Rubel D, Majuba P, Van Rie A. Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study. J Int AIDS Soc. 2009 Dec 17;12:38.	2009	Johannesburg, South Africa	7583 patients initiating ART	Observational cohort	Maximum 4 years, median 20.3 months	More than 3 months for a scheduled visit and unable to trace	Baseline CD4 (≤50 vs >200, ref.)	Mortality, LTFU, CD4 response, viral suppression	K-M estimates of retention in care; Cox PH regression modeling	Crude HR: Mortality: 4.87 (95% CI: 2.94, 8.09) LTFU: 1.18 (95% CI: 0.96, 1.43) Monthly attrition rate: 1.43 in first 12 mos Death rate in first 90 days of HAART: 8.4 per 100 py Over 4 years, 16.4% LTFU	Low overall mortality, LTFU highest in first year of care. Short-term estimations of LTFU may underestimate retention in care.
13 Toro PL, Katyal M, Carter RJ, Myer L, El-Sadr WM, Nash D, Abrams EJ; MTCT-Plus Initiative. Initiation of antiretroviral therapy among pregnant women in resource-limited countries: CD4+ cell count response and program retention. AIDS. 2010 Feb 20;24(4):515-24.	2010	MTCT-Plus program sites: Cameroon, Cote d'Ivoire, Kenya, Mozambique, Rwanda, South Africa, Uganda, Zambia and Thailand	2229 treatment-naïve patients initiating ART, of whom 605 were pregnant women (27.1%)	Observational cohort	Minimum 6 months, maximum 4 years	At least 3 failed attempts to trace a patient following a missed appointment or failure to attend the facility for >6 mos after the last visit or lab test	Gender and pregnancy	LTFU and mortality	Survival analysis: mortality-specific rates, K-M estimates of retention in care	At censoring, 3.5% mortality (1.8 per 100 py) and 8.6% LTFU (4.6 per 100 py) No significant difference in mortality and LTFU by gender or pregnancy status	Overall retention in care was high (85%) and did not differ significantly by gender or pregnancy status. The healthier status of MTCT-Plus patients, as well as heavy emphasis on psychosocial support, likely contributed to lower mortality risk and high retention rates

	Citation	Year published	Location	Sample size/population	Study design	Follow-up period	LTFU definition	Exposure(s)	Outcome(s)	Statistical methods	Results	Conclusion
14	Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, Martin D, Lu Z, Freedberg KA, Wood R. Loss to follow-up in a community clinic in South Africa--roles of gender, pregnancy and CD4 count. S Afr Med J. 2011 Apr;101(4):253-7.	2011	One NGO HIV clinic near Rustenburg (NW), South Africa	925 adult (>14 years) patients initiating ART	Observational cohort	Minimum 6 months, maximum 2.5 years	Clinic-based definition: failure to return for scheduled visit or med pick-up within 6 mos of ART initiation; Data-based definition: no recorded information in the database on a patient returning for a 6-mo visit	Gender, pregnancy and CD4 count	LTFU (analysis used the clinic-based definition)	K-M estimates of retention in care; Cox PH regression modeling	<p>Cumulative probability of LTFU at 6 mos: pregnant women (12%), non-pregnant women (6%), men (3%)</p> <p>Crude HR: Age ≤30: HR 2.14 (95% CI: 1.05, 4.38) Pregnancy: HR 3.75 (95% CI: 1.53, 9.16)</p> <p>Pregnant women with baseline CD4 ≤200 had the highest risk of LTFU of all after 6 mos on ART: HR 6.06, 95% CI: 2.30, 16.71</p>	Gender and pregnancy status were significantly associated to LTFU and pregnant women had the highest risk of LTFU of all patients.

Table A.2. Summary table of post-ART retention in HIV care literature

1	Amuron B, Namara G, Birungi J, Nabiryo C, Levin J, Grosskurth H, Coutinho A, Jaffar S. Mortality and loss-to-follow-up during the pre-treatment period in an antiretroviral therapy programme under normal health service conditions in Uganda. BMC Public Health. 2009 Aug 11;9:290.	2009	Jinja, southeast Uganda	2483 patients eligible for ART at one rural/semi-urban NGO clinic	Observational cohort	Median: 351 days	Could not be traced for follow-up after about a year (median 351 days) from point of ART eligibility	Gender, age, baseline CD4, WHO stage	Completed screening and on ART, died, on ART with another provider, alive and not on ART, LTFU	Logistic regression of association between exposures and starting ART K-M estimates of survival time Poisson regression modeling of the association between baseline CD4 and mortality	88% of eligible patients returned for the 2nd visit (median interval: 14 days) and were told of eligibility; 74% returned for 3rd visit (median interval: 33 days) and started ART Not completing screening associated with low baseline CD4 and male sex After about a year, patients who didn't start ART were followed-up at home: 28% had died, 30% self-reported being on ART with a different provider, 25% were alive and chose not to be on ART and 17% were LTFU	Mortality rate during screening procedures was very high About 1/4 did not complete screening and start ART. Of these, almost half only came to one visit and never learned their eligibility, and half learned their eligibility but did not come back Patients presented with advanced HIV stage Almost half of patients said they did not start treatment due to transport costs
2	Bassett IV, Regan S, Chetty S, Giddy J, Uhler LM, Holst H, Ross D, Katz JN, Walensky RP, Freedberg KA, Losina E. Who starts antiretroviral therapy in Durban, South Africa?... not everyone who should. AIDS. 2010 Jan;24 Suppl 1:S37-44.	2010	Durban, South Africa	538 adult (≥18) ART-eligible pts (CD4 <200)	Observational cohort	12 months	Missed visit + not returning after 3 phone call attempts	Baseline characteristics (gender, employment, CD4, known HIV family/friend, site of care, distance to clinic, transport mode, ever TB, HIV testing history)	ART initiation within 12 months of enrollment in the STIAL study	Multivariate Poisson regression, adjusting for gender, location of employment, known HIV-infected family/friend, site of care, baseline CD4 and HIV testing history (ever/never) K-M estimate of time from HIV testing to ART initiation, stratified by gender Difference of proportions (mortality)	Adjusted RR (95% CI): Male: 1.32 (1.14, 1.54) Known HIV-infected family/friend: 1.35 (1.08, 1.68) 20% mortality (highest among those with CD4 <50); most deaths were pre-initiation Median time to ART start was 6.6 months	Less than half eligible started ART within 12 mos Men are more likely to fail to initiate ART, as are those pts with a friend or family member known to be HIV-positive. No association between failure to initiate and age and baseline CD4.
3	Bassett IV, Wang B, Chetty S, Mazibuko M, Bearnot B, Giddy J, Lu Z, Losina E, Walensky RP, Freedberg KA. Loss to care and death before antiretroviral therapy in Durban, South Africa. J Acquir Immune Defic Syndr. 2009 Jun 1;51(2):135-9.	2009	Durban, South Africa	501 adult (≥18) ART-eligible pts (CD4 <200)	Observational cohort	6 months	ART-eligible patients scheduled for ART training who did not start ART and were lost to care ≤3 mos of final ART training visit	Baseline characteristics (gender, employment, CD4)	Pre-ART loss to care	Multivariate logistic regression, adjusting for gender, age, marital status, and time from CD4 count to date of ART training	Adjusted odds ratios (95% CI): Low baseline CD4 (≤100): 2.13 (1.22, 3.71) Unemployed: 1.88 (1.09, 3.23) 16.4% lost to care before ART	Those lost pre-ART were more likely to be male, unemployed and a baseline CD4 below 100.
4	Fairall LR, Bachmann MO, Louwagie GM, van Vuuren C, Chikobvu P, Steyn D, Staniland GH, Timmerman V, Msimanga M, Seebregts CJ, Boule A, Nhlwitiwa R, Bateman ED, Zwarenstein MF, Chapman RD. Effectiveness of antiretroviral treatment in a South African program: a cohort study. Arch Intern Med. 2008 Jan 14;168(1):86-93.	2008	Free State province, South Africa	14267 patients (age ≥16) enrolled in public-sector treatment program	Observational cohort with repeated measures	Up to 20 months	Not starting ART when eligible	Baseline characteristics, started ART or CPT, and months since starting ART	Death, incident TB, change in CD4 count and weight	Marginal structural regression models to account for time-varying covariates; Cox PH regression models of association between exposures and death or incident TB	Of patients eligible by CD4, 45.3% started ART during the study period. Of over 4500 patients followed for 1 year, 53.2% died, 87% without receiving ART.	Article doesn't talk about patients LTFU, but found high rates of mortality and low rates of linkage to care. Delays starting ART contribute to high mortality rates.

5	Ingle SM, May M, Uebel K, Timmerman V, Kotze E, Bachmann M, Sterne JA, Egger M, Fairall L; leDEA-Southern Africa. Outcomes in patients waiting for antiretroviral treatment in the Free State Province, South Africa: prospective linkage study. <i>AIDS</i> . 2010 Nov 13;24(17):2717-25.	2010	Free State province, South Africa	22,083 patients (age ≥15) enrolled in public-sector treatment program and eligible for ART (CD4s 200)	Observational cohort	Minimum 1 year, maximum 4.5 years	Not starting ART when eligible	Baseline characteristics (sex, age, weight, CD4 count, year of enrollment, facility size, facility location, facility distance from home)	Time to starting treatment and time to pre-ART death	Competing risk framework used to estimate the cumulative incidence of starting ART (overall and stratified by CD4, competing risk: death), and also pre-ART death (competing risk: starting ART); competing risk Cox PH regression modeling (subdistribution hazard ratios) of association of patient and facility characteristics with starting ART and pre-ART, adjusting for baseline characteristics	86% of patients were eligible for ART at first CD4; After 2 years, among those eligible for treatment, 67.7% had started and 26.2% had died before starting, 6% were alive and untreated. Among those with baseline CD4 ≤ 25, 48% died before ART and 51% started ART	High mortality among eligible patients waiting for ART; the most immunocompromised patients had the lowest probability of starting ART; unusually low rates of LTFU (not discussed at all in the paper)
6	Kaplan R, Orrell C, Zwane E, Bekker LG, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. <i>AIDS</i> . 2008 Aug 20;22(13):1679-81.	2008	Gugulethu, South Africa	2131 ART-naïve women referred for ART, of whom 318 (15%) were pregnant at time of screening	Observational cohort	3 years	Percentage of patients referred for ART who refused treatment or did not return to the clinic	Pregnant at the time of ART referral	LTFU and mortality during pre-ART period	Comparing proportions	Women pregnant at ART referral were more likely to be LTFU than non-pregnant women (13.2% vs 6.0%, $p<0.001$) but mortality was lower among pregnant women (0.3% vs 4.7%, $p<0.001$)	Pregnant women are at higher risk of LTFU during the pre-ART and post-ART periods, despite being at lower risk of mortality during these times. This finding highlights the need for programmatic interventions to address retention in care for this patient population.
7	Kranzer K, Zeinecker J, Ginsberg P, Orrell C, Kalawe NN, Lawn SD, Bekker LG, Wood R. Linkage to HIV care and antiretroviral therapy in Cape Town, South Africa. <i>PLoS One</i> . 2010 Nov 2;5(11):e13801.	2010	Cape Town, South Africa	988: random sample of adults testing HIV-positive through ANC, STI or VCT + all testing HIV-positive through TB services	Observational cohort	5 years	1) "Linkage to HIV care": CD4 result within 6 mos of diagnosis 2) "Linkage to ART care" Initiated ART within 6 mos of HIV testing, if eligible (CD4 ≤ 200)	Age, gender, year tested Stratified all results by type of pt: ANC, STI, TB or VCT	Linkage to HIV care and linkage to ART care	Multivariate log-binomial regression, adjusting for covariates listed in Exposure category	62.6% received CD4 result w/in 6 mos, highest among ANC and STI pts, lowest among VCT 66.7% of eligible pts accessed ART care within 6 mos Linkage to HIV care RR: Tested in 2007-2009 (vs 2004-2006): TB pts: 1.67 (95% CI: 1.27, 2.21); VCT pts: 1.60 (95% CI: 1.40, 1.84); ANC pts: 0.87 (95% CI: 0.74, 0.99)	People who test on their own are less likely to have a timely CD4 TB patients did not receive concomitant HIV treatment Men and younger adults were less likely to link to care overall Linkage to care improved over more recent years ANC pts more likely to link to ART care
8	Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I, Fox MP. Early loss to follow up after enrolment in pre-ART care at a large public clinic in Johannesburg, South Africa. <i>Trop Med Int Health</i> . 2010 Jun;15 Suppl 1:43-7.	2010	Johannesburg, South Africa	356 patients newly enrolled in the pre-ART program and not yet eligible for ART	Observational cohort	13 months	Failure to attend the first medical visit within 1 year (scheduled for 6 mos after dx if CD4 >350 and 3 mos after dx if CD4 251-350)	Age, gender, employment, marital status, baseline CD4	Early LTFU	Modified Poisson regression using robust standard errors	Adjusted RR for pt returning for first visit: Employed: 1.41 (95% CI: 1.03, 1.92) CD4 351-450: 0.66 (95% CI: 0.46, 0.96) CD4 451+: 0.61 (95% CI: 0.42, 0.88) Overall, 69% of pts didn't return for first medical visit within 1 year: 74% of pts w/CD4 >350 and 59% of pts with CD4 251-350	Less than 1/3 of HIV-positive patients enrolled in pre-ART care returned for their first medical visit within 1 year. Pre-ART care is a "broken link" that should connect HIV testing to ART Risk of returning was positively associated with being employed and negatively associated with higher baseline CD4

	Citation	Year published	Location	Sample size/population	Study design	Follow-up period	LTFU definition	Exposure(s)	Outcome(s)	Statistical methods	Results	Conclusion
9	Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I, Fox MP. Lost opportunities to complete CD4+ lymphocyte testing among patients who tested positive for HIV in South Africa. Bull World Health Organ. 2010 Sep 1;88(9):675-80.	2010	Johannesburg, South Africa	352 walk-in VCT clients who tested HIV-positive	Observational cohort	12 weeks	Failure to have CD4 test and collect result	Gender, age, marital status, employment status, baseline CD4	Pts collecting CD4 result within 6 weeks and 12 weeks of diagnosis	Multivariate logistic regression, adjusted for gender, age, employment status, marital status and baseline CD4	35% overall completed CD4 testing: 51.3% of patients eligible for ART completed CD4 testing within 12 wks; only 14.9% of patients not eligible (CD4>200) completed within 12 wks	The higher the baseline CD4 count, the lower the odds of completing CD4 testing within 12 weeks Losing patients at the CD4 stage results in delayed ART care
10	Losina E, Bassett IV, Giddy J, Chetty S, Regan S, Walensky RP, Ross D, Scott CA, Uhler LM, Katz JN, Holst H, Freedberg KA. The "ART" of linkage: pre-treatment loss to care after HIV diagnosis at two PEPFAR sites in Durban, South Africa. PLoS One. 2010 Mar 4;5(3):e9538.	2010	Durban, South Africa	454 adult (≥18) patients newly testing HIV-positive	Observational cohort	8 weeks	"PTLC" (pre-treatment loss to care): Failure to have a CD4 count within 8 weeks of HIV diagnosis	Distance ≥10 km from home to clinic, history of TB treatment, self-referral vs. medical referral for HIV test	PTLC	Multivariate log-linear regression modeling, adjusted for covariates listed in Exposure category	45% PTLC overall Lived ≥10 km from clinic: RR 1.37 (95% CI: 1.11, 1.71) History TB treatment: RR 1.26 (95% CI: 1.00, 1.58) Medical referral: RR 1.61 (95% CI: 1.22, 2.13) 21% of those PTLC had none of these risk factors	Nearly half of pts failed to have CD4 counts after diagnosis
11	Rosen S, Fox MP. Retention in HIV Care between Testing and Treatment in Sub-Saharan Africa: A Systematic Review. PLoS Med. 2011 July; 8(7): e1001056.	2011	Sub-Saharan Africa (7 countries)	28 studies	Systematic review	Varied	Failing to reach the next step in the care sequence for any reason (including death)	---	Median proportion of patients completing each stage of the pre-ART process: 1) testing positive to completing CD4 staging, 2) if not eligible for ART, pre-ART care to eligibility for ART, 3) ART eligibility to beginning ART	When possible, calculated 95% CI for proportion of pts retained or linked; grouped the findings into the 3 stages and illustrated results using forest plots; estimated the median proportion of pts completing each stage and reported the median and range	Median (range) retained at each stage: Stage 1: 59% (35% - 88%) Stage 2: 46% (31%-95%) Stage 3: 68% (14%-84%) Multiplying the 3 medians: 18%	Substantial LTFU at every stage of pre-ART care Need to look at the proportion of pts who complete all stages within a single setting Need to report results up to a clinically meaningful end point within a stage, not just to the point of censoring
12	Taylor-Smith K, Zachariah R, Massaquoi M, Manzi M, Pasulani O, van den Akker T, Bemelmans M, Bauernfeind A, Mwagomba B, Harries AD. Unacceptable attrition among WHO stages 1 and 2 patients in a hospital-based setting in rural Malawi: can we retain such patients within the general health system? Trans R Soc Trop Med Hyg. 2010 May;104(5):313-9.	2010	Thyolo District (rural), Malawi	1,633 adults in WHO stages 1 and 2	Observational cohort	Minimum 1 month, maximum 13 months	One month or more from last scheduled visit	Starting ART or not starting ART (in Malawi, only patients on ART are traced after defaulting)	Alive, dead, LTFU, transferred facilities	K-M estimates of cumulative incidences of attrition (death and LTFU and stopping treatment); Cox PH regression modeling of the association between starting/not starting ART and attrition and LTFU	Attrition rates were 31 times higher among pre-ART group vs ART group, after adjusting for age, sex and baseline CD4 (adjusted HR: 31.0, 95% CI: 21.9, 44.0) Of the 824 patients lost prior to ART, 95% were lost prior to getting their CD4 count and first counseling appt (2-4 weeks after registration)	Very high early LTFU among pre-ART patients Nearly all pre-ART patients LTFU were lost within 2-4 weeks, which was before CD4 staging Pre-ART patients were managed differently, followed-up differently, and used different facilities (outpatient vs. ART-specialized clinic)

Table A.3. Summary table of early ART initiation literature

	Citation	Year published	Location	Sample size/population	Study design	Follow-up period	LTFU definition	Exposure(s)	Outcome(s)	Statistical methods	Results	Conclusion
1	Ford N, Kranzer K, Hilderbrand K, Jouquet G, Goemaere E, Vlahakis N, Triviño L, Makakole L, Bygrave H. Early initiation of antiretroviral therapy and associated reduction in mortality, morbidity and defaulting in a nurse-managed, community cohort in Lesotho. AIDS. 2010 Nov 13;24(17):2645-50.	2010	Lesotho	1177	Prospective, observational cohort	Minimum 1 year, maximum 2 years	Missing an apt for more than 90 days	Baseline CD4 count: early initiation (200-350) vs late (<200, ref.)	Mortality, morbidity, LTFU and hospitalization	K-M estimates to describe cumulative probability of progression to outcome; Cox PH regression modeling to estimate HR (adjusting for sex, age, pregnant at initiation, TB at initiation and migrant worker Y/N); possible misclassification of mortality assessed through sensitivity analysis using competing risks framework	Adjusted HR (95% CI): Mortality: 0.32 (0.20, 0.50) LTFU: 0.61 (0.43, 0.87) Incident morbidity: 0.73 (0.65, 0.82) Hospitalization: 0.37 (0.19, 0.73)	Early initiation is feasible and reduces mortality, morbidity, LTFU and hospitalization
2	Fox MP, Sanne IM, Conradie F, Zeinecker J, Orrell C, Ive P, Rassool M, Dehlinger M, van der Horst C, McIntyre J, Wood R. Initiating patients on antiretroviral therapy at CD4 cell counts above 200 cells/microl is associated with improved treatment outcomes in South Africa. AIDS. 2010 Aug 24;24(13):2041-50.	2010	Johannesburg and Cape Town, South Africa	812	Observational cohort; part of unblinded RCT	Minimum 2 years, median 27.5 months	Missing 3 or more consecutive study visits	Baseline CD4 count: early initiation (200-350, ref.) vs late (<200)	Treatment failure, incident TB and program failure	K-M estimates of the rate of treatment failure by baseline CD4; Cox PH regression modeling (adjusting for age, sex [stratified at baseline into men, pregnant women and non-pregnant women], study site and randomization group). Dose response model with finer categorizations of baseline CD4. Explored interaction of CD4 with baseline immunosuppression markers (VL, WHO stage, BMI, etc)	Adjusted HR (95% CI): Death/virologic failure: 1.9 (1.1, 3.3) Incident TB: 1.9 (0.89, 4.04) LTFU: 0.79 (0.50, 1.25)	Initiating ART early results in reduced mortality, TB and less virologic failure. CD4 cell count eligibility criteria should be increased.
3	Mills EJ, Bakanda C, Birungi J, Mwesigwa R, Chan K, Ford N, Hogg RS, Cooper C. Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda. AIDS. 2011 Mar 27;25(6):851-5.	2011	10 clinics throughout Uganda	22,315 patients ≥14 years initiating ART	Observational cohort	Median: 31 months	3 month untraceable absence from a clinic	Baseline CD4: (<50, 50-99, 100-149, 150-199, 200-249, 250-299, ≥300)	Mortality	K-M estimates of survival by baseline CD4; weighted analysis where 30% of LTFU patients were assumed dead, weighted by baseline CD4, age and male sex; Cox PH regression modeling of association between baseline CD4 and mortality, adjusting for age, sex and WHO clinical stage	6.7% of patients died and 6.4% were LTFU; mortality highest within first year and among patients with CD4 <50 Compared to baseline CD4 <50, CD4 ≥250, HR of mortality: 0.41 (95% CI: 0.33, 0.51)	Initiating ART late is associated with reduced survival time; decreased baseline CD4 is a strong predictor of mortality Early initiation appears to reduce mortality and also may offer fewer co-infections, lower resource costs and possibly prevention Sites involved in this study employ a mobile tracing team, so rates of LTFU were low
4	Severe P, Juste MA, Ambroise A, Eliacin L, Marchand C, Apollon S, Edwards A, Bang H, Nicotera J, Godfrey C, Gulick RM, Johnson WD Jr, Pape JW, Fitzgerald DW. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. N Engl J Med. 2010 Jul 15;363(3):257-65.	2010	Port au Prince, Haiti	816	RCT	Median: 21 months	None, and field workers visited patients at home to ensure retention	Early initiation (CD4 201-349) vs. standard initiation (≤200)	Primary: Survival Secondary: incident TB	K-M estimates of survival by study arm; log-rank test to evaluate the survival curves; Cox PH regression modeling	Adjusted HR (95% CI): Death w/standard therapy: 4.0 (1.6, 9.8) Incident TB w/standard therapy: 2.0 (1.2, 3.6)	When ART is initiated earlier in a resource-poor area, a 75% reduction in the rate of death and a 50% decrease in the incidence of TB was found. Access to ART should be expanded in resource-poor areas.

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