AN INVESTIGATION OF THE IMPACT OF EXPANDING ACCESS TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON SEXUAL AND REPRODUCTIVE DECISION-MAKING AND BEHAVIOURS OF WOMEN IN HIGH HIV PREVALENCE SETTINGS IN SUB-SAHARAN AFRICA

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ABSTRACT

Background: Given a paucity of information regarding the impact of expanding access to highly active antiretroviral therapy (HAART) on sexual and reproductive decision-making and behaviours of women in high HIV prevalence settings in sub-Saharan Africa, the objectives of thesis were: To assess whether use and duration of HAART was associated with (1) recent sexual activity among HIV-positive women across three high HIV prevalence settings; (2) fertility intentions and (3) contraceptive use and method mix patterns among women in Soweto, South Africa. And, (4) to develop a reliable HAART optimism scale for use among HIV-positive women and to test the scale's validity against measures of sexual and reproductive decision-making and behaviours among women in Mbarara, Uganda.

Methods: Quantitative data were drawn from surveys and medical record reviews conducted among 751 women attending the Perinatal HIV Research Unit in Soweto, South Africa (253 HAART-experienced, 249 HAART-naïve, and 249 HIV-negative) and 540 HIV-positive women (half of whom were receiving HAART) attending Mbarara University's HIV clinic in Uganda. Surveys assessed socio-demographics, HIV status and HAART history, sexual and reproductive health decision-making and behaviours, HIV-related clinical assessments, and HAART optimism.

Results: The analyses revealed that HIV-positive women receiving HAART are more likely to use contraception overall and dual protection in particular, with minimal differences in fertility intentions or sexual activity relative to their HAART-naïve counterparts. Moreover, optimism about the effects of HAART, rather than actual use or non-use, may be a more important predictor of fertility intentions and sexual activity of HIV-positive women. Overall, HIV-positive women are less likely to report fertility intentions and more likely to use contraception (and condoms in particular) relative to HIV-negative women from the same community.

Conclusions: The findings highlight the potential great value and urgent need for improved integration between HIV prevention, testing, and HAART services and sexual and reproductive health (SRH) programming to address the diverse SRH needs of HIV-infected and –affected women in HIV endemic settings. Such integration is essential to better support the rights of all women to be sexually active and safely achieve their reproductive goals, while minimizing HIV transmission risks.

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DEDICATION

I would like to dedicate this work to the women of sub-Saharan Africa.

Wanawake ni msingi wa maendeleo.

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Nyinyi ni furaha ya moyo wangu. Ninawapenda sana.

CO-AUTHORSHIP STATEMENT

This is to certify that the work presented in this thesis was conceived, instrumented, written, and disseminated by the PhD candidate. The co-authors of the manuscripts that constitute part of this thesis made contributions only as is commensurate with committee or collegial duties. The co-authors reviewed each manuscript prior to submission for publication and offered critical evaluations; however, the candidate was responsible for conducting data analyses and preparing the initial drafts of all manuscripts. In addition, the candidate was responsible for revising the manuscripts based on the suggestions of the co-authors, submitting manuscripts for publication and preparing final revisions based on the comments of the journal editors and external peer reviewers.

CHAPTER 1:

BACKGROUND, STUDY JUSTIFICATION, AND OBJECTIVES

1.1 Overview of HIV, HAART, and sexual and reproductive health in sub-Saharan Africa

With women accounting for over half of the world's HIV-infected population and an increasing proportion of incident infections each year, there is clear evidence of the feminization of the global HIV pandemic [1]. The vast majority live in sub-Saharan Africa where over 12 million women are currently living with HIV, accounting for 61% of the region's HIV-infected adult population [1]. While HIV-positive women face many of the same sexual and reproductive health burdens and challenges as HIV-negative women, HIV-infection among women of reproductive age raises additional personal, clinical, and public health concerns about the incidence of pregnancy. Such concerns relate to the health and survival of the mother and risks of HIV transmission to sero-discordant sexual partners and to infants during pregnancy, childbirth, and breastfeeding [2].

A sizable body of literature has examined the impact of HIV infection on the predictors, incidence, and outcomes of pregnancy [3-5]; however, there remains a paucity of research that addresses these relationships in the context of sustained use

of antiretroviral therapy. There is now unequivocal evidence that receipt of highly active antiretroviral therapy (HAART) among HIV-infected individuals dramatically improves viral suppression, reduces morbidity and mortality at the individual level, and increases life expectancy at the population level [6-9]. Recent global efforts to expand access to HAART and clinical care are delivering these positive outcomes to an increasing number of HIV-infected individuals living in high HIV prevalence, limited-resource settings [10]. The scale-up process has been dramatic; by the end of 2008 an estimated 2.9 million people in sub-Saharan Africa were receiving antiretroviral therapy, a 30-fold increase since the end of 2003 [10].

In addition to the clinical and survival benefits, appropriate use of HAART also dramatically reduces the risks of vertical [11] and horizontal transmission [12, 13] of HIV. Accordingly, increased HAART availability is anticipated to influence sexual and reproductive decision-making and behaviours of HIV-infected and –affected women. There remains, however, limited information concerning these associations given both the recency of HAART scale-up in settings with generalized HIV epidemics as well as the prevailing under-emphasis of reproductive health within HIV programming.

Using an approach that recognizes and supports the rights of all women, including women living with HIV, to safely achieve their reproductive goals [14, 15],

this thesis aims to investigate the impact of HAART on sexual and reproductive decision-making and behaviours among HIV-infected and –affected women in two high HIV prevalence settings in sub-Saharan Africa (Soweto, South Africa and Mbarara, Uganda) during a time of expanding HAART access.

1.2 Situational analysis of HIV infection and sexual and reproductive health in the context of expanding access to HAART in sub-Saharan Africa

In sub-Saharan Africa, HIV is predominantly transmitted through heterosexual intercourse [1], which further entangles the impact of the HIV epidemic on women's sexual and reproductive health. The common transmission pathway suggests that both the risk of HIV infection and pregnancy share similar risk factors and distribution in the female population. At the population level, however, substantial evidence indicates that in the absence of antiretroviral treatment, HIV-infected women in sub-Saharan Africa have between 25-40% lower fertility rates than non-infected women [3]. The decrease in fertility is more pronounced among women with advanced HIV disease and lower CD4 cell counts [16-18]. This fertility differential is largely explained by premature mortality among HIV-infected women and/or their sexual partners in addition to HIV-associated morbidity contributing to reduced fecundity [3].

Despite a noted relative lower fertility, each year the absolute number of pregnancies among women living with HIV in sub-Saharan Africa exceeds 1.4 million [10], of which an estimated 50-84% are unintended [19-21]. Many of these pregnancies contribute to distressing adverse outcomes for women, children, and their families. Every year nearly 350,000 infants are infected with HIV via mother-to-child transmission (MTCT) [1]. Maternal mortality, the world's worst health inequity, is exacerbated in the context of HIV with reports indicating that HIV-related maternal deaths have increased dramatically in regions of high HIV prevalence [22]. In addition, across sub-Saharan Africa, there are an estimated 8.9 million maternal orphans due to HIV/AIDS-associated mortality [23].

In 2002, the World Health Organization (WHO) highlighted HIV infection among infants and young children as a major global public health priority and recommended a four-pronged approach for preventing mother-to-child transmission of HIV (PMTCT): (i) primary prevention of HIV infection among women of childbearing age; (ii) preventing unintended pregnancies among HIV-infected women; (iii) preventing HIV transmission from women living with HIV to their infants and; (iv) providing appropriate treatment, care, and support to mothers living with HIV and their children and families [24]. While the recommendations support scaling-up this comprehensive range of interventions across the pre-pregnancy to postpartum continuum, most of the focus has centred on antenatal

HIV testing and the provision of antiretrovirals to prevent MTCT [10]. Indeed, others have argued that the prevailing view of PMTCT as a pediatric rather than maternal health issue has hampered efforts towards full realization of the WHO's recommended strategy [25]. Particularly lacking has been an adequate consideration of the intersecting goals of supporting women's overall sexual and reproductive health needs within HIV prevention, care, and treatment programming and vice versa.

The seven years since the WHO's recommendations have witnessed an unprecedented global commitment and roll-out of antiretroviral therapy to people living with HIV in sub-Saharan Africa and other resource-limited settings. In 2008, over 1.7 million HIV-infected women in the region were receiving antiretroviral therapy, accounting for an estimated 46% of those in need of treatment [10]. In addition, nearly 45% of pregnant women living with HIV in sub-Saharan Africa received antiretroviral therapy to prevent HIV transmission to their infants, of whom nearly 10% were receiving HAART for their own health [10]. While there remains a high level of unmet need, this level of antiretroviral coverage represents a substantial increase from previous years. Between 2007 and 2008 alone, nearly one million more HIV-infected individuals in need of treatment in sub-Saharan Africa commenced antiretroviral therapy [10].

Through improvements in health and survival and reductions in the incidence of MTCT and sexual transmission of HIV, this era of expanding access to HAART has the potential to decrease risks and barriers to reproduction among women living with HIV. This emerging reality of HIV as a manageable chronic disease has corresponded with increasing calls for a rights- and evidenced-based approach to support the sexual and reproductive health needs of HIV-infected women [14, 15, 26, 27]. However, little is known about whether or how access to HIV treatment services may influence the sexual and reproductive health decision-making, behaviours, or outcomes of women in high HIV prevalence settings.

Available information about the role of HAART access in resource-rich settings (primarily among men who have sex with men (MSM)) have shown minimal impact of individual receipt of HAART on sexual risk behaviours [28]. However, these studies do report a significant relationship between beliefs about the role of HAART in reducing health and transmission risks (regardless of actual HAART use and HIV status) and the prevalence of unprotected sex [28]. If women in sub-Saharan Africa exhibit HAART-associated behaviour changes similar to those reported from high-income countries, changes in sexual behaviour may yield an increased risk of HIV transmission and pregnancy, especially in regions with both high HIV prevalence and fertility rates.

However, the generalizability of studies from high resource settings where HIV is concentrated within particular sub-populations to HIV-positive women in hyper-endemic sub-Saharan African settings remains uncertain. There remain great differences between resource-rich settings and sub-Saharan African countries with respect to HIV prevalence, the level of HAART accessibility, prevailing fertility rates and trends, access to HIV and reproductive and sexual health services, and socio-cultural environments, which are likely to influence the direction and magnitude of the effect of HAART access on sexuality and reproduction. Moreover, while the potential health risks may dampen the reproductive goals of some HIV-positive women, stigma associated with childlessness in many sub-Saharan African societies [29] and the strong personal desires and community expectations for biological parenthood [30] remain potent drivers of pregnancy, irrespective of HIV status. In many such cultural contexts, remaining childless can be a societal norm violation more stigmatizing than HIV infection itself [30, 31].

Understanding the role that increasing access to HAART may have on sexual and reproductive decision-making and behaviours has implications for the long-term sustainability and effects of HAART scale-up initiatives. Recent reports have raised concern regarding potential shortages of HAART funding at global levels [32] concomitant with the largely stagnant resourcing for family planning and reproductive health programming in low-income countries [33]. Now is the time to

document the ways in which HAART may be impacting the sexual and reproductive decision-making and behaviours of HIV-affected women in feminized epidemic settings. In addition, this understanding will contribute critical information towards efforts aimed at improved integration between policies, programs, and services that intersect the sexual, reproductive, and HIV needs of women in high HIV prevalence settings.

Below, the context of HIV, HAART accessibility, and sexual and reproductive health in the two study settings (Soweto, South Africa and Mbarara, Uganda) is briefly described.

1.3 Brief situational analysis of HIV, HAART scale-up, and sexual and reproductive health in South Africa and Uganda

South Africa and Uganda represent important and appropriate countries within which to investigate the impact of HAART on sexual and reproductive decision-making and behaviours given the unique epidemiology and trends of the HIV epidemic in each country, the different levels of HAART coverage, and the diverse fertility rates and trends. In addition, each country has high quality clinical and research institutions committed to investigating the impact of HAART on their populations.

1.3.1 South Africa

With 5.5 million HIV-infected residents, South Africa has the world's largest absolute number of people living with HIV. The national HIV prevalence among South African adults is 18.8%, a prevalence that has remained relatively stable over several years [1]. The epidemic is highly feminized as women currently account for nearly 60% of all HIV-infected adults [1] and among 15-24 year-olds, women account for 90% of incident HIV infections [34]. HIV prevalence in the study site Soweto, an urban township of Johannesburg, is among the highest in the country. An estimated 30% of women attending antenatal clinics in Soweto test HIV-positive [35].

Each year an estimated 220,000 women living with HIV in South Africa become pregnant [10]. Although the coverage of antiretroviral therapy to prevent MTCT increased from 15% in 2004 to 73% in 2008 [10], each year over 64,000 infants are infected with HIV via MTCT [36].

In 2006, the South African government released the '*HIV & AIDS and STI Strategic Plan for South Africa, 2007-2011*' [37], a long overdue commitment to providing antiretroviral therapy (among other HIV treatment, prevention, and control strategies) to medically eligible South Africans. Although government and multinational efforts are improving access to antiretroviral therapy, there remains a

high level of unmet need. At the end of 2007, an estimated 700,000 adults were receiving ARV, accounting for approximately a third of those in need of treatment [10]. Despite a high level of unmet need, South Africa is operating the largest HIV treatment program in the world with an average of 16,000 people starting HAART each month.

The total fertility rate (TFR) of South Africa is 2.0, which is the lowest fertility rate in sub-Saharan Africa. Use of modern contraceptive methods is estimated at 65% among sexually active women [38]. Available estimates for Gauteng province (in which Soweto is located) estimate a TFR of 2.3 and a contraceptive prevalence rate of 63%, although there is substantial variation by population sub-group [38]. Nearly two-thirds of South African adults reported using a condom at last sex [39]. Family planning services in South Africa are widely and freely available and termination of pregnancy services are legal and available free-of-charge at designated primary health care facilities.

The South African portion of this thesis was conducted at the Perinatal HIV Research Unit (PHRU), which is housed in Chris Hani Baragwanath Hospital in Soweto. The PHRU, established in 1996, is one of Africa's largest HIV/AIDS research and clinical service centres. Over the last decade, the PHRU's focus has extended beyond prevention of MTCT services to include HIV treatment, prevention, and

psychosocial research and services for adults and children. The PHRU clinics see over 5,000 adult patient visits monthly and provide antiretroviral therapy and clinical care free-of-charge to medically eligible HIV-positive individuals.

1.3.2 Uganda

In Uganda, 46% of the estimated 1 million HIV-infected adults are women of reproductive age. National adult HIV prevalence is 6.7% and is significantly higher among women (7.5%) than among men (5%) [1]. Between the early 1990s to the early 2000s, Uganda was the first country in sub-Saharan Africa to show a decrease in HIV prevalence [40]. The drop in prevalence is largely attributed to changes in preventive sexual behaviors including an increase in primary and secondary sexual abstinence, a reduction in multiple concurrent partnerships, and an increase in condom use [41]. Since then, however, studies have reported a concerning recent rise in HIV incidence in some population sub-groups as well as an increase in the overall population prevalence [42].

The well-known 'ABC' approach (abstinence, be faithful, and condom use) has been the foundation of HIV prevention activities in the country. More recently, the ABC strategy has expanded to include Voluntary Testing and Counselling, PMTCT, and improved access to antiretroviral therapy and HIV care and support

services. An estimated 82,000 HIV-positive Ugandan women become pregnant each year and in 2008, only half received antiretrovirals for preventing MTCT [10].

In June 2004, Uganda began to offer free antiretroviral treatment to people living with HIV through the Ugandan Antiretroviral Drug Policy. However, only more recently through concerted global efforts have no-cost HAART services been made more widely available. In 2000 an estimated 1,000 Ugandans were receiving HAART compared with an estimated 140,000 at the end of 2008. The HAART coverage rate is 33% meaning that one-third of all those who need treatment are receiving it [10].

At 6.7 births per woman, Uganda has one of the total highest fertility rates in the world. Although levels vary by region, overall use of family planning by married women is low and estimated at 15%; with a sizable proportion of those reporting use of traditional methods [43]. In the absence of HAART, the Ugandan HIV epidemic has had a dramatic impact of population fertility. The combined effect of premature mortality and reduced fertility among HIV-positive women of reproductive age resulted in an estimated 700,000 fewer births than expected between 1980 and 2000. By the year 2000, this estimate represented 6% of all births that would have occurred in Uganda that year [3].

The Ugandan portion of this thesis emerges from studies conducted at the Mbarara Regional Referral Hospital located in Mbarara District in southwest Uganda and led by investigators at Harvard Medical School/Massachusetts General Hospital in Boston and the Mbarara University of Science and Technology. Mbarara is 265 km southwest of the capital city, Kampala. The hospital serves a population of approximately 1.1 million people and HIV prevalence in the region is estimated at 10% [44]. Housed within the Mbarara Regional Referral Hospital is the Mbarara University HIV clinic, the Immune Suppression Syndrome (ISS) Clinic. The ISS clinic currently serves more than 13,000 patients, 65% of whom are women. The clinic offers comprehensive HIV care services, including provision of HAART, free of charge. Approximately 35% of the clinic's population is currently receiving HAART.

1.4 Outstanding Questions and Study Justification

Unprotected sexual activity required for conception carries a risk of HIV transmission to uninfected sexual partners [45] and, among HIV-positive women who do become pregnant, carries a risk of mother-to-child-transmission of HIV [46, 47]. In addition, HIV-positive women have a lower life expectancy than negative women [48], increasing the risk of maternal orphanhood [49]. In light of these concerns, early reproductive guidelines for people living with HIV were dissuasive

[50] and HIV-positive women who express fertility desires continue to encounter community and healthcare worker disapproval [30, 51]. Despite these concerns, a plethora of evidence indicates that many women living with HIV continue to desire children [30, 52-55], become pregnant [19, 52, 53], and give birth [52, 53, 56] after knowing their HIV-positive status. Evidence also suggests that pregnancy is an important risk factor for acquiring HIV infection [57].

Through measured reductions in morbidity and mortality of HIV-infected individuals and reductions in the risk of vertical and horizontal HIV transmission, expanding access to HIV treatment services in high prevalence settings in sub-Saharan Africa is anticipated to impact sexual and reproductive decision-making and behaviours. To date, there is a paucity of empirical data that describes how increased access and receipt of HAART influences the underlying determinants of pregnancy including sexual behaviours, fertility decision-making, and contraceptive use. In addition, it remains unknown the degree to which use of HAART itself, enrolment in HAART treatment clinics and associated increased access to health care services, and/or the effect of HAART optimism is the primary pathway through which HAART may impact these aspects of sexuality and reproduction. Moreover, the few recently available studies neglect to consider duration of HAART use and have tended to conduct analyses only among HIV- positive women, without including comparisons with HIV-negative women from the same community [52-

54]. The lack of an HIV-negative comparison group in previous studies precludes the opportunity to assess whether HAART users begin to resemble HIV-negative women in their sexual and reproductive decision-making and behaviours, particularly as HIV is increasingly recognized as a manageable chronic disease. Moreover, neglecting to assess the role of duration of HAART precludes the opportunity to investigate how decisions and behaviours may change over increasing lengths of time on therapy.

In settings experiencing generalized HIV epidemics with a higher proportion of infections among women of reproductive age, there is a desperate need to understand the impact of expanding access to HAART on sexual and reproductive health. This information is critically required to help develop sexual and reproductive programs, services, and policies that support the rights of all women to safely achieve their reproductive goals, while minimizing risks to maternal, child, and partner health.

1.5 Purpose, Objectives, and Hypotheses

Given the paucity of available information, the overall purpose of this thesis is to examine whether sexual and reproductive decision-making and behaviours vary by HIV status and receipt of HAART among women in two HIV-endemic settings in

sub-Saharan Africa.

The study purpose is supported by the following five objectives:

(1) **To review the literature on the known and potential impact of antiretroviral therapy on the fertility of HIV-positive women in sub-Saharan Africa and to develop a conceptual framework to guide investigations aimed at understanding how widespread access to and use of antiretroviral therapy may impact fertility and its proximate and underlying determinants.**

(2) **To estimate the association between current HAART use and recent sexual activity among HAART-naïve and HAART-experienced HIV-positive women of reproductive age in three global settings with high HIV prevalence (Rio de Janeiro, Brazil, Soweto, South Africa, and Mbarara, Uganda).** A secondary objective was to explore the association between current HAART use and sexual behaviours, including use of condoms and contraception. It was hypothesized that through improvements in health and well-being, receipt of HAART would be associated with an increased prevalence of recent sexual activity.

(3) **To assess the prevalence of fertility intentions and to determine whether fertility intentions vary according to HIV status and use and duration of HAART among women of reproductive age in Soweto, South Africa.** Based on the review and conceptual framework presented in Chapter 2, it was hypothesized that HIV-positive women would have lower fertility intentions compared with HIV-negative women. In addition, it was hypothesized that HIV-positive women receiving HAART would have higher fertility intentions than HAART-naïve women, with increasing duration of HAART treatment associated with incrementally higher fertility intentions. Overall, it was hypothesized that HAART use would be associated with narrower differences in fertility intentions between HIV-positive and HIV-negative women.

(4) **To assess the prevalence of contraceptive use and to determine whether contraceptive use varies according to HIV status and use and duration of HAART among sexually active women in Soweto, South Africa.** A secondary objective was to determine the types of contraceptive methods used and whether contraceptive method profiles vary by HIV status and HAART use. Based on the review and conceptual framework presented in Chapter 2, it was hypothesized that HIV-positive women receiving HAART

would be less likely to use contraception compared with HIV-positive women not receiving HAART, with increasing duration of HAART use associated with incrementally lower contraceptive use. It was also hypothesized that contraceptive prevalence among HIV-positive women receiving HAART and HIV-negative women would be similar.

(5) To develop a reliable HAART optimism scale for HIV-positive women in high HIV prevalence settings and to test the scale's validity against a measure of fertility intentions and two measures of sexual behaviour (i.e., sexual abstinence and unprotected sex) among HAART-naïve and HAART-experienced women in Mbarara, Uganda. Upon development of a reliable HAART optimism scale, it was hypothesized that HIV-positive women with higher HAART optimism would be more likely to report intentions to have children and would be more likely to be sexually active and practice risky sexual behaviours.

1.6 Overview of thesis

This manuscript-based thesis is comprised of seven separate chapters that represent a progression of investigations that address the objectives listed above. This first chapter provides background regarding the feminization of the HIV pandemic in sub-Saharan Africa, intersections between HIV and sexual and reproductive health, an overview of global HAART scale-up efforts and potential impact on sexual and reproductive decision-making and behaviours, and related background to the study settings in Soweto and Mbarara. In addition, this chapter lists the overall purpose and five associated objectives of this thesis.

Chapter 2, published in *Current HIV/AIDS Reports* in 2006 [58], provides a literature review of the known and potential impacts of highly active antiretroviral therapy on fertility of HIV-positive women in high HIV prevalence settings of sub-Saharan Africa. The review was conducted in 2005 and is therefore limited to data available at that time. Using Bongaarts' proximate determinants of fertility framework (adapted for conditions of generalized HIV epidemics) [59], the review paper proposes a conceptual model to examine how use of HAART may mediate the impact of HIV infection on fertility through biological and behavioral determinants. The conceptual framework highlights related research priorities and guided the development of subsequent epidemiological thesis research presented in Chapters 3

to 6. Each of these chapters provides an updated review of the literature specific to the determinant of fertility under investigation.

Chapter 3, published in *AIDS Care* in January 2008 [60], presents the results of a 2005 pilot study that investigated the impact of HAART on recent sexual activity among HIV-positive women in three global settings: Rio de Janiero, Brazil; Soweto, South Africa; and Mbarara, Uganda. In addition to the findings and interpretations presented, the pilot study informed the subsequent development of larger HIV, HAART, and sexual and reproductive health-related epidemiological studies in each of the three sites. Data from the Brazil study are not further included in this thesis.

Chapters 4 (in press at the *American Journal of Public Health* [61]), 5 (under review), and 6 (published in *AIDS and Behavior* in 2009 [62]) provide detailed epidemiologic investigations of the relationships between HIV, HAART, and specific sexual and reproductive decision-making and behaviours. The analyses in Chapters 4 and 5 relate to the impact of HAART on fertility intentions and contraceptive use, respectively. These findings emerged from a study that the candidate developed and led in collaboration with the Perinatal HIV Research Unit (PHRU) in Soweto, South Africa. The analysis in Chapter 6 relates to the development and testing of a HAART optimism scale. These findings emerged from a study led by investigators at Harvard Medical School/Massachusetts General

Hospital and the Mbarara University of Science and Technology in Mbarara, Uganda. Chapter 7 provides a summary of the key findings, unique contributions of this dissertation, recommendations, and priorities for future research.

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CHAPTER 2[1]:

THE POTENTIAL IMPACT OF ANTIRETROVIRAL THERAPY ON FERTILITY IN SUB-SAHARAN AFRICA

2.1 INTRODUCTION

Women of reproductive age comprise 46% of the world's HIV-infected adult population. The majority live in sub-Saharan Africa (SSA), where approximately 14 million women of child-bearing age are currently living with HIV/AIDS [1]. HIV infection in these women raises important individual and public health concerns about the incidence of pregnancy. Such concerns relate to the survival and health of the mother and the health of her baby, including risk of vertical disease transmission, orphanhood, and other adverse pregnancy outcomes [2].

In SSA, HIV is predominantly transmitted through heterosexual intercourse [1], which further entangles the impact of the HIV epidemic on fertility. The common pathway suggests that both the risk of HIV infection and pregnancy may share similar risk factors and distribution in the population. Yet, substantial evidence indicates that HIV-infected women in SSA have between 25-40% lower

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fertility than non-infected women [3,4]. It should be noted that the term *fertility* is used here in the demographic sense, as in the actual level of reproduction based on the number of live births that occur, rather than the biologic capability to reproduce (termed *fecundity*).

The evidence for reduced fertility arises from settings with limited (or no) access to HIV/AIDS treatment. Recently, however, access to antiretroviral (ARV) treatment in SSA is improving considerably [5,6]. The potential impact of ARV therapy on the survival and quality of life of individuals with HIV infection has been demonstrated in numerous studies from developed and developing countries [7-10]. As ARV therapy becomes increasingly accessible in SSA, it is important to understand whether and how the associated clinical improvements correspond with changes in the incidence of pregnancy and fertility among women with HIV infection.

Thus, the purpose of this article is to review the literature regarding the potential impact of ARV therapy on fertility in SSA. First, evidence for lower fertility among women with HIV infection (not on therapy) compared with uninfected women is briefly reviewed. Then, the literature on ARV therapy and fertility in SSA is examined. Owing to limited empirical evidence from this setting, the evidence from developed countries is reviewed and implications for developing regions are

discussed. Next, Bongaart's proximate determinants of fertility framework (adapted for conditions of a generalized HIV epidemic) [11,12] is used to examine the underlying mechanisms through which use of ARV therapy may impact the fertility of HIV-infected women in SSA. Finally, a conceptual framework is proposed to guide future research aimed at understanding how widespread use of ARV therapy may impact fertility in sub-Saharan Africa.

2.2 HIV AND FERTILITY IN SUB-SAHARAN AFRICA

In societies with low contraceptive use, women with HIV infection have lower fertility than non-infected women. This finding is explained by increases in HIV-associated mortality and both the direct biological effects of HIV on the fecundity of infected women and the indirect impact of the virus on the behavioural determinants of fertility [3,4].

Two review articles have examined the relationship between HIV and fertility in SSA [3,4]. In 1998, Zaba and Gregson [3] reviewed six studies from SSA and concluded that HIV-infected women have between 25-40% lower fertility than non-infected women for most age groups. Only in the youngest age group (15-19 years) was HIV-infection associated with higher fertility, presumably due to selection for early sexual activity. A more recent review of an additional 13 studies similarly

concluded that HIV-infected women in SSA experienced lower fertility than their non-infected counterparts [4]. The authors estimated that each 1% increase in population prevalence of HIV in SSA countries results in a population-attributable decline in fertility of 0.37% (95% CI: 0.30%, 0.44%) [4]. The investigators used mathematical modelling to demonstrate the substantial impact of such a reduction in population fertility. They estimated that the combined effect of increased mortality among women with HIV infection and an assumed 20% reduction in fertility resulted in 700,000 fewer births in Uganda between 1980 and 2000.

These findings have been further substantiated by recent studies from SSA that report similar decreases in fertility among HIV-infected women compared with uninfected women [13,14]. Recent studies have also shown that fertility decreases dramatically by HIV disease progression [14,15] and decreasing CD4 cell counts [14-16].

2.3 ARV THERAPY AND FERTILITY IN SUB-SAHARAN AFRICA

Between June and December 2004, the number of people on ARV therapy in SSA doubled from 150,000 to 310,000 [6]. Although coverage varies dramatically by country, in Botswana, Namibia, and Uganda greater than 25% of those who need

treatment are receiving it; 13 other countries in the region have greater than 10% coverage [6].

As ARV therapy becomes increasing accessible in SSA, the associated improvements in health, quality of life, and survival are anticipated to influence both the biological and behavioural fertility determinants of infected women. There remains, however, little empirical evidence to support this claim due, in part, to the recency of ARV treatment programs in the region.

2.4 ARV THERAPY AND FERTILITY IN DEVELOPED COUNTRIES

Research in developed countries suggests that HIV is associated with a decline in fertility and that ARV therapy reverses this decline. Studies conducted before the widespread availability of ARV therapy have shown that HIV-infected women in developed countries are less likely to become pregnant [17-21] and give birth [21,22] compared with uninfected women. Studies also report that the incidence of pregnancy and livebirth declines as AIDS develops [23] and that women with HIV infection suffer higher rates of adverse outcomes (including voluntary and spontaneous abortions) than uninfected women [19-21].

Current hypotheses suggest that the observed decline in fertility will be largely reversed with the introduction of highly active antiretroviral therapy (HAART), however, available studies have yielded somewhat differing results.

Blair et al [24] found that HIV-infected women in the United States were 20% more likely to become pregnant in the "HAART era" (1997-2001) than in previous years (1992-1996) (adjusted Relative Risk (ARR): 1.2; 95% CI: 1.1, 1.4). The higher pregnancy rate during the HAART era was thought to be due to both increased survival times and delayed progression to AIDS, which resulted in more opportunities to become pregnant.

Another American cohort study of HIV-infected women followed between 1994 and 2002 revealed somewhat different results. Massad et al [25] reported that use of ARVs at baseline was associated with a decreased incidence of pregnancy compared with HIV-infected women not on therapy (Odds Ratio (OR): 0.34; 95% CI: 0.49-0.98 for mono- or combination therapy; OR: 0.34; 95% CI: 0.03-4.28 for HAART). The study also reported that induced abortion became less common in the later HAART era (1999-2002) compared with earlier periods. The net impact of these findings (i.e., decreased incidence of pregnancy and increased incidence of livebirth) on fertility in the HAART era remains uncertain.

Finally, a European prospective cohort study of HIV-infected women followed between 1985 and 1998 found no statistically significant increased trend in the age-adjusted incidence of pregnancy after HIV diagnosis over time [17]. In particular, the rate of pregnancy did not change in the HAART era (1997-1998) compared with earlier periods. However, because the study included only the first two years of widespread HAART use, it may be too early to conclude that HAART did not influence reproductive decision-making.

Delineating the impact of HAART on fertility is complicated by the lack of information about changes in other determinants of fertility over the follow-up period of these studies. It is unclear, for example, whether women altered contraceptive or sexual practices or experienced changes in other variables important to understanding fertility differentials. Indeed, an observed increase in fertility may be a reaction to the availability of treatment to prevent mother-to-child-transmission (MTCT), rather than to the impact of HAART. Furthermore, the overall low fertility rate and HIV prevalence in these settings, compared with rates in SSA, may minimize the observed differential impact of ARVs on fertility. There may also be important cultural differences that influence fertility decisions in various contexts, including societal expectations to bear children [26]. Thus, while informative, the prevailing evidence from developed countries may not be fully applicable to settings in SSA.

2.5 BONGAARTS' PROXIMATE DETERMINANTS OF FERTILITY FRAMEWORK: UNDERSTANDING THE MECHANISMS THROUGH WHICH ARV THERAPY MAY INFLUENCE FERTILITY

We used Bongaarts' proximate determinants of fertility framework (adapted for conditions of a generalised HIV epidemic) to explore the underlying mechanisms through which ARV therapy may influence fertility of HIV-infected women in SSA [11,12]. An overview of the framework is shown in Figure 2.1.

The proximate determinants of fertility are the biological and behavioural factors that directly influence fertility over a woman's reproductive life span. It is through these proximate determinants that broader social, economic, and cultural variables act to affect fertility. As shown in Figure 2.1, two proximate determinants, marriage (or stable sexual union) and onset of permanent sterility, determine the duration of a woman's reproductive period. The other five proximate determinants influence the rate of childbearing and the duration of birth intervals. These include post-partum infecundability, natural fecundability or frequency of intercourse, use and effectiveness of contraception, spontaneous intrauterine mortality, and induced abortion. A thorough description of these seven proximate determinants has been provided elsewhere [11].

Other investigators have adapted Bongaarts' framework to describe how HIV influences the proximate determinants to impact fertility in SSA [27,28]. The

following section outlines how the use of ARV therapy may mediate the influence of HIV on fertility through the proximate determinants. This discussion is summarized in Table 2.1.

2.5.1 Marriage/Sexual debut

Bongaarts and Potter [11] denoted marriage, a proxy for sexual debut and sexual activity, as the time on the reproductive life span when a woman is most "at risk" for pregnancy. Since then, however, data on sexual debut and activity have become increasingly available and investigators have advised using these variables instead [29]. This may be particularly pertinent in some regions of SSA where pre-marital fertility is common [30,31].

Whichever the measure, it is clear that the HIV epidemic is altering many of the basic demographic features that comprise this proximate determinant of fertility in SSA. In many countries, the epidemic is increasing both the age of sexual debut and age at first marriage [32-34], which shortens the reproductive life span, thereby lowering fertility [11,27,28].

For already married couples, reports suggest that the HIV epidemic is shortening the duration of marriage through increased incidence of divorce and

widowhood [35-37]. Since birth rates are lower outside of marriage [27], high rates of divorce and widowhood decrease fertility. Reports from Uganda suggest that widows and divorced women find it more difficult to remarry due to fears of infecting new partners [28,36]. Fears of infection may also be reducing pre- and extra-marital sexual relations and polygamous unions [28]. This increase in monogamous relationships may lead to higher fertility [28,38].

How ARVs mitigate the relationship between HIV and age at marriage/sexual debut remains unknown. It is particularly difficult to hypothesize the direction of ARV influence because these are population-level rather than individual-level determinants. As such, even as ARV therapy becomes more widely available to HIV-infected individuals in SSA, it may be unlikely to drastically alter population-level trends for increasing age at sexual debut and marriage in the short term of the epidemic. However, by increasing the survival time and health of infected individuals, ARVs are hypothesized to prolong the duration of marriage and extend the reproductive period, thereby potentially increasing fertility.

2.5.2 Onset of permanent sterility

The onset of permanent sterility demarcates the end of a woman's reproductive period [11]. Untreated sexually transmitted infections (STIs) can lead to

earlier onset of permanent sterility [39-41]. Studies from SSA reveal that HIV-infected women have a higher rate of prior syphilis infection [42] and current STIs [43] than HIV-negative women, which can cause sterility, especially if left untreated. Earlier onset of permanent sterility reduces fertility [11].

The STI treatment campaigns that have accompanied HIV prevention efforts in Tanzania and Uganda have reduced the population-level incidence of STIs [44,45]. In the absence of increased rates of contraceptive use, such reductions in untreated STIs are anticipated to increase fertility [27,28,46].

The impact of widespread use of ARVs on this proximate determinant is currently unknown. It is anticipated, however, that increased access to ARVs will increase patient contact with the healthcare system thereby increasing opportunities for STI education, testing, and treatment. Collectively, a decrease in the incidence of untreated STIs may increase fertility. In the absence of STI treatment services, however, the availability of ARV therapy will not impact sub-fertility associated with STIs.

2.5.3 Post-partum infecundability

Both breastfeeding and post-partum abstinence from sexual intercourse contribute to post-partum infecundability [11] and are important determinants of birth interval length [47,48].

In an attempt to minimize the risk of MTCT of HIV, there is evidence that some infected women decide to reduce or forego breastfeeding [34]. Such reductions in breastfeeding may shorten a women's short-term infecundability, leading to earlier pregnancy and higher fertility [27,28].

Women in SSA have historically practiced periods of post-partum abstinence. Recent reports indicate that the mean duration of postpartum abstinence varies substantially by country, ranging from a low of four months in Zimbabwe to a high of 19 months in Burkina Faso [49]. Reports from Zimbabwe and Benin suggest that husbands may be more likely to engage in extra-marital sex during this period [34,50]. Anecdotal evidence suggests that in regions with high HIV prevalence, women may shorten the duration of post-partum abstinence to decrease their chances of acquiring HIV through the extra-marital activities of her husband [27,28]. Shorter periods of post-partum abstinence are hypothesized to increase fertility [3,28,51].

The impact of widespread ARV therapy on breastfeeding practises is largely unknown. Recent evidence suggests that provision of ARVs during late pregnancy and lactation lowers the viral load in breast milk and substantially reduces the risk of transmission by breastfeeding [52]. If future studies corroborate these results, women on ARV therapy in SSA may be encouraged to initiate and prolong breastfeeding at lower risk to their infants. Increased rates of breastfeeding can be expected to result in decreased fertility [47].

The impact of ARV therapy on duration of post-partum abstinence is currently unknown. There may, however, be a relationship between general abstinence and ARV therapy. A study from Cote d'Ivoire reported that HIV-infected women on ARVs were less likely to be sexually abstinent (for 6 or more months) compared with women not on therapy, although the relationship was only marginally significant (53% vs. 63%, respectively; p=0.08) [53]. A similar pattern was reported for HIV-infected men. If additional evidence supports the finding that ARV therapy reduces rates of sexual abstinence, fertility may be expected to increase, in the absence of contraceptive use.

2.5.4 Natural fecundability or frequency of intercourse

The components of this proximate determinant of fertility include coital frequency, incidence of amenorrhea, and natural fecundability (including spermatogenesis), all three of which are impacted by HIV.

In the absence of treatment, HIV-infected women have lower levels of coital frequency owing to higher morbidity in the women [54] or their male partners [4]. Studies from Uganda [54,55] and North America [56] have shown that HIV significantly increases the incidence of amenorrhea. Other studies have shown that HIV reduces the fecundability of women with infected partners due to decreased sperm production [57,58]. In sum, available evidence suggests that HIV functions to decrease coital frequency, increase incidence of amenorrhea, and decrease sperm production of male sexual partners, and thus decreases fertility.

The health improvements associated with the use of ARV therapy are anticipated to increase coital frequency [59]. The impact on amenorrhea and spermatogenesis remains unknown but is expected to result in improvements due to reduced morbidity [60]. Thus, the net effect of ARV therapy on this proximate determinant may be to increase fertility.

2.5.5 Use and effectiveness of contraception

Use of effective contraception is a main determinant of fertility [11]. Survey data from SSA countries with high HIV prevalence reveal increased rates of condom use to protect against STIs and HIV [28,61,62]. If this increased prevalence of condom use is among previous non-contraceptive users, then it can be expected to decrease fertility. If however, increased condom use occurs at the expense of more effective contraceptive methods (such as oral contraceptives), this may result in an increase in fertility [28,34].

Women with HIV infection may be concerned about MTCT and the potential for leaving orphans and thus may be more likely to use hormonal contraceptives to prevent pregnancy [63-65]. These actions would serve to decrease fertility [28]. On the other hand, owing to high infant mortality associated with HIV/AIDS, women may want more children to maximize the chances that at least a few will survive and/or to replace children who have previously died [27]. Such actions will serve to increase fertility.

The impact of ARV therapy on condom use is unknown. It is hypothesized, however, that the improved health associated with ARVs will increase desire for children since a woman may feel more confident that she and her children will survive [66]. This may result in decreased contraceptive use and thus increased

fertility. Similarly, it is hypothesized that women on ARV therapy will be less likely to use contraception and undergo fewer abortions due to reduced fears of infant infection and orphanhood, thereby increasing fertility [27,28].

2.5.6 Spontaneous intra-uterine mortality

Incidence of spontaneous abortion and stillbirths are important determinants of the rate of childbearing and the birth interval length [11]. The limited available evidence supports a possible increased risk of both spontaneous abortion and stillbirth among HIV-infected women in developing countries. A systematic review reported that HIV-infected women in developing countries had a statistically significant increased risk of stillbirth [summary OR: 4.15; 95% CI: 2.81-6.15] and spontaneous abortion [summary OR: 4.05; 95% CI: 2.75-5.96] compared with non-infected women [67]. Higher incidence of spontaneous abortion and stillbirth translates to decreased fertility [11].

The evidence regarding the impact of ARVs on spontaneous intra-uterine mortality remains inconclusive. For instance, while there are reports that HIV-infected women treated with HAART prior to pregnancy have a significantly higher risk of experiencing fetal death [68], and miscarriage [20], other studies have not found an increased incidence of stillbirths [69]. In spite of inconclusive findings,

investigators have concluded that the overall risks of adverse pregnancy outcomes that are attributable to ARV therapy are low and are likely to be outweighed by the known benefits of therapy during pregnancy [70,71]. In the absence of conclusive results on the impact of ARVs on spontaneous intra-uterine mortality, the subsequent impact on fertility remains unknown.

2.5.7 Induced abortion

Incidence of induced abortion is the final proximate determinant of fertility [11]. Studies from Uganda [54], Cote d'Ivoire [72], Cameroon and Kenya [62] report higher rates of induced abortion among HIV-infected women compared with HIV-negative women, which decreases fertility [28]. Induced abortions may be more likely among HIV-infected women due to concerns about vertical transmission and fear of leaving orphans [27,28].

The impact of ARVs on rates of induced abortion in SSA is largely unknown. Results from an American study revealed that abortion became less common after the introduction of HAART [25]. This may reflect women's improved outlook for their own health and survival and reduced concerns about the risks of MTCT. It is therefore hypothesized that the widespread availability of ARV therapy in SSA will similarly result in a reduced rate of induced abortion, thereby increasing fertility.

2.6 CONCEPTUAL FRAMEWORK FOR ANALYSING THE POTENTIAL NET IMPACT OF ARV THERAPY ON FERTILITY

The previous section provided a synthesis of the real and hypothesized impacts of ARVs on the behavioural and biological proximate determinants of fertility in the context of high HIV prevalence. As shown, ARV therapy acts to orient some determinants towards increased fertility, whereas others offset this effect. For yet other proximate determinants, the impact of ARVs remains unknown. Of course, the net impact on fertility is influenced by social, economic, cultural, and gender-related factors beyond simply HIV status and ARV use. Thus, the following framework is proposed to conceptualize the hierarchy of factors that determine fertility and to identify where and how ARVs may operate within this hierarchy.

In Figure 2.2, the proximate determinants have been separated into their biological and behavioural components and are oriented in terms of their influence on fertility in the presence of a generalized HIV epidemic. As shown, the proximate determinants directly influence fertility at varying stages within a woman's reproductive life span, either affecting the duration of the reproductive period or the rate of childbearing and birth intervals.

The proximate determinants are influenced by broader social, economic, cultural, and gender-related determinants of fertility (e.g., economic development,

urbanization, and maternal education). As depicted in the framework, these broader determinants operate at three levels, the individual (which includes fertility goals and desires), the household/family (which includes considerations of household gender equity and family wealth), and the community (which includes the political economy and cultural forces).

ARV therapy has been placed in the middle of the framework to indicate its potential to influence the proximate determinants through improvements in health, quality of life and survival of women with HIV infection, and "ARV optimism". The placement of ARVs in the framework also indicates that the provision of therapy is similarly influenced by broader social, economic, cultural, and gender-related determinants.

As shown in Figure 2.2, ARV therapy is hypothesized to increase fertility of women with HIV infection by reversing trends of reduced rates of coital frequency and spermatogenesis (among infected men) and by reversing trends of increased rates of amenorrhea and induced abortion. In contrast, ARV therapy is anticipated to decrease fertility by reversing trends of reduced rates of breastfeeding. The impact of ARV therapy on the remaining proximate determinants is largely unknown.

This framework is, of course, highly simplified since it does not show the complex interactions that may occur between the proximate determinants nor does it reveal the numerous possible feedback loops. Rather, by providing an overview of the hierarchical relationships between determinants of fertility, it is hoped that this framework can inform future research aimed at understanding how widespread use of ARV therapy may impact fertility in SSA.

2.7 CONCLUSION

The reductions in morbidity and mortality associated with ARV therapy have the potential to reverse some of the trends towards decreased fertility of women living with HIV in SSA. As ARVs become increasingly available in the region, issues related to the sexual and reproductive health and fertility of HIV-infected and –affected women must be addressed. Future research should focus on:

1. Estimating the impact of ARV therapy on sexual behaviour and contraceptive practices.
2. Assessing whether the improved health status associated with the use of ARV therapy impacts fertility intentions of HIV-infected women, men, and couples.

3. Estimating the impact of ARV therapy on maternal survival and fertility, including consideration of the impact on rates of MTCT.
4. Estimating the impact of ARV therapy on the ability of women to conceive and bear (more) children.
5. Understanding the gender dynamics of fertility decision-making in the context of ARV therapy, including consideration of the role of male sexual partners.

Table 2.1: Use of Bongaarts' Proximate Determinants of Fertility framework to describe the potential impact of antiretroviral (ARV) therapy on fertility in sub-Saharan Africa

Proximate Determinant of Fertility (P.D.)	Impact of HIV on P.D.	[Ref]	Possible Impact on Fertility	[Reference]	Impact of ARVs on P.D.	[Ref]	Reason	Hypothesized Impact of ARVs on Fertility
1. Marriage/Stable sexual union								
1.1 Age at sexual debut	Increase	[32-34]	Decrease fertility	[27,28]	Unknown			
1.2 Age at marriage	Increase	[32-34]	Decrease fertility	[27,28]	Unknown			
1.3 Incidence of pre- and extra-marital sexual relations	Reduce	[28]	Decrease fertility	[27,28]	Unknown			
1.4 Incidence of polygamy	Reduce	[28]	Increase fertility	[27,28,38]	Unknown			
1.5 Incidence of divorce	Increase	[34,36,37]	Decrease fertility	[27,28]	Decrease		Improved survival and health prolongs marriage, which leads to increased reproductive opportunities	Increase fertility
1.6 Incidence of remarriage	Reduce	[34,36]	Decrease fertility	27,28,36]	Unknown			

Table 2.2 (continued): Use of Bongaarts' Proximate Determinants of Fertility framework to describe the potential impact of antiretroviral (ARV) therapy on fertility in sub-Saharan Africa

Proximate Determinant of Fertility (P.D.)	Impact of HIV on P.D.	[Ref]	Possible Impact on Fertility	[Reference]	Impact of ARVs on P.D.	[Ref]	Reason	Hypothesized Impact of ARVs on Fertility
1.7 Incidence of widowhood	Increase	[34,36,37]	Decrease fertility	[27,28]	Decrease		Improved survival and health prolongs marriage, which leads to increased reproductive opportunities	Increase fertility
2. Onset of permanent sterility (induced or menopause)								
2.1 Incidence of STIs (and associated sub-fertility)	Reduce	[44,45]	Increase fertility	[27,28,46]	Unknown, but no difference in the absence of STI treatment			
3. Post-partum infecundability								
3.1 Rate of Breastfeeding	Reduce	[34]	Increase fertility	[27,28]	Increase	[52]	Women encouraged to prolong breastfeeding at lower risk to infant	Decrease fertility
3.2 Rate of post-partum abstinence	Reduce	[27,28]	Increase fertility	[3,28,51]	Unknown			

Table 2.3 (continued): Use of Bongaarts' Proximate Determinants of Fertility framework to describe the potential impact of antiretroviral (ARV) therapy on fertility in sub-Saharan Africa

Proximate Determinant of Fertility (P.D.)	Impact of HIV on P.D.	[Ref]	Possible Impact on Fertility	[Reference]	Impact of ARVs on P.D.	[Ref]	Reason	Hypothesized Impact of ARVs on Fertility
4. Natural fecundability or frequency of intercourse								
4.1 Coital Frequency	Reduce	[4,54]	Decrease fertility	[3,28,54]	Increase	[59]	Decreased morbidity may increase coital frequency	Increase fertility
4.2 Incidence of amenorrhea	Increase	[54-56]	Decrease fertility	[3,28,55]	Decrease	[60]	Improved health may reduce incidence of amenorrhea	Increase fertility
4.3 Natural fecundability (spermatogenesis)	Decrease	[57,58]	Decrease fertility	[3,28,57,58]	Increase	[28]	Improved health may increase spermatogenesis of male partner	Increase fertility
5. Use and effectiveness of contraception								
5.1 Switching contraceptive method from the pill to condoms	Increase	[28,34]	Increase fertility	[27,28]	Unknown			
5.2 Condom use among previous non-contraceptive users	Increase	[28,60, 61]	Decrease fertility	[27,28]	Unknown			

Table 2.4 (continued): Use of Bongaarts' Proximate Determinants of Fertility framework to describe the potential impact of antiretroviral (ARV) therapy on fertility in sub-Saharan Africa

Proximate Determinant of	Impact of	[Ref]	Possible Impact on	[Reference]	Impact of	[Ref]	Reason	Hypothesized Impact

Fertility (P.D.)	HIV on P.D.		Fertility		ARVs on P.D.			of ARVs on Fertility
5.3 Contraceptive use for child "insurance and replacement" desires	Reduce	[27]	Increase fertility	[27,28]	Further reduce	[66]	Better health may increase desire to insure and/or replace children	Increase fertility
5.4 Contraceptive use & abortion to avoid infant infection & orphanhood	Increase	[28,62-64]	Decrease fertility	[3,27,28]	Decrease	[27,28]	Less contraceptive use due to reduced fears of infant infection and orphanhood	Increase fertility
6. Spontaneous intra-uterine mortality								
6.1 Incidence of spontaneous abortion	Increase	[67]	Decrease fertility	[27,28]	Inconclusive	[20,68]	Mixed empirical findings	Inconclusive
6.2 Incidence of stillbirth	Increase	[67]	Decrease fertility	[27,28]	Inconclusive	[69]	Mixed empirical findings	Inconclusive
7. Induced abortion								
7.1 Incidence of induced abortion	Increase	[54,62,72]	Decrease fertility	[27,28]	Decrease	[25]	Reduced concerns about MTCT and therefore reduced incidence of induced abortion	Increase fertility

Notes: Ref = Reference

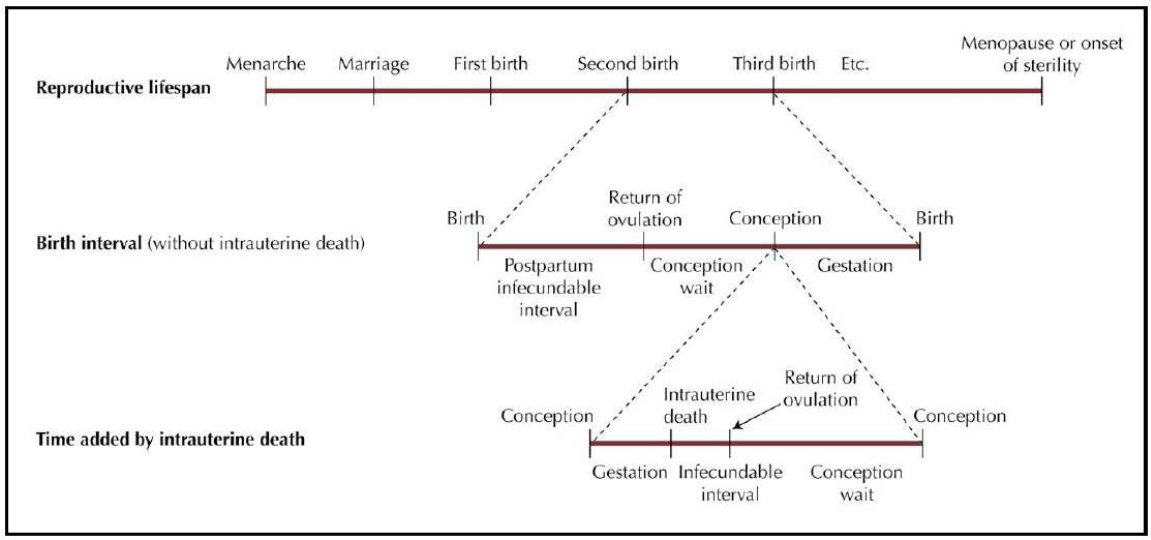

Figure 2.1 Bongaarts' proximate determinants of fertility framework over the reproductive lifespan ***(adapted with permission from Bongaarts and Potter [11])***

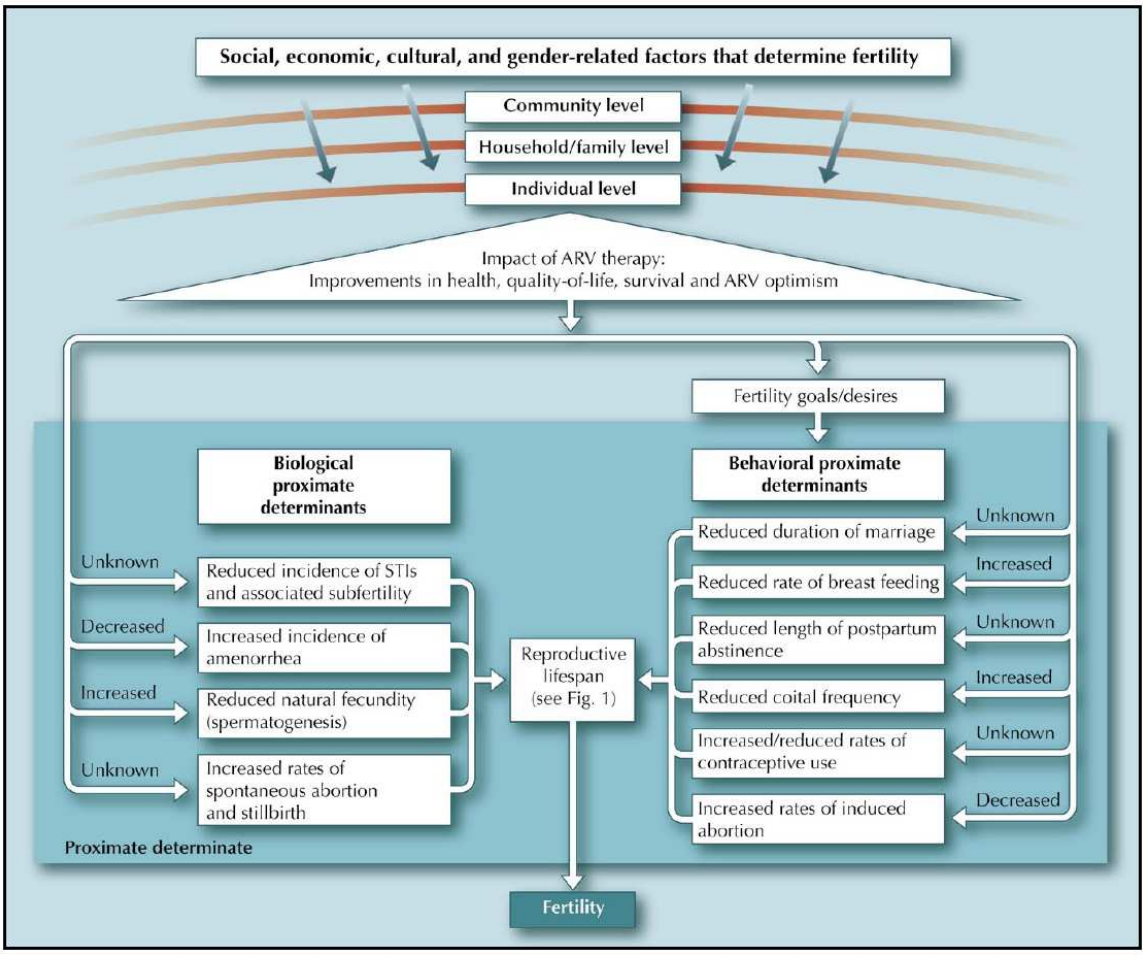

Figure 2.2 Conceptual framework for the potential impact of antiretroviral (ARV) therapy on fertility in sub-Saharan Africa.

Notes:

(i) The proximate determinates are oriented for the impact of HIV in the absence of ARV therapy
(ii) The arrows indicate the potential impact of ARV therapy.
(iii) STIs—sexually transmitted infections.

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CHAPTER 3[2]:

THE RELATIONSHIP BETWEEN HAART USE AND SEXUAL ACTIVITY AMONG HIV-POSITIVE WOMEN OF REPRODUCTIVE AGE IN BRAZIL, SOUTH AFRICA, AND UGANDA

3.1 INTRODUCTION

The vast majority of the world's 14 million HIV-infected women live in developing and transitional countries where sexual contact is the primary mode of HIV transmission [1]. A growing body of evidence from such countries reveals that antiretroviral therapy has dramatically improved the survival and quality of life for HIV-infected individuals [2, 3, 4, 5]. Recent global efforts to improve access to highly active antiretroviral therapy (HAART) and clinical care should serve to deliver these positive outcomes to more HIV-infected women in high prevalence and low-resource settings [6].

In addition to the anticipated clinical effects, HAART use may influence the sexual behaviour of HIV-infected women. Earlier research demonstrated that in the absence of treatment, HIV-infected women were less sexually active than HIV-

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negative women owing, in part, to higher morbidity [7, 8]. The health improvements associated with the use of HAART are anticipated to increase sexual activity due to improved health status [9] and perceptions of reduced infectivity [10], however, related empirical evidence is lacking.

Given the close relationship between sexual transmission of HIV and the incidence of pregnancy, information about the sexual behaviours of HIV-positive women on HAART constitute a critical component of comprehensive initiatives aimed at improving the quality of life of HIV-infected women, including sexual and reproductive decision-making.

The purpose of this study was to determine whether current HAART use is associated with recent sexual intercourse among HIV-infected women of reproductive age (18-49 years) from Brazil, South Africa, and Uganda. A secondary purpose was to estimate differences in protected sex and contraceptive use among sexually active HAART users and non-users.

3.2 METHODS

3.2.1 Study design

This analysis is based on data collected from a cross-sectional survey conducted in Brazil, South Africa, and Uganda. The primary outcome was recent sexual activity defined as vaginal intercourse in the previous month. The secondary outcomes were protected vaginal intercourse (defined as "always used a condom") and contraceptive use in the previous six months. The key explanatory variable was current HAART use.

The study was conceived as a pilot project to determine the feasibility of conducting more comprehensive sexual and reproductive health studies among a larger sample of HIV-positive women in Brazil, South Africa, and Uganda.

3.2.2 Study setting and sample population

A total of 179 HIV-positive women in patient care were randomly selected for participation through the Mbarara Hospital HIV Clinic in Mbarara, Uganda (n=85); the Perinatal HIV Research Unit in Soweto, South Africa (n=50); and the IPEC-Fiocruz cohort in Rio de Janeiro, Brazil (n=44) [11].

Eligible women had to have documented HIV status, be of reproductive age (defined as 18-49 years), and be seeking regular care at one of the three study centres.

3.2.3 Data collection

A consecutive sample of HIV-positive women accessing services at each study site was selected to participate. A study representative explained the study purpose, procedures, risks, and benefits as part of the informed consent process. Participation rates exceeded 90% in each of the study sites.

Upon identification and consent, study participants responded to an interviewer-administered questionnaire in either English or the local language. Measures included: socio-demographics; HIV/AIDS history, diagnosis, and treatment; self-reported health; sexual and contraceptive behaviour; fertility desires; and HAART optimism (a 13-item scale yielding a range of scores from 13-52, with higher scores indicating greater optimism) [12].

The interviewers at each study site were women from the local community. They were trained in survey research, including instruction on how to conduct an

interview and how to obtain informed consent. Data collection took place between March and June 2005.

3.2.4 Data analysis

We compared the prevalence of recent sexual intercourse across groups (i.e., sexually active non-HAART users vs. sexually active HAART users). Unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) were computed to determine the magnitude of the association between independent variables and recent sexual intercourse.

Multivariate logistic regression was used to model the association between HAART use and the likelihood of recent sexual intercourse, while controlling for covariates. All independent variables were tested for colinearity. It was suspected *a priori* that the variables 'marital Status' and 'HIV-infected partner/spouse' would be highly associated and this was empirically confirmed. Therefore, only 'marital status' was considered for entry into the multivariate model. To yield adjusted odds ratios (AOR) and 95% CIs, a stepwise procedure was used to enter HAART use and all variables significant in the univariate analysis into a logistic regression model [13]. The variables 'country' and 'age' were forced into the model to obtain adjusted estimates of effect.

Prevalence of Contraceptive Use and Protected Sexual Activity

Among women reporting recent sexual intercourse, we compared the proportion that report using condoms (i.e., "protected sex") and contraceptives between HAART users and non-users. Crude odds ratios and 95% CIs were computed to determine the magnitude of the association between HAART use and protected sex and contraceptive use. Given that this was a secondary objective of the analysis and owing to the small sample size, multivariate analysis was not conducted for these two outcome variables.

All statistical tests are two-sided and considered significant at $\alpha = 0.05$. Statistical analyses were done using SAS for Windows (version 9.1) [14].

3.2.5 Ethical considerations

Ethics approval for this study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand in Johannesburg, South Africa, the Faculty of Medicine Research and Ethics Committee and the Institutional Ethics Review Board of Mbarara University, and the local and national Institutional Review Boards (IRBs) in Brazil. Study investigators only had access to de-identified data.

3.3 RESULTS

Overall, 46% of the participants reported sexual intercourse in the previous month (83/179). By study site, 33% of women in Uganda, 55% of women in Brazil, and 62% of women in South Africa reported recent sexual intercourse.

3.3.1 Baseline characteristics

Distributions of baseline covariates are presented in Table 3.1. Nearly two-thirds (65%) of women reported currently using HAART (56% in Uganda, 64% in Brazil, and 80% in South Africa). The mean age of women was 34.5 years [SD=6.9]. Only 22% were employed full-time and the mean years of formal schooling was 7.2 [SD=4.0]. Thirty-four percent (34%) were currently married and nearly one-third (32%) reported knowing that their primary partner/spouse was HIV-infected. Sixty-eight percent (68%) reported having been diagnosed with AIDS, however, 66% reported their current health status as "Excellent, very good, or good", and the mean HAART optimism score was 30 [SD=6.7]. The majority of women did not want any (more) children (65%).

3.3.2 Univariate analyses

Women on HAART were just as likely as women not on HAART to report recent sexual intercourse (OR: 0.93; 95% CI: 0.50-1.71) (Table 3.2). Women who reported recent sexual intercourse were, however, more likely to have higher HAART optimism scores, have more education, be currently married, have an HIV-positive primary partner/spouse, desire more children, and not have been diagnosed with AIDS.

3.3.3 Adjusted analyses

After adjusting for potential confounders, there remained no association between HAART use and recent sexual activity (adjusted odds ratio (AOR): 0.76; 95% CI: 0.34, 1.72; see Table 3.2). Being currently married, desiring more children, and having a higher HAART optimism score remained most strongly associated with recent sexual intercourse.

3.3.4 Contraceptive use and protected sexual activity

Of the 83 women reporting recent sexual intercourse, 76% were using contraceptive methods and 63% were engaging in protected sex (i.e., using condoms). Women using HAART were significantly more likely to practice protected sex (crude OR: 3.64; 95% CI: 1.41-9.38) and non-significantly more likely to use contraceptive methods (crude OR: 2.15; 95% CI: 0.77-5.99) than non-users.

3.4 DISCUSSION

We found that, among HIV-infected women in Brazil, South Africa, and Uganda, HAART users and non-users were equally likely to report recent sexual intercourse. This finding is consistent with other reports of HIV-infected men and women in Uganda [15, 16] and Côte d'Ivoire [17].

In sub-analyses, we investigated the association between HAART use and recent sexual activity for each country. While the effect of socio-demographic covariates varied, none of the country-specific models showed a significant relationship between HAART use and recent sexual activity.

Recent sexual activity among HIV-positive women in our study appears to be most strongly influenced by factors unrelated to HAART use, including being

currently married and wanting more children. This finding was expected based on the literature on predictors of sexual activity and coital frequency among women in general [18, 19]. Interestingly, HAART optimism was also associated with recent sexual activity suggesting that being optimistic about the benefits of HAART is a better predictor of recent sexual intercourse than HAART use itself. It is difficult to compare these findings since the vast majority of literature on the impact of HAART optimism comes from MSM populations in resource-rich areas [20, 21].

Of note, while HAART use wasn't associated with recent sexual intercourse overall, it was positively associated with other sexual behaviours, including protected sex and contraceptive use. Recently, others have similarly reported that HAART users in developing countries are more likely to practice protected sex [15, 16, 17], however, there is limited comparative literature on the impact of HAART on contraceptive use.

The relatively small sample size and the diversity of the countries involved may constitute important limitations to this study. These features of the study design are a consequence of conducting a pilot study. Presently, however, larger, separate studies are being conducted in each of the three study settings to further verify the results presented here.

In conclusion, this study supports an absence of association between HAART use and recent sexual intercourse. Sexually active HAART users may, however, be more likely to practice protected sex and use contraceptives. This information is important for the development of comprehensive sexual and reproductive health services for HIV-infected women.

Table 3.1: Baseline characteristics of study population: HIV-infected women of reproductive age in Brazil, South Africa, and Uganda (n=179)

Characteristic	Frequency (n)	Percent (%)
Country		
South Africa	50	28%
Uganda	85	48%
Brazil	44	25%
Socio-demographic variables		
Mean Age [SD]	34.5 [6.9]	
Mean Years of Schooling [SD]	7.2 [4.0]	
Employed Fulltime		
Yes	39	22%
No	139	78%
Marital Status		
Currently married	61	34%
Not currently married	118	66%
Fertility desire & Health Status variables		
Want more children?		
Yes	62	35%
No	117	65%
Self-reported health status		
Excellent, Very good, or Good	116	66%
Fair or Poor	61	35%
HIV-related variables		
HIV-infected primary partner/spouse		
Yes	57	32%
No or unknown	122	68%
AIDS diagnosis		
Yes	122	68%
No or unknown	57	32%
Current HAART Use		
Yes	116	65%
No	63	35%
Mean HAART optimism score [SD]	30 [6.7]	

Table 3.2: Unadjusted and adjusted Odds Ratios and 95% Confidence Intervals (95% CI) of variables associated with recent sexual intercourse (in the previous month) among HIV-infected women in Brazil, South Africa, and Uganda (n=179)

Characteristic	Sexual intercourse in the past month		Unadjusted OR [95% CI]	Adjusted OR* [95% CI]
	Yes (n=83) %	No (n=96) %		
Country				
Brazil	29%	21%	Reference	--
Uganda	37%	20%	1.36 [0.60-3.10]	
South Africa	34%	59%	**0.41 [0.19-0.86]**	
Age (Mean [SD])	33.8 [6.4]	35.1 [7.2]	0.97 [0.93-1.02]	--
Years of Schooling (Mean [SD])	8.2 [3.5]	6.4 [4.3]	**1.12 [1.04-1.21]**	--
Employed Fulltime			1.70 [0.83-3.49]	--
Yes	27%	18%		
No	73%	82%		
Currently Married			**3.71 [1.93-7.14]**	**6.68 [2.79-16.0]**
Yes	49%	21%		
No	51%	79%		
Desires more children?			**3.89 [2.02-7.49]**	**4.09 [1.71-9.81]**
Yes	51%	21%		
No	49%	79%		
Self-reported health status			1.49 [0.80-2.80]	--
Excellent, very good, or good	70%	61%		
Fair or Poor	30%	39%		
HIV-infected spouse/partner			**4.32 [2.19-8.52]**	--
Yes	48%	18%		
No or Unknown	52%	82%		
AIDS diagnosis			**0.37 [0.19-0.70]**	**--**
Yes	57%	78%		
No or Unknown	43%	22%		
HAART Use			0.93 [0.50-1.71]	0.76 [0.34-1.72]
Yes	64%	66%		
No	36%	34%		
HAART optimism score (Mean [SD])	31.3 [6.1]	27.8 [6.8]	**1.09 [1.03-1.14]**	**1.11 [1.04-1.17]**

Notes: * Adjusted odds ratios obtained from a stepwise procedure to choose a logistic regression model with forced entry of the variables 'Age' and 'Country'.

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CHAPTER 4[3]:

FERTILITY INTENTIONS OF HIV-POSITIVE WOMEN OF REPRODUCTIVE AGE IN SOWETO, SOUTH AFRICA: THE INFLUENCE OF EXPANDING ACCESS TO HAART IN AN HIV HYPER-ENDEMIC SETTING

4.1 INTRODUCTION

In sub-Saharan Africa (SSA), women of childbearing age comprise 61% of people living with HIV, accounting for over 12 million women [1]. In many regions, HIV incidence is increasing most dramatically among young women aged 18-30 years [1, 2], which coincides with their peak reproductive years [3]. Globally, a plethora of evidence indicates that many women living with HIV continue to desire children [4-8], become pregnant [5, 6, 9], and give birth [5, 6, 10] after knowing their HIV-positive status.

Irrespective of HIV seropositivity, fertility decision-making can be complex [11]; however, reproduction among HIV-infected women introduces additional

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personal, public health, and clinical care issues [12]. The vast majority of conceptions occur without the use of reproductive technologies such as sperm washing and artificial insemination [13]. Thus, the unprotected sexual activity required for conception carries a risk of HIV transmission to uninfected sexual partners [14]. Reproduction among HIV-positive women also carries a risk of vertical transmission during pregnancy, labour, and through breastfeeding [15, 16]. Moreover, HIV-positive women have a lower life expectancy than negative women [17], increasing the risk of maternal orphanhood [18]. In light of these concerns, early reproductive guidelines for people living with HIV were dissuasive [19] and HIV-positive women who express fertility desires continue to encounter community and healthcare worker disapproval [4, 20].

Nonetheless, while the potential health risks may have dampened the fertility intentions of some HIV-positive women, stigma associated with childlessness in many societies [21] and the strong personal desires for biological parenthood [4] remain potent drivers of fertility intentions, despite an HIV-positive status. Indeed, in some cultural contexts, remaining childless can be a societal norm violation more stigmatizing than the HIV infection itself [4, 22].

Expanding access to highly active antiretroviral therapy (HAART) is changing the landscape of fertility decision-making for people living with HIV [23].

HAART increases life expectancy [24-26], decreases morbidity [25, 27], and dramatically reduces the risks of vertical [28] and horizontal transmission [29, 30]. In this era of expanding HAART access, the significant reductions in health risks and barriers to reproduction among people living with HIV has corresponded with increased calls for a rights- and evidenced-based approach to reproduction [31, 32]. Since fertility intentions are the strongest predictor of eventual fertility [33], creating effective and responsive sexual and reproductive health services for HIV-positive women in the context of expanding HAART access requires a clear understanding of expressed fertility intentions.

Existing evidence concerning the influence of expanding HAART access on fertility intentions is largely incomplete. While recent regional studies have shown that HAART use is associated with higher fertility intentions, these studies have neglected to consider the duration of HAART use [6, 8] and tended only to compare fertility intentions of positive women, without conducting a comparison with HIV-negative women from the same community [6-8]. Moreover, the lack of an HIV-negative comparison group precludes the opportunity to assess whether HAART users begin to resemble HIV-negative women in their fertility intentions, particularly as HIV is increasingly recognized as a manageable chronic disease.

Given the high HIV prevalence among women of reproductive age in Soweto, South Africa [1], the objective of this study was to assess the prevalence of fertility intentions and to determine whether fertility intentions varied according to HIV status and HAART use among women. We hypothesized that HIV-positive women would have lower fertility intentions compared with HIV-negative women. In addition, we hypothesized that HIV-positive women receiving HAART would have higher fertility intentions than HIV-positive women who were HAART-naive, with increasing duration of HAART treatment associated with incrementally higher fertility intentions. Overall, we hypothesized that HAART use would narrow the measurable differences in fertility intentions between HIV-positive and HIV-negative women [23].

4.2 METHODS

4.2.1 Study design

This analysis is based on cross-sectional survey data of HIV-positive (HAART receiving and HAART-naïve) and HIV-negative women seeking services at the Perinatal HIV Research Unit (PHRU) in Soweto, South Africa. A medical chart

review was also conducted to confirm HIV serology and HAART use history of HIV-positive women.

4.2.2 Study setting

The PHRU, one of Africa's largest HIV research and clinical service centres, is housed within the Chris Hani Baragwanath Hospital in Soweto, an urban South African township located 15km outside of Johannesburg. The PHRU clinic sees over 5,000 patient visits monthly and provides free antiretroviral therapy and clinical care to medically eligible HIV-positive individuals and on-going wellness care for those not medically eligible for antiretroviral treatment. The PHRU also operates a Prevention Studies area that includes a Voluntary Counseling and Testing (VCT) centre.

4.2.3 Eligibility criteria

To be eligible to participate in the study, women were required to be 18-49 years of age, attending a PHRU clinic, residing in Soweto, competent to give informed consent, and willing to allow medical record review for the purposes of confirming HIV status and HAART history. We considered women to be HAART

users if they had been taking HAART medications for at least one month. We considered women to be non-HAART users if they had never taken HAART, except for vertical transmission prophylaxis.

4.2.4 Study sample

We enrolled 751 women into the study, including 253 HIV-positive women receiving HAART, 249 HIV-positive but HAART-naïve women, and 249 HIV-negative women. This sampling strategy provided one case group (HAART users) and two comparison groups (HAART-naïve and HIV-negative women).

HAART users were sampled from the PHRU's PEPFAR Clinic which has provided free antiretroviral therapy to medically eligible patients since July 2004. Currently, the PEPFAR clinic has over 1,000 patients receiving HAART, 75% of whom are female. PEPFAR patients are followed-up every three months and generally receive one of two standard HAART regimens: Regimen 1 is d4T/3TC/EFV or NVP and Regimen 2 is Kaletra/ddI/AZT [34].

HIV-positive, HAART-naïve women were sampled from the PHRU's Wellness Clinic, initiated in January 2003 with the goal of providing preventive care to HIV-positive individuals. Wellness patients are followed-up approximately every

six months. When patients are medically eligible for HAART, they are referred to the PEPFAR clinic or to one of the nearby government ART clinics. There are approximately 3,000 active patients in the Wellness Clinic.

HIV-negative women were sampled from the VCT clinic, which was initiated in mid-2002 and sees approximately 400 people per month. Testing is conducted onsite during visits that last an average of two hours. Approximately 65% of attendees are women and approximately 30% of all attendees are HIV-positive.

For this analysis on fertility intentions, we restricted the study sample to women aged 18-44 years of age who were not sterilized (i.e., did not report hysterectomy or female sterilization). This yielded an analytic sample of 674 women including 217 HAART users, 215 HAART-naïve women, and 242 HIV-negative women.

4.2.5 Data collection

Every female patient attending the PEPFAR Clinic and the VCT clinic was consecutively approached by a research assistant to assess eligibility and interest in participating in the study. Since many more women attend the Wellness Clinic, a list was made of chart numbers of women attending the clinic each day. A random sample of chart numbers (40% of the total number of charts present) was then drawn

and the corresponding women were approached to assess eligibility and interest in participating in the study.

After confirming eligibility and seeking informed consent, all participants were asked to complete a 15-25 minute interviewer-administered questionnaire in English. The study interviewers were multilingual and trained to ensure accurate and consistent translation of the questionnaire if required or requested by the participant. Pilot testing of 45 women revealed that women were able to understand and answer the questionnaire.

Approximately 12 women were interviewed daily by three trained research assistants between May and December, 2007. Participants were reimbursed 20 Rand for their transportation costs to and from the PHRU (~ $3.00 USD). Research assistants were women from the local community who had previous research experience and were recent Social Sciences' graduates of a local university.

4.2.6 Data collection instruments

The questionnaire assessed socio-demographic characteristics (e.g., age, education, employment status, marital status, parity); HIV serostatus and date of HIV-positive diagnosis; clinical stage of disease (CD4 cell count and viral load); HAART history; fertility intentions; fertility history (number and timing of

pregnancies, abortions, stillbirths, miscarriages, and live births); contraceptive practices; and sexual history.

For all HIV-positive women, medical records were reviewed to confirm HIV status, HAART history, and to obtain clinical data including WHO stage of disease [35] and CD4 cell count. Viral load assessments were only conducted on women from the PEPFAR clinic (i.e., HAART users). The medical record was considered the referent measure for inconsistencies between self-reported and medical record data.

4.2.7 Measures

The primary outcome was self-reported fertility intentions, which was defined by answers to the question: "Are you planning to have (any more) children in the future?". Women were free to respond "Yes", "No", or "Don't know". Given recent findings suggesting that the undecided tend to more closely resemble the expressed fertility intentions of the majority of those with stated desires [36], the small proportion of women who responded "Don't Know" (5%) were included in the "No" category. There was little difference in the proportion of women reporting "Don't know" by HIV and HAART use status.

The primary explanatory variable was current HAART use. The secondary explanatory variable was HIV status. Variables known to be associated with fertility intentions were included in the analysis to provide an adjusted estimate of the association. Covariates included age, education, employment, monthly household income, current sexual partnership status, number of living children, and HIV clinical variables including most recent CD4, nadir CD4, and WHO Stage of Disease.

4.2.8 Statistical analysis

We computed the prevalence of fertility intentions among each of the three groups of women in our study. We conducted two separate models to measure the presence and strength of the association between HAART use and the likelihood of reporting fertility intentions, while controlling for covariates. The first model compared HAART users and non-HAART users to HIV-negative women. The second model compared HAART users to non-HAART users and allowed adjustment for HIV-associated clinical characteristics.

In both models, univariate analyses were used to assess the relationship between fertility intentions and HAART use and covariates. Differences in fertility intentions between groups are reported using Pearson's chi-squared test (for categorical covariates), ANOVA, or Student's independent t-test (for continuous

variables). The association between fertility intentions and HAART use is reported using a crude odds ratio with a 95% confidence interval (95% CI). After testing for co-linearity (using Spearman's rho (ρ)) [37] and interaction [38], all covariates with significant associations ($p<0.10$) in the univariate analysis were included in the final multivariate logistic regression model to obtain adjusted odds ratios and 95% confidence intervals. All statistical tests were two-sided and were considered significant at $\alpha = 0.05$. The data were analyzed using SAS version 9.1 [39].

4.2.9 Sub-analyses

We conducted the same analyses described above but restricted our sample to women aged 18-30 years, the peak childbearing years among women in South Africa [3].

4.3 RESULTS

4.3.1 Study sample

A total of 801 women were approached for participation, of whom 751 consented, completed the questionnaire and underwent a medical record review

(response rate = 94%). The analysis of fertility intentions was restricted to women aged 18-44 years who were not sterilized, yielding a study sample of 674 women.

4.3.2 Baseline characteristics

There were important differences in baseline covariates by HIV and HAART use status (Table 4.1). Mean age was 30 years [SD=6.7], with HIV-negative women being significantly younger than HIV-positive women. Overall, 51% of women had less than a grade 12 education, 61% were unemployed, and 71% had a monthly household income less than 3,000 ZAR ($ 350 USD). A small proportion of women were married (8%) but the vast majority were currently in a sexual relationship (78%), with a mean of 0.90 [SD=0.68] sexual partners in the previous six months. One quarter reported that their primary sexual partner was HIV-positive, one-third reported that he was HIV-negative, and the remaining 42% did not know the HIV status of their sexual partners. The mean number of lifetime sexual partners was 5.3 [SD=5.6]. Overall, mean parity was 1.4 [SD=1.1]. Of women with at least one livebirth, 14% had lost a child. Overall, 41% of women had two or more living children.

Among HIV-positive women, mean time since HIV diagnosis was 59 months [SD=36]; 58% of HAART users had recent CD4 counts ≥ 350 cells/uL compared with

45% of HAART-naïve women. Overall, 15% had nadir CD4 counts < 50 cells/uL. Nearly all were in WHO Stage of Disease I or II (97%) and 94% had disclosed their HIV status to someone.

Among HAART users, median duration of HAART use of 31 months [IQR: 28, 33], ranging from 1 month to 89 months. Most (81%) had undetectable viral loads (< 50 copies/ml).

4.3.3 Prevalence of fertility intentions

Overall, 44% of women reported that they intended to have (more) children. This varied significantly by HIV status with 31% of HAART users, 29% of HAART-naïve women, and 68% of HIV-negative women reporting fertility intentions ($p<0.0001$).

4.3.4 Factors associated with fertility intentions in the overall sample

In the unadjusted analyses, many of the measured covariates were significantly associated with fertility intentions (Table 4.2). Compared with HIV-negative women, HIV-positive women were significantly less likely to report

fertility intentions (HAART users OR: 0.21; 95% CI: 0.14, 0.32; HAART-naïve women OR: 0.20; 95% CI: 0.13, 0.29).

After adjusting for covariates shown in Table 4.1, HIV status remained significantly associated with fertility intentions. Compared with HIV-negative women, HIV-positive women were significantly less likely to report fertility intentions (HAART users AOR: 0.40; 95% CI: 0.23, 0.69; HAART-naive women AOR: 0.35; 95% CI: 0.21, 0.60). Currently being in a sexual relationship and having fewer living children also remained independently associated with fertility intentions.

4.3.5 Factors associated with fertility intentions among HIV-positive women

As seen in Table 4.3, in an analysis restricted to HIV-positive women, HAART users and non-users were equally likely to report fertility intentions (OR: 1.08; 95% CI: 0.71, 1.63). There were no significant differences in fertility intentions by any of the measured clinical characteristics including duration of HIV diagnosis, recent CD4, nadir CD4, WHO Stage of Disease, or disclosure.

After adjusting for covariates shown in Table 4.1, HAART users and non-users remained equally likely to report fertility intentions (AOR: 1.16; 95% CI: 0.72,

1.86). Currently being in a sexual relationship and having fewer living children remained independently associated with fertility intentions.

As shown in Figure 4.1, there was no association between length of time on HAART and reported fertility intentions.

4.3.6 Sub-analyses

Although fertility intentions among young women (18-30 years) are higher than among the total sample, they still varied significantly by HIV status: 38% of HAART users, 34% of HAART-naïve women, and 75% of HIV-negative women aged 18-30 years expressed fertility intentions ($p<0.0001$). In multivariate analyses we found that the same variables that were associated with fertility intentions in the overall sample were similarly associated with fertility intentions among young women in both direction and magnitude (data not shown). This was the case for both models (i.e., all women and only HIV-positive women).

4.4 DISCUSSION

In contrast with our primary hypothesis, we found that fertility intentions of HIV-positive women did not differ by use or duration of HAART. Consistent with our secondary hypothesis, however, HIV-positive women were significantly less likely to report fertility intentions compared with HIV-negative women.

Our findings of nearly one-third of HIV-positive women reporting fertility intentions largely irrespective of HAART use, contrast with findings from other sub-Saharan African sites, which report threefold higher fertility intentions among HAART users [6] and higher fertility intentions associated with increasing duration of HAART use [7]. A recent American study showed that HAART use was associated with a lower prevalence of fertility desires [40]. Our findings are, however, consistent with those of a Canadian study which reported no association between HAART use and fertility intentions [41].

Potential reasons for our findings may relate to the nature of HAART and HIV care services at the PHRU. Namely, HAART has been available at the PHRU since July 2004, nearly three years longer than at government clinics in South Africa [42] and at least two years longer than most sub-Saharan African settings [43]. The lack of association between HAART use and fertility intentions in our study may reflect the fact that HIV-positive women who are not yet receiving HAART can be

confident that treatment is available once they are medically eligible, thereby minimizing differences between groups. Moreover, HAART-naïve women were sampled from the Wellness clinic, which provides regular clinical care to HIV-positive women. Thus, any influence that regular contact with health care providers has on fertility decision-making is likely to be similar in both groups. In this way, the PHRU setting may be more comparable to Canadian study findings [41], where HAART has been available at no charge to medically eligible HIV-infected individuals since 1996 [26, 41]. Consistent with other studies of HIV-positive and negative women around the world, number of living children and current partnership status were also strongly associated with fertility intentions.

While HAART use did not affect fertility intentions among HIV-positive women, we did find that HIV-positive women were 60% less likely to report an intention to have (more) children compared with HIV-negative women. It is difficult to compare these findings to other settings since we could identify no studies that directly measured differences in fertility intentions between HIV-negative and positive women. Moreover, while the expressed fertility intentions of HIV-positive women were lower than for HIV-negative women, they remain substantial. In our study, nearly one-third of HIV-positive women reported fertility intentions, a proportion that increased significantly by younger age and fewer living children.

Our findings are at the upper range of fertility intentions for HIV-positive women reported from other settings [6-8, 41, 44].

All women, including women living with HIV, should be supported to achieve their reproductive goals in the healthiest and safest possible manner [32]. Given the noted prevalence of fertility intentions among HIV-positive women, it is critical that factual and non-stigmatizing information and support be incorporated into HIV treatment services to optimize positive outcomes for mother, father, and baby. This includes counseling services regarding HAART and pregnancy [45], safer options to conceive (including HAART as prevention [46]), safer labour options, PMTCT services, antenatal and postnatal care, and infant feeding options. Currently, no clear guidelines are available regarding the ideal time for pregnancy for an HIV-positive woman (with respect to CD4 level, stage of treatment, treatment regimen, viral load, or HIV and health status of her partner) and this information is urgently needed.

Although 30% of HIV-positive women reported intentions to have (more) children in our study, 70% did not. Thus, it is critical to ensure that effective, non-judgmental family planning services (including access to termination of pregnancy services) are available to all women who need them. This is of particular importance since evidence has shown that despite lower fertility intentions, infected women

may be similarly likely to become pregnant [47-49] and terminate a pregnancy [48] as uninfected women. More work must be done on the provision of contraceptive options to close the gap between reported fertility intentions and fertility.

It must be highlighted that the fertility intentions of HIV-negative women in this HIV hyper-endemic setting were very high (68%). In South Africa overall, the prevalence of HIV infection is highest among young women, which corresponds with the peak reproductive years [3]. Conception requires unprotected sexual activity and the HIV status of the sexual partners for many of these women is unknown. Indeed, only 20% of the general adult population of South Africa knows their HIV status [50, 51]. As such, reproduction for HIV-negative women in Soweto must be considered an important risk for HIV acquisition.

The limitations of this study must be acknowledged. First, the cross-sectional nature of this analysis precludes us from determining causality between the explanatory variable and the outcome, even though fertility intentions were assessed as a future event while HIV and HAART use status were assessed in the present. Although reverse causality is considered unlikely, longitudinal studies are needed to investigate a potentially time-sensitive relationship between HIV status, HAART use, and fertility intentions. Second, there is a risk of social desirability bias whereby HIV-positive women may under-report their fertility intentions because of

disapproving views expressed by community health workers and community members [4, 20] . If under-reporting was differential, then our effect estimates are likely somewhat inflated. We took precautions against reporting bias by using standardized questions of fertility intentions and employing non-clinic staff to conduct the interviews. Third, recent literature has described the limitations of using dichotomized measures of "fertility intentions". Moreover, others have emphasized the dynamic nature of fertility intentions, which we were unable to fully capture in this study [4, 52, 53]. Fourth, there were important baseline differences between the HIV-positive and HIV-negative women in our study, which cannot be fully adjusted for in the analyses. In particular, HIV-positive women in our study were significantly older than HIV-negative women and age is both a known and important predictor of fertility intentions and is associated with a number of other covariates (e.g., parity, education status). In an attempt to address this difference in age, we conducted a sub-analysis of fertility intentions restricted to women less than 30 years of age. We found no differences in the variables that predicted fertility intentions nor the magnitude of the associations. The results of the sub-analysis suggest that our overall findings are robust, despite differences in age at baseline. Finally, a quantitative analysis such as this fails to capture the salient influence of cultural dynamics on fertility decision-making. Cultural beliefs and practices have often and consistently been discussed as critical determinants of

fertility intentions [54, 55]. HIV status and HAART use alone are unlikely to be the sole or even primary drivers of reproductive decision-making [23]. Indeed, qualitative studies have highlighted that the desire for motherhood, opinions of partners and health care providers, religious values, and the perceived capacity to successfully parent emerge as critical factors influencing fertility decision-making of HIV-positive women [4, 52].

4.5 CONCLUSION

Our findings suggest important associations between fertility intentions and HIV status, largely irrespective of HAART use. The fertility intention profile of HIV-positive women in Soweto demands that integrated HAART, HIV care, and reproductive health services be made available to support the rights of HIV-positive women to safely achieve their fertility goals, while minimizing risks of vertical and horizontal transmission. The substantial fertility intentions of HIV-negative women in this HIV hyper-endemic region are of great importance and demand consideration of targeted reproductive health services to minimize their risks of HIV acquisition through realization of their reproductive goals.

Table 4.1: Baseline characteristics of HAART users, non-HAART users, and HIV-negative women (aged 18-44 years and non-sterilized) in Soweto, South Africa (n=674)

Variable	HAART users (n=217) n (%)	Non-HAART users (n=215) n (%)	HIV-negative (n=242) n (%)	Overall (n=674) n (%)	p-value¥
Socio-demographic Characteristics					
Mean Age (yrs) [SD]	33.5 [5.0]	32.0 [5.7]	25.0 [6.0]	30.0 [6.7]	<0.0001
Age Group (yrs)					<0.0001
18-24	6 (3%)	22 (10%)	138 (57%)	166 (25%)	
25-29	38 (18%)	47 (22%)	47 (19%)	132 (20%)	
30-34	83 (38%)	75 (35%)	41 (17%)	199 (30%)	
35-39	59 (27%)	45 (21%)	7 (3%)	111 (17%)	
40-44	30 (14%)	25 (12%)	9 (4%)	64 (10%)	
Education					<0.0001
Less than Grade 12	138 (64%)	128 (60%)	75 (31%)	341 (51%)	
Grade 12 or higher	78 (36%)	87 (40%)	167 (69%)	332 (49%)	
Employment Status					0.0718
Employed	89 (41%)	91 (43%)	80 (33%)	260 (39%)	
Unemployed	127 (59%)	122 (57%)	162 (67%)	411 (61%)	
Household income (per month)					<0.0001
Less than 3000 ZAR	182 (84%)	169 (79%)	125 (52%)	476 (71%)	
3,000 or more ZAR	21 (10%)	35 (16%)	75 (31%)	131 (19%)	
Don't know/Refused	14 (6%)	11 (5%)	42 (17%)	67 (10%)	
Currently in a sexual relationship					0.0004
No	62 (29%)	51 (24%)	33 (14%)	146 (22%)	
Yes	155 (71%)	164 (76%)	209 (86%)	528 (78%)	
Mean # of sexual partners in the previous 6 months [SD]	0.77 [0.48]	0.82 [0.53]	1.09 [0.88]	0.90 [0.68]	<0.0001

Table 4.1 (continued): Baseline characteristics of HAART users, non-HAART users, and HIV-negative women (aged 18-44 years and non-sterilized) in Soweto, South Africa (n=674)

Variable	HAART users (n=217) n (%)	Non-HAART users (n=215) n (%)	HIV-negative (n=242) n (%)	Overall (n=674) n (%)	p-value¥
HIV status of regular sexual partner/husband*					<0.0001
Don't Know	57 (38%)	72 (49%)	78 (41%)	207 (42%)	
HIV-negative	28 (19%)	24 (16%)	109 (58%)	161 (33%)	
HIV-positive	66 (44%)	52 (35%)	2 (1%)	120 (25%)	
Mean parity [SD]	1.8 [1.1]	1.8 [1.1]	0.80 [0.9]	1.4 [1.1]	<0.0001
Ever lost a child**					<0.0001
No	152 (78%)	168 (87%)	132 (99%)	452 (86%)	
Yes	44 (22%)	25 (13%)	2 (1%)	71 (14%)	
Number of living children					<0.0001
0	29 (13%)	24 (11%)	109 (45%)	162 (24%)	
1	80 (37%)	77 (36%)	82 (34%)	239 (35%)	
2 or more	108 (50%)	114 (53%)	51 (21%)	273 (41%)	
HIV history and clinical characteristics					
Mean # of months since HIV diagnosis [SD]	67.6 [35.8]	49.8 [33.1]	N/A	58.7 [35.6]	<0.0001
Recent CD4 count					0.0088
< 200	37 (17%)	39 (18%)	N/A	76 (18%)	
200 to < 350	52 (24%)	79 (37%)		131 (31%)	
350 or greater	124 (58%)	95 (45%)		219 (51%)	
Nadir CD4 count					<0.0001
< 50	62 (29%)	3 (1%)	N/A	65 (15%)	
50 to < 200	139 (65%)	44 (21%)		183 (43%)	
200 to < 350	5 (2%)	83 (39%)		88 (21%)	
350 or greater	7 (3%)	83 (39%)		90 (21%)	

Table 4.1 (continued): Baseline characteristics of HAART users, non-HAART users, and HIV-negative women (aged 18-44 years and non-sterilized) in Soweto, South Africa (n=674)

Variable	HAART users (n=217) n (%)	Non-HAART users (n=215) n (%)	HIV-negative (n=242) n (%)	Overall (n=674) n (%)	p-value¥
WHO Stage of Disease					0.5868
Stage I/II	207 (97%)	205 (96%)	N/A	412 (97%)	
Stage III/IV	6 (3%)	8 (4%)		14 (3%)	
Disclosed HIV status to					0.0032
anybody	5 (2%)	19 (9%)	N/A	24 (6%)	
No	211 (98%)	196 (91%)		407 (94%)	
Yes					

Notes:
¥ Differences between groups are reported using Pearson's chi-squared test statistic (for categorical variables) and Student's independent t-test or ANOVA (for continuous variables).
* Restricted to those who reported having a regular sexual partner/husband and who responded to the question about partner's status (n=488)
** Restricted to those who reported having had a livebirth (n=523)
SD = Standard Deviation

Table 4.2: Univariate and Adjusted analyses of variables associated with fertility intentions among non-sterilized women aged 18-44 years in Soweto, South Africa (n=674)

Variable	Fertility intentions		Crude OR		Adjusted OR	
	No (%) (n=380)	Yes (%) (n=294)	OR	95% CI	AOR	95% CI
HIV & HAART Use						
HIV-negative	78 (21%)	164 (56%)	Ref.	Ref.	**Ref.**	**Ref.**
HIV-positive, HAART-naive	152 (40%)	63 (21%)	0.20	0.13, 0.29	**0.35**	**0.21, 0.60**
HIV-positive, receiving HAART	150 (39%)	67 (23%)	0.21	0.14, 0.32	**0.40**	**0.23, 0.69**
Age Group (yrs)						
18-24	52 (14%)	114 (39%)	Ref.	Ref.	Ref.	Ref.
25-29	68 (18%)	64 (22%)	0.43	0.27, 0.69	1.88	1.00, 3.52
30-34	124 (33%)	75 (26%)	0.28	0.18, 0.43	1.44	0.78, 2.64
35-39	83 (22%)	28 (10%)	0.15	0.09, 0.26	1.29	0.62, 2.71
40-44	52 (14%)	12 (4%)	0.11	0.05, 0.21	0.84	0.34, 2.06
Education						
Less than Grade 12	222 (59%)	119 (40%)	Ref.	Ref.	Ref.	Ref.
Grade 12 or higher	157 (41%)	175 (60%)	2.08	1.53, 2.84	0.92	0.61, 1.39
Employment Status						
Unemployed	230 (61%)	181 (62%)	Ref.	Ref.	**--**	**--**
Employed	147 (39%)	113 (38%)	0.98	0.71, 1.34		
Household income (per month)						
Less than 3000 ZAR	305 (80%)	171 (58%)	Ref.	Ref.	Ref.	Ref.
3,000 or more ZAR	50 (13%)	81 (28%)	2.89	1.94, 4.31	1.40	0.84, 2.33
DK/Refused	25 (7%)	42 (14%)	3.00	1.77, 5.09	1.73	0.90, 3.33

Table 4.2 (continued): Univariate and Adjusted analyses of variables associated with fertility intentions among non-sterilized women aged 18-44 years in Soweto, South Africa (n=674)

Variable	Fertility intentions		Crude OR		Adjusted OR	
	No (%) (n=380)	Yes (%) (n=294)	OR	95% CI	AOR	95% CI
Currently in a sexual relationship						
No	111 (29%)	35 (12%)	Ref.	Ref.	**Ref.**	**Ref.**
Yes	269 (71%)	259 (88%)	3.05	2.01, 4.63	**3.07**	**1.86, 5.05**
Number of living children						
0	33 (9%)	129 (44%)	Ref.	Ref.	**Ref.**	**Ref.**
1	117 (31%)	122 (42%)	0.27	0.17, 0.42	**0.30**	**0.18, 0.50**
2+	230 (61%)	43 (15%)	0.05	0.03, 0.08	**0.06**	**0.03, 0.11**

Notes:
'Ref.' refers to the 'Reference category'.

Table 4.3: Univariate and adjusted analyses of variables associated with fertility intentions among non-sterilized HIV-positive women aged 18-44 years in Soweto, South Africa (n=432)

Variable	Fertility Intentions		Crude OR		Adjusted OR	
	No	Yes	OR	95% CI	OR	95% CI
HAART Use						
HAART-naive	152 (50%)	63 (48%)	Ref.	Ref.	Ref.	Ref.
Receiving HAART	150 (50%)	67 (52%)	1.08	0.71, 1.63	1.16	0.72, 1.86
Age (per increase in year)	33.2 [5.6]	31.7 [4.9]	0.95	0.91, 0.99	0.99	0.94, 1.04
Education						
Less than Grade 12	110 (37%)	55 (42%)	Ref.	Ref.	--	--
Grade 12 or higher	191 (63%)	75 (58%)	1.27	0.84, 1.94		
Employment Status						
Unemployed	179 (60%)	70 (54%)	Ref.	Ref.	--	--
Employed	120 (40%)	60 (46%)	1.28	0.84, 1.94		
Household income (per month)						
< than 3000 ZAR	256 (85%)	95 (73%)	Ref.	Ref.	Ref.	Ref.
≥ 3,000 or more	32 (11%)	24 (18%)	2.02	1.13, 3.61	1.64	0.85, 3.17
Don't Know	14 (5%)	11 (8%)	2.13	0.93, 4.83	1.90	0.75, 4.80
Currently in a sexual relationship						
No	94 (31%)	19 (15%)	Ref.	Ref.	**Ref.**	**Ref.**
Yes	208 (69%)	111 (85%)	2.64	1.53, 4.55	**2.98**	**1.63, 5.46**
Number of living children						
0	19 (6%)	34 (26%)	Ref.	Ref.	**Ref.**	**Ref.**
1	92 (30%)	65 (50%)	0.40	0.21, 0.75	**0.36**	**0.18, 0.71**
2+	191 (63%)	31 (24%)	0.09	0.05, 0.18	**0.09**	**0.04, 0.17**
Mean # of months since HIV dx [SD]	58.2 [35.2]	59.9 [36.3]	1.00	1.00, 1.01	--	**--**

Table 4.3 (continued): Univariate and adjusted analyses of variables associated with fertility intentions among non-sterilized HIV-positive women aged 18-44 years in Soweto, South Africa (n=432)

Variable	Fertility Intentions		Crude OR		Adjusted OR	
	No	Yes	OR	95% CI	OR	95% CI
Recent CD4						
< 200	55 (19%)	21 (16%)	Ref.	Ref.	--	--
200 to < 350	89 (30%)	42 (33%)	1.25	0.66, 2.30		
350 or greater	153 (52%)	66 (51%)	1.13	0.63, 2.02		
Nadir CD4						
< 50	45 (15%)	20 (16%)	Ref.	Ref.	--	--
50 to < 200	124 (42%)	59 (46%)	1.07	0.58, 1.97		
200 to < 350	64 (22%)	24 (19%)	0.84	0.42, 1.71		
350 or greater	64 (22%)	26 (20%)	0.91	0.46, 1.83		
WHO Stage of Disease					--	--
Stage I/II	286 (96%)	126 (98%)	Ref.	Ref.		
Stage III/IV	11 (4%)	3 (2%)	0.62	0.17, 2.26		
Disclosed HIV status to anybody					--	--
No	18 (6%)	6 (5%)	Ref.	Ref.		
Yes	283 (94%)	124 (95%)	1.31	0.51, 3.39		

Notes:
'Ref.' refers to the 'Reference category'.

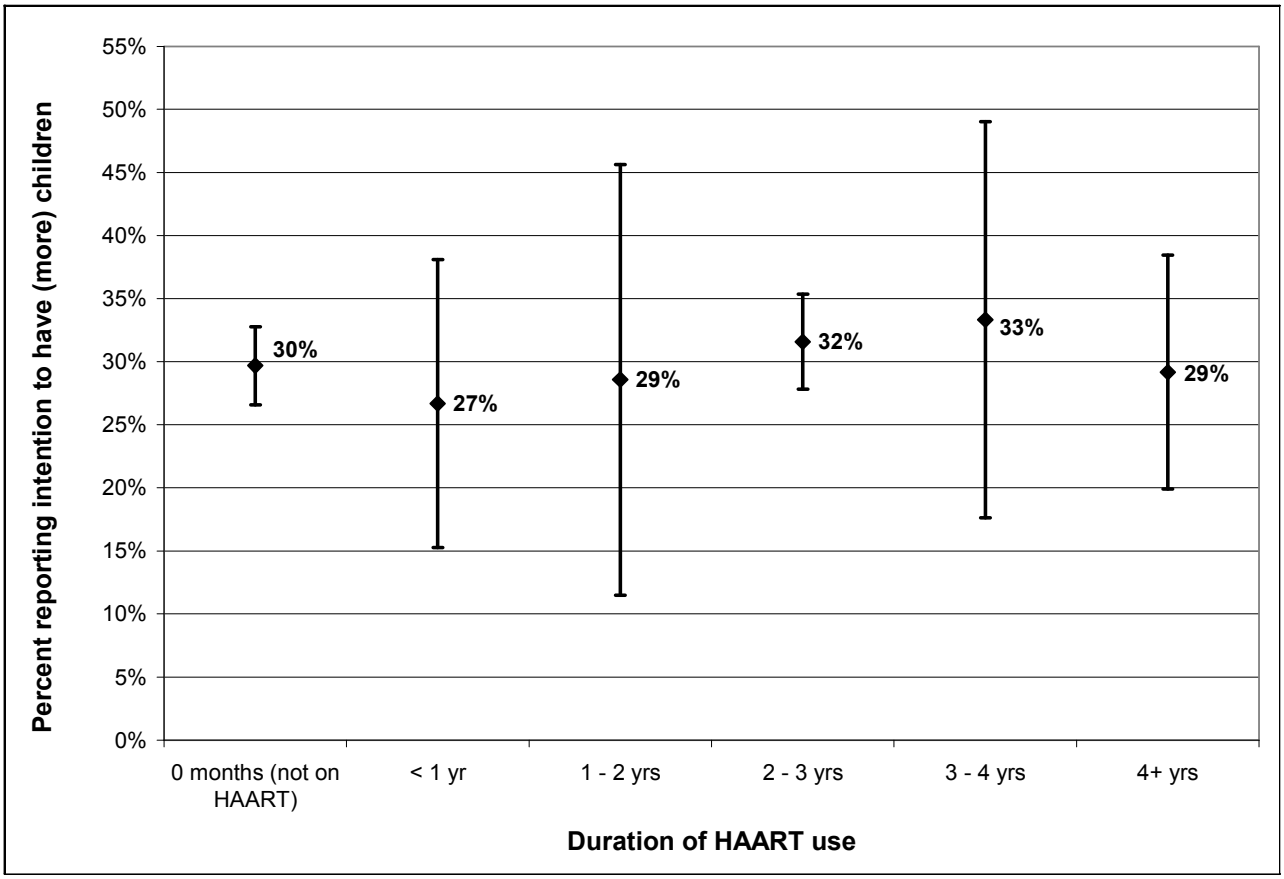

Figure 4.1: Percent of women (aged 18-44 years and non-sterilized) who intend to have (more) children by length of time on HAART among HIV-positive women in Soweto, South Africa (n=426)

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CHAPTER 5[4]:

CONTRACEPTIVE USE AND METHOD MIX PATTERNS AMONG HIV-POSITIVE AND HIV-NEGATIVE WOMEN IN SOWETO, SOUTH AFRICA IN THE CONTEXT OF EXPANDING ACCESS TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

5.1 INTRODUCTION

Nearly 80% of the world's 15.5 million HIV-infected women live in sub-Saharan Africa, where heterosexual intercourse is the primary mode of HIV transmission [1]. Women living with HIV face many of the same contraceptive and reproductive decision-making challenges as HIV-negative women in addition to the HIV-specific risks to maternal, fetal, and partner health associated with conception and pregnancy.

Increasing use of effective contraception is an important strategy towards preventing unintended pregnancies in all women and a critical factor towards

[4] A version of this chapter has been submitted for publication. Kaida A, Laher F, Strathdee SA, Money D, Janssen PA, Hogg RS, Gray G. Contraceptive use and method mix patterns among HIV-positive and HIV-negative women in Soweto, South Africa in the context of expanding access to highly active antiretroviral therapy.

reducing maternal and infant mortality [2]. Among HIV-positive women, provision of contraceptive services to prevent unwanted pregnancies remains the "best kept secret" [3] of the four WHO pillars for preventing mother-to-child-transmission (PMTCT) of the virus. A recent modeling study showed that a PMTCT strategy focused on increasing contraception among HIV-positive women could avert 29% more HIV-positive births than prophylactic nevirapine alone, at the same level of expenditure [4]. However, the prevailing under-emphasis of reproductive health within HIV programming is evident in the numbers: an estimated 50-84% of pregnancies among HIV-infected women are unintended [5-7] and each year in sub-Saharan Africa nearly 350,000 infants are infected with HIV via MTCT [1].

The little that is known about the prevalence and type of contraceptive use among HIV-infected women originates from studies conducted prior to widespread availability of highly active antiretroviral therapy (HAART) in sub-Saharan Africa [5, 8-10]. This is due, in part, to the recency of the dramatic HAART scale-up effort in the region [11]. By increasing life expectancy [12-14], decreasing morbidity [13, 15], and reducing vertical [16] and sexual [17] transmission risks, expanding access to HAART is dramatically reducing the health risks and barriers to reproduction among HIV-affected individuals and couples. This emerging reality of HIV as a manageable chronic disease, with HIV-infected individuals anticipated to live well into (and past) their peak reproductive years, has highlighted the importance of

assessing the potential behavioral and biological impacts of HAART on contraceptive use, safety, and efficacy [18-25].

Given the HIV hyper-endemic context of reproduction in Soweto, South Africa [1, 26], the primary objective of this study was to assess the prevalence of contraceptive use and to determine whether contraceptive use varies according to HIV serostatus and use and duration of HAART among sexually active women aged 18-44 years. A secondary objective was to determine the types of contraceptive methods used and whether contraceptive method profiles vary by HIV and HAART use. This research was conducted within *Kaida et al's* conceptual framework of the potential impact of HAART on fertility in sub-Saharan Africa [19], where HAART use is hypothesized to reduce individuals' perceived risk of HIV transmission and disease progression, ease concerns about the risks of reproduction, and alter contraceptive use patterns. As such, we hypothesized that HIV-positive women receiving HAART would be less likely to use contraception compared with HIV-positive women not receiving HAART, with increasing duration of HAART use associated with incrementally lower contraceptive use. Also, we hypothesized that contraceptive prevalence among HIV-positive women receiving HAART and HIV-negative women would be similar.

5.2 METHODS

5.2.1 Study setting

At 5.7 million, South Africa has the largest absolute number of people living with HIV in the world, 60% of whom are women [1]. The adult (aged 15-49 years) prevalence of HIV is 19% [1] and in 2006, 30% of pregnant women tested during antenatal clinic surveillance were HIV-positive. Gauteng province, where Soweto is located, has an antenatal HIV prevalence of 31% [26].

HAART became available in public sector clinics in 2004 and by the end of 2007 an estimated 460 000 patients were receiving HAART, an antiretroviral therapy coverage of 28% [11]. Contraceptive methods, including injectables, oral contraceptives, and male condoms, are available at no-cost in government health centres.

This study was conducted at the Perinatal HIV Research Unit (PHRU), a large clinical and research site housed within Chris Hani Baragwanath Hospital in Soweto. The PHRU sees over 5,000 adult patient visits monthly and provides antiretroviral therapy and clinical care to medically-eligible HIV-positive individuals and ongoing wellness care for those not yet eligible for HAART. The PHRU also operates a Prevention Studies area that includes a Voluntary Counseling and Testing (VCT) centre. All PHRU services are provided free-of-charge.

5.2.2 Study design

This analysis is based on cross-sectional survey data of HIV-positive (HAART receiving and HAART-naïve) and HIV-negative women seeking services at the PHRU. A medical chart review was also conducted to confirm HIV serology and HAART use history of HIV-positive women.

5.2.3 Eligibility criteria

To be eligible to participate in the study, women were required to be 18-49 years of age, attending a PHRU clinic, residing in Soweto, competent to give informed consent, and willing to allow medical record review for the purposes of confirming HIV status and HAART history. We considered women to be HAART users if they had been receiving HAART for at least one month. We considered women to be HAART-naïve if they had never taken HAART, except for vertical transmission prophylaxis.

5.2.4 Study sample

We enrolled 751 women, including 253 HIV-positive women receiving HAART, 249 HIV-positive but HAART-naïve women, and 249 HIV-negative women. This sampling strategy provided one case group (HAART users) and two comparison groups (HAART-naïve and HIV-negative women).

HAART users were sampled from the PHRU's PEPFAR Clinic which has provided free antiretroviral therapy to medically eligible patients since July 2004. Currently, the PEPFAR clinic has over 1,000 patients receiving HAART, 75% of whom are female. PEPFAR patients are followed-up every three months and generally receive one of two standard HAART regimens: Regimen 1 is d4T/3TC/EFV or NVP and Regimen 2 is Kaletra/ddI/AZT [27].

HIV-positive HAART-naïve women were sampled from the PHRU's Wellness Clinic, initiated in January 2003 with the goal of providing preventive care to HIV-positive individuals. Wellness patients are followed-up approximately every six months. When patients are medically eligible for HAART, they are referred to the PEPFAR clinic or to one of the nearby government ART clinics. There are approximately 3,000 active patients in the Wellness Clinic.

HIV-negative women were sampled from the VCT clinic, which was initiated in mid-2002 and sees approximately 400 people per month. Testing is conducted

onsite during visits that last an average of two hours. Approximately 65% of attendees are women and 30% of all attendees test HIV-positive.

For this analysis on contraceptive use, we restricted the study sample to women aged 18-44 years who were currently sexually active (i.e., reported sexual activity in the previous six months) and not currently pregnant. This was done to enhance the comparability of findings with other studies investigating reproductive and sexual health among HIV-positive populations. The restriction yielded an analytic sample of 563 women (75% of total sample), including 171 women on HAART, 178 HAART-naïve women, and 214 HIV-negative women.

5.2.5 Data collection

Every female patient attending the PEPFAR Clinic and the VCT clinic was consecutively approached by a research assistant to assess eligibility and interest in participating in the study. Since many more women attend the Wellness Clinic, a list was made of chart numbers of women attending the clinic each day. A random sample of chart numbers (40% of the total number of charts present) was then drawn and the corresponding women were approached to assess eligibility and interest in participating in the study.

After confirming eligibility and seeking informed consent, all participants were asked to complete a 15-25 minute interviewer-administered questionnaire in English. The study interviewers were multilingual and trained to ensure accurate and consistent translation of the questionnaire if required or requested by the participant. Pilot testing of 45 women revealed that women were able to understand and answer the questionnaire.

Approximately 12 women were interviewed daily by three trained research assistants between May and December 2007. Research assistants were women from the local community who had previous research experience and were recent Social Sciences' graduates of a local university. Interviewers were supervised by an experienced research nurse. Two research nurses with HIV training conducted the medical record review. Participants were given transport reimbursement as compensation.

5.2.6 Data collection instruments

The questionnaire assessed socio-demographic characteristics; HIV status, diagnosis, and treatment; clinical stage of disease; HAART history; fertility intentions; fertility history; contraceptive practices; and sexual history.

We reviewed medical records of HIV-positive women to confirm HIV status and HAART history, and to obtain clinical data including CD4 cell counts and WHO stage of disease. Viral load assessments are only available from women in the PEPFAR Clinic (i.e., HAART users). The medical record was considered the referent measure for inconsistencies between self-reported and medical record data.

5.2.7 Measures

The primary outcome was self-reported contraceptive use in the previous six months. Contraceptive methods queried included male and female condoms (restricted to those reporting "Always" use), injections (*depomedroxyprogesterone acetate* (DMPA) or *norethisterone enantate),* oral contraceptive pill, diaphragm, IUD, female sterilization, and hysterectomy. In assessing the contraceptive method profile, dual protection was defined as use of both a barrier contraceptive method (primarily the male condom) and use of a hormonal or permanent contraceptive method [28].

The primary explanatory variable was current HAART use. The secondary explanatory variable was HIV status. Covariates included age, education, employment, household income, current sexual partnership, HIV status of regular

sexual partners, parity, number of living children, fertility intentions, and HIV clinical variables.

5.2.8 Statistical analysis

We computed and compared the prevalence of contraceptive use between HIV-positive women and HIV-negative women and then between each of the three groups of women. We conducted two separate models to measure the presence and strength of the association between HAART use and the odds of contraceptive use, controlling for covariates. The first model compared HAART users and HAART-naïve women to HIV-negative women. The second model compared HAART users to HAART-naïve women and allowed adjustment for HIV-associated clinical characteristics.

In both models, univariate analyses were used to assess the relationship between HIV status, receipt of HAART, contraceptive use, and covariates. Differences in contraceptive use between groups are reported using Pearson's chi-squared test (for categorical variables) and ANOVA, or Student's independent t-test (for continuous variables). After testing for co-linearity (using Spearman's rho (ρ)) [29] and interaction [30], all covariates with significant associations in the univariate analysis were included in multivariate logistic regression models to obtain adjusted estimates of the

association. Age was forced into both multivariate models regardless of its univariate associations. All statistical tests were two-sided and considered significant at $\alpha = 0.05$.

Among women who reported using contraception, we analyzed types of methods used by women in each of the three groups and overall. In addition to reporting use of each contraceptive method individually, we collapsed women into four mutually exclusive groups including "Dual protection", "Consistent condom use only", "Hormonal/Permanent method only", and "Not using any contraceptive method" and tested for differences by HIV and HAART use status using Pearson's chi-squared test.

We assessed the association between duration of HAART use and prevalence of contraceptive use using Pearson's test for trend. HAART-naïve women were included in the "0 months on HAART" category.

5.2.9 Sub-analyses

We conducted the same analyses described above but restricted our sample to women aged 18-34 years to investigate the potential impact of differences in mean baseline age between HIV-positive and HIV-negative women in our study. In addition, this age group corresponds with the peak childbearing years among women in South Africa [31].

5.2.10 Ethical considerations

All participants provided informed consent and all procedures were approved by the Human Research Ethics Committee of the University of the Witwatersrand, the University of British Columbia Health Research Ethics Board, the Simon Fraser University Office of Research Ethics, and the University of California San Diego Institutional Review Board. Information letters and consent forms were available in English and two local languages (isi-Zulu and Sesotho) to ensure comprehensive understanding of the study objectives, potential risks, and benefits.

5.3 RESULTS

Of 801 women approached for participation, 751 consented, completed the questionnaire, and had their medical records reviewed (participation rate = 94%). This analysis was restricted to 563 sexually active, non-pregnant women aged 18-44 years.

5.3.1 Baseline characteristics

As shown in Table 5.1, there were important differences in baseline characteristics by HIV and HAART use status. Mean age was 30 years [SD=6.7], however, HIV-negative women were significantly younger than HIV-positive women. Half of women had less than a grade 12 education, 62% were unemployed, and 71% had a monthly household income less than 3,000 ZAR ($380 USD). Nearly one-quarter (23%) reported that her primary sexual partner was HIV-positive, 29% reported that he was HIV-negative, and 42% did not know her partner's HIV status. Mean parity was 1.5 [SD=1.2] and 44% of women had two or more living children. Nearly half (45%) reported that they intended to have more children.

Among HIV-positive women (n=349), mean time since first HIV diagnosis was 59.7 months [SD=35.4]. Half had recent CD4 counts ≥ 350 cells/mm^3 and 12% had nadir CD4 counts < 50 cells/mm^3. Nearly all women were in WHO Stage of Disease I or II (98%) and 95% had disclosed their HIV status to someone.

Among HAART users (n=171), median duration of HAART use was 31 months [IQR: 28, 33], ranging from one to 89 months. Eighty percent of HAART users with recorded viral load measures were virally suppressed (<50 copies/ml).

5.3.2 Prevalence of contraceptive use

Overall contraceptive prevalence was 78%. This varied significantly by HIV status with 84% of HIV-positive women (including 86% of HAART users and 82% of HAART-naïve women) and 69% of HIV-negative women reporting current contraceptive use ($p<0.0001$).

5.3.3 Types of contraceptive methods used

The contraceptive method profiles are shown in Table 5.2. Part (a) of the Table 5.2 shows mutually exclusive groups of contraceptive users. As shown, HIV-positive women overall were significantly more likely to use practice dual protection compared with HIV-negative women (33% and 14%, respectively). Much of this difference was accounted for by HAART users, of whom 40% reported using dual protection compared with 24% of HAART-naïve women and 14% of HIV-negative women. HAART users were also significantly more likely to report using condoms (with or without hormonal/permanent methods) (68%) and hormonal/permanent methods (with or without condoms) (58%) compared with non-HAART users and HIV-negative women ($p<0.0001$).

Of the 411 women reporting contraceptive use (Table 5.2 part (b)), 56% used hormonal contraception, 69% used barrier methods (mainly the male condom), and 7% used permanent methods (i.e., hysterectomy and/or female sterilization) with significant differences by HIV status and HAART use. Across all three groups, hormonal contraceptive users utilised injectables more commonly than oral contraceptives. HAART users were significantly more likely to use condoms (79%), compared with non-HAART users (72%), and HIV-negative women (57%) (p=0.0001). Higher proportions of HIV-positive women had a tubal ligation or hysterectomy compared with HIV-negative women (p=0.014).

5.3.4 Univariate and adjusted analysis of contraceptive use: HAART users, HAART non-users, and HIV-negative women

In the unadjusted analyses, many of the measured baseline covariates were significantly associated with contraceptive use (Table 5.3). Compared with HIV-negative women, HIV positive women were significantly more likely to use contraceptive methods (HAART users OR: 2.73; 95% CI: 1.62, 4.59; and non-HAART users OR: 2.04; 95% CI: 1.26, 3.29).

In adjusted analyses, compared with HIV-negative women, HAART users remained significantly more likely to use contraception (OR: 2.40; 95% CI: 1.25, 4.62)

while non-HAART users were marginally more likely to use contraception (OR: 1.59; 95% CI: 0.88, 2.85). Overall, HIV-positive women (combining HAART users and HAART-naïve women) had increased adjusted odds of 1.75 (95% CI: 1.02, 2.99) of using contraception compared with HIV-negative women. Younger age, having two or more living children, and expressing an intention not to have (more) children also remained significantly associated with contraceptive use.

5.3.5 Univariate and adjusted analysis: HIV-positive women

As shown in Table 5.4, HAART users and non-users were equally likely to report contraceptive use in unadjusted analyses (OR: 1.34; 95% CI: 0.75, 2.39). There were no significant differences in contraceptive use by HIV clinical characteristics.

In adjusted analyses, HAART users were marginally more likely than non-users to report contraceptive use (AOR: 1.55; 95% CI: 0.84, 2.88). Younger age, having two or more living children, and expressing an intention not to have more children remained most strongly associated with contraceptive use.

5.3.6 Contraceptive use by duration of HAART use

There was no association between duration of HAART use and prevalence of contraceptive use, although there was an apparent lower level of contraceptive use for women receiving HAART between one and two years (Figure 5.1).

5.3.7 Sub-analyses

Contraceptive prevalence of young women (18-34 yrs, n=420) was similar to the overall sample and still varied significantly by HIV and HAART use status: 88% of HAART users, 82% of HAART non-users, and 70% of HIV-negative young women reported using contraception (p=0.0007). In multivariate analyses we found that the same variables associated with contraceptive use in the overall sample were similarly associated with contraceptive use among young women. Compared with HIV-negative women, HAART users remained significantly more likely to use contraception (AOR: 2.24; 95% CI: 1.05, 4.99) while HAART-naïve women were similarly likely to use contraception (AOR: 1.27, 95% CI: 0.65, 2.48).

5.4 DISCUSSION

We found that HIV-positive women overall were significantly more likely to use contraception compared with HIV-negative women. In particular, and in contrast with our hypothesis, women receiving HAART were significantly more likely to report contraceptive use while HIV-positive HAART-naïve women were marginally more likely to use contraception compared with HIV-negative women. Overall, over 80% of HIV-positive women in our study reported contraceptive use, which falls within the upper range reported for HIV-positive women elsewhere in sub-Saharan Africa (46%-85%) [9, 10, 18, 25, 32, 33]. Contraceptive prevalence among HIV-negative women in our study was 69%, which is highly comparable to estimates among women in the general South African population [31].

Among HIV-positive women, our finding indicating marginally higher prevalence of contraceptive use among HAART users compared with HAART-naïve women is broadly consistent with recent findings from Uganda [18]. To the best of our knowledge, this is the first study to show a stable effect of contraceptive use by duration of HAART use. Other factors associated with contraceptive use included younger age, having two or more living children, and a lack of intention to have more children, all of which are widely reported to influence contraceptive decision-making [10, 18, 34].

The reasons for higher contraceptive prevalence among HIV-positive women in general and HAART users in particular were not directly explored in this study. However, an important possible reason for the observed differences is that women receiving HIV treatment and care have more regular contact with health care professionals as a function of the clinical follow-up required to monitor the health of individuals receiving therapy. During these regular clinic visits, reproductive and sexual health issues are addressed and the opportunity to discuss and commence use of contraception is presented.

Contraceptive method choice may have implications for both HIV transmission and pregnancy risks and we found important differences in the types of contraceptive methods used by women in each of our three groups. While condoms are recommended to prevent HIV transmission to uninfected sexual partners, they are less effective than hormonal contraception and sterilization at preventing pregnancy [28]. Overall, a substantial proportion of women in this setting report relying exclusively on the male condom for preventing pregnancy (29%). An additional 25% of women report using condoms in conjunction with a hormonal/permanent method of contraception, resulting in over half of our sample reporting consistent condom use with or without another method. HAART users reported the highest prevalence of consistent condom use. Indeed much of the difference in contraceptive prevalence between our three groups was accounted for

by the significantly lower prevalence of condom use among HIV-negative women. Reported rates of condom use among HIV-negative women in our study are comparable to those reported in South Africa overall [31].

Unlike barrier methods, permanent and hormonal contraceptive methods are highly effective at preventing pregnancy but have no role in the prevention of HIV transmission [28]. Overall, 7% of women used permanent methods (hysterectomy and/or female sterilization) with small differences by HIV status and HAART use. The overall prevalence of sterilization is slightly lower than reported rates from South African women in general [31].

Compared with HAART-naïve women, HAART users were more likely to use hormonal contraception, and uptake of DMPA injectables exceeded oral contraceptive use. Reports from other settings suggest that DMPA use is rising owing to its discretion and convenient three-month dosing which corresponds with the HAART follow-up schedule [35]. Higher uptake of progesterone-only injectables in HAART users may also reflect provider preference based on concerns about possible interactions between HAART and estrogen-containing oral contraceptives [36]. Available guidelines advise that women receiving antiretroviral agents should use alternative or additional methods of contraception, beyond oral contraceptives [36].

There is no single method that can reliably assist HIV-positive women who wish to avoid pregnancy and HIV transmission to sero-discordant partners. Moreover, given concerns noted above about potential interaction between hormonal contraception and antiretroviral agents, dual protection is encouraged. In our study, not only were HAART users significantly more likely to use contraceptive methods overall, they were more likely than non-HAART users and HIV-negative women to use dual protection. Low prevalence of dual protection among HAART-naïve women (24%) may reflect a population at risk of transmitting HIV to sero-discordant partners and, if they do become pregnant, are a population most requiring antiretroviral prophylaxis through PMTCT services.

Overall, 14% of HAART users, 18% of HAART-naïve women, and 31% of HIV-negative women were not using any form of contraceptive, suggesting risk for unintended pregnancy. A high proportion of women were also unaware of their partner's HIV status (42% overall). As such, the risks of conception-related HIV acquisition or transmission between sero-discordant couples are serious and integrated HIV and sexual and reproductive health services must be provided to help HIV-affected couples safely achieve their fertility goals.

Limitations of this study must be acknowledged. First, the cross-sectional nature of this analysis precludes us from determining causality between the

explanatory variable and the outcome, particularly since contraceptive use, HIV status, and HAART use were assessed at the same point in time. Although reverse causality is considered unlikely (i.e., contraceptive use leading to HAART use), longitudinal studies are needed to investigate this relationship and would enable examination of duration of contraceptive use. Second, there is a risk of social desirability bias whereby HIV-positive women may over-report their contraceptive use (and condom use, in particular) because of pressure from health workers and community members to practice protected sex [37, 38] . If over-reporting was differential, then our effect estimates are likely somewhat inflated. We took precautions against reporting bias by using standardized questions of contraceptive use and employing non-clinic staff to conduct the interviews. Third, there were important baseline differences between the HIV-positive and HIV-negative women in our study, a potential source of selection bias, which cannot be fully adjusted for in the analyses. In particular, HIV-positive women in our study were significantly older and age is a known predictor of contraceptive use and is associated with a number of other covariates (e.g., parity, education status). In an attempt to address this limitation, we conducted a sub-analysis of contraceptive use restricted to women less than 35 years of age. We found no differences in the variables that predicted contraceptive use nor the magnitude of the associations. The results of the sub-analysis suggest that our overall findings are robust, despite differences in age

at baseline. Finally, a quantitative analysis such as this fails to capture the salient influence of cultural and gender dynamics on contraceptive decision-making. Indeed, qualitative studies from this setting have highlighted the importance of considering the real and perceived side effects of contraceptives and partner influence and status as mitigating factors influencing contraceptive decision-making of HIV-positive women [39].

In conclusion, our results demonstrate that HIV-positive women overall and women accessing HAART services in particular, are more likely to use contraception overall, and more likely to use barrier, permanent, and dual protection methods in particular, compared with their HIV-negative and HAART-naïve counterparts. The contraceptive use profile of HIV-positive and HIV-negative women in Soweto demands further integration of HIV treatment and care services with reproductive and sexual health services, including the provision of effective contraception. Through the prevention of unintended pregnancy, integrated services are likely to benefit maternal and child health, increase primary prevention of vertical transmission, and decrease incidence of conception-related horizontal transmission to discordant sexual partners.

Table 5.1: Baseline characteristics of HAART users, non-HAART users, and HIV-negative women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=563)

Variable	HAART users (n=171) n (%)	Non-HAART users (n=178) n (%)	HIV-negative (n=214) n (%)	Overall (n=563) n (%)	p-value[¥]
Socio-demographic Characteristics					
Mean Age (yrs) [SD]	33.7 [5.0]	32.3 [5.6]	25.3 [6.0]	30.0 [6.7]	<0.0001
Age Group (yrs)					<0.0001
18-24	4 (2%)	15 (8%)	119 (56%)	138 (25%)	
25-29	30 (18%)	41 (23%)	43 (20%)	114 (20%)	
30-34	66 (39%)	63 (36%)	37 (17%)	166 (30%)	
35-39	43 (25%)	35 (20%)	7 (3%)	85 (15%)	
40-44	27 (16%)	23 (13%)	8 (4%)	58 (10%)	
Education					<0.0001
Less than Grade 12	114 (67%)	109 (61%)	60 (28%)	283 (50%)	
Grade 12 or higher	56 (33%)	69 (39%)	154 (72%)	279 (50%)	
Employment Status					0.0962
Employed	71 (42%)	75 (42%)	70 (33%)	216 (38%)	
Unemployed	100 (58%)	103 (58%)	144 (67%)	347 (62%)	
Household income (per month)					<0.0001
Less than 3000 ZAR	142 (83%)	146 (82%)	111 (52%)	399 (71%)	
3,000 or more ZAR	16 (9%)	24 (13%)	65 (30%)	105 (19%)	
Don't know/Refused	13 (8%)	8 (4%)	38 (18%)	59 (10%)	

Table 5.1 (continued): Baseline characteristics of HAART users, non-HAART users, and HIV-negative women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=563)

Variable	HAART users (n=171) n (%)	Non-HAART users (n=178) n (%)	HIV-negative (n=214) n (%)	Overall (n=563) n (%)	p-value[¥]
Currently in a sexual relationship					0.6337
No	12 (7%)	16 (9%)	14 (7%)	42 (7%)	
Yes	159 (93%)	162 (91%)	200 (93%)	521 (93%)	
HIV status of regular sexual partner/husband					<0.0001
Don't Know	64 (37%)	87 (49%)	83 (39%)	234 (42%)	
HIV-negative	30 (18%)	22 (12%)	111 (52%)	163 (29%)	
HIV-positive	69 (40%)	59 (33%)	2 (1%)	130 (23%)	
Single	8 (5%)	10 (6%)	18 (8%)	36 (6%)	
Mean parity [SD]	1.9 [1.1]	1.9 [1.2]	0.85 [0.9]	1.5 [1.2]	<0.0001
Number of living children					<0.0001
0	19 (11%)	19 (11%)	96 (45%)	134 (24%)	
1	58 (34%)	56 (31%)	68 (32%)	182 (32%)	
2 or more	94 (55%)	103 (58%)	50 (23%)	247 (44%)	
Fertility Intentions					
Yes	55 (32%)	55 (31%)	146 (68%)	256 (45%)	<0.0001
No	116 (68%)	123 (69%)	68 (32%)	307 (55%)	

Table 5.1 (continued): Baseline characteristics of HAART users, non-HAART users, and HIV-negative women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=563)

Variable	HAART users (n=171) n (%)	Non-HAART users (n=178) n (%)	HIV-negative (n=214) n (%)	Overall (n=563) n (%)	p-value[¥]
HIV history and clinical characteristics					
Mean # of months since HIV diagnosis [SD]	69.0 [36.3]	50.8 [32.1]	N/A	59.7 [35.4]	<0.0001
Recent CD4 count					0.0003
< 200	28 (17%)	34 (19%)	N/A	62 (18%)	
200 to < 350	38 (23%)	72 (40%)		110 (32%)	
350 or greater	102 (61%)	72 (41%)		174 (50%)	
Nadir CD4 count					<0.0001
< 50	41 (24%)	2 (1%)	N/A	43 (12%)	
50 to < 200	116 (69%)	39 (22%)		155 (45%)	
200 to < 350	5 (3%)	73 (41%)		78 (23%)	
350 or greater	6 (4%)	64 (36%)		70 (20%)	
WHO Stage of Disease					0.5267
Stage I/II	165 (98%)	173 (97%)	N/A	338 (98%)	
Stage III/IV	3 (2%)	5 (3%)		8 (2%)	
Disclosed HIV status to anybody					0.0493
No	4 (2%)	12 (7%)	N/A	16 (5%)	
Yes	167 (98%)	166 (93%)		333 (95%)	

Notes:

[¥] Differences between groups are reported using Pearson's chi-squared test statistic (for categorical variables) and Student's independent t-test or ANOVA (for continuous variables).

SD = Standard Deviation
N/A = Not Applicable

Table 5.2: Types of contraceptive methods used by HIV-positive (HAART users and non-HAART users) and HIV-negative women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa

	HIV-positive women			HIV-negative women (n=214)	Overall (n=563)	p-value§
	HAART users (n=171) n (%)	HAART non-users (n=178) n (%)	All HIV-positive women (n=349) n (%)	n (%)	n (%)	
Overall Contraceptive Prevalence	**86%**	**82%**	**84%**	**69%**	**78%**	**<0.0001**
(a) Mutually exclusive categories of type of contraceptive method used:						
Dual protection (Hormonal/ permanent method AND consistent condom use)	40%	24%	33%	14%	25%	
Hormonal/Permanent method only	18%	23%	20%	30%	24%	
Consistent condom use only	28%	35%	31%	25%	29%	
Not using any contraceptive method	14%	18%	16%	31%	22%	
						<0.0001

Table 5.2 (continued): Types of contraceptive methods used by HIV-positive (HAART users and non-HAART users) and HIV-negative women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa

	HIV-positive women			HIV-negative women (n=148)	Overall (n=441)	p-value§
	HAART users (n=146) n (%)	HAART non-users (n=147) n (%)	All HIV-positive women (n=293) n (%)	n (%)	n (%)	
(b) Contraceptive method mix among contraceptive users (n=411)*:						
Hormonal Methods	**88 (60%)**	**68 (47%)**	**156 (53%)**	**89 (60%)**	**245 (56%)**	**0.0211**
Injections	82 (56%)	49 (34%)	131 (45%)	66 (45%)	197 (45%)	0.0007
Oral Contraceptive Pill	6 (4%)	19 (13%)	25 (9%)	23 (16%)	48 (11%)	0.0041
Barrier Methods	**116 (79%)**	**105 (72%)**	**221 (75%)**	**85 (57%)**	**306 (69%)**	**0.0001**
Consistent male condom use	116 (79%)	105 (72%)	221 (75%)	84 (57%)	305 (69%)	0.0001
Diaphragm	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)	n/a
Permanent methods	**12 (8%)**	**20 (14%)**	**32 (11%)**	**4 (3%)**	**33 (7%)**	**0.0140**
Hysterectomy	4 (3%)	5 (3%)	9 (3%)	0 (0%)	9 (2%)	0.0897
Female sterilization	8 (5%)	15 (10%)	23 (8%)	4 (3%)	27 (6%)	0.0234

Notes: § p-value from chi-squared test statistics comparing proportions across three groups: HAART-users, HAART-naïve, and HIV-negative women; * Values may not total 100% because one woman may report using more than one method.

Table 5.3: Univariate and adjusted analyses of variables associated with contraceptive use among women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=563)

Variable	Contraceptive Use		Crude OR		Adjusted OR	
	No (%) (n=122)	Yes (%) (n=441)	OR	95% CI	AOR	95% CI
HIV and HAART Use Status						
HIV-negative	66 (54%)	148 (34%)	**Ref.**	**Ref.**	**Ref.**	**Ref.**
HIV-positive, HAART-naïve	32 (26%)	146 (33%)	**2.04**	**1.26, 3.29**	**1.59**	**0.88, 2.85**
HIV-positive, receiving HAART	24 (20%)	147 (33%)	**2.73**	**1.62, 4.59**	**2.40**	**1.25, 4.62**
Age (per increase in year)	29.0 [SD=7.4]	30.3 [SD=6.5]	**1.03**	**1.00, 1.06**	**0.94**	**0.90, 0.98**
Education						
Less than Grade 12	45 (37%)	238 (54%)	**Ref.**	**Ref.**	Ref.	Ref.
Grade 12 or higher	77 (63%)	202 (46%)	**0.50**	**0.33, 0.75**	0.70	0.44, 1.13
Employment Status						
Unemployed	67 (55%)	280 (63%)	Ref.	Ref.	--	--
Employed	55 (45%)	161 (37%)	0.70	0.47, 1.05		
Household income (per month)						
Less than 3000 ZAR	72 (59%)	327 (74%)	**Ref.**	**Ref.**	Ref.	Ref.
3,000 or more ZAR	33 (27%)	72 (16%)	**0.48**	**0.30. 0.78**	0.94	0.55, 1.63
DK/Refused	17 (14%)	42 (10%)	**0.54**	**0.29, 1.01**	0.73	0.37, 1.43
Currently in a sexual relationship						
No	12 (10%)	30 (7%)	Ref.	Ref.	--	--
Yes	110 (90%)	411 (93%)	1.50	0.74, 3.02		

Table 5.3: (continued) Univariate and adjusted analyses of variables associated with contraceptive use among women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=563)

Variable	Contraceptive Use		Crude OR		Adjusted OR	
	No (%) (n=122)	Yes (%) (n=441)	OR	95% CI	AOR	95% CI
HIV status of regular sexual partner/ husband					--	--
Don't Know	50 (41%)	184 (42%)	Ref.	Ref.		
HIV-negative	42 (34%)	121 (27%)	0.78	0.49, 1.25		
HIV-positive	22 (18%)	108 (25%)	1.33	0.77, 2.32		
Single	8 (7%)	28 (6%)	0.95	0.41, 2.22		
Number of living children						
0	43 (35%)	91 (21%)	**Ref.**	**Ref.**	**Ref.**	**Ref.**
1	50 (41%)	132 (30%)	**1.25**	**0.77, 2.03**	**1.01**	**0.59, 1.73**
2+	29 (24%)	218 (49%)	**3.55**	**2.09, 6.04**	**2.39**	**1.17, 4.89**
Fertility Intentions						
Yes	81 (66%)	175 (40%)	**Ref.**	**Ref.**	**Ref.**	**Ref.**
No	41 (34%)	266 (60%)	**3.03**	**1.96, 4.55**	**1.96**	**1.17, 3.29**

Notes:

Ref. = Reference category

SD = Standard Deviation

Table 5.4: Univariate and adjusted analyses of variables associated with contraceptive use among HIV-positive women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=349)

Variable	Contraceptive Use		Crude OR		Adjusted OR	
	No (%) (n=56)	Yes (%) (n=293)	OR	95% CI	OR	95% CI
HAART Use						
HAART-naive	32 (57%)	146 (50%)	Ref.	Ref.	Ref.	Ref.
Receiving HAART	24 (43%)	147 (50%)	1.34	0.75, 2.39	1.55	0.84, 2.88
Age (per increase in year)	33.3 [SD=5.6]	32.9 [SD=5.3]	0.99	0.94, 1.04	**0.93**	**0.88 0.99**
Education						
Less than Grade 12	29 (52%)	194 (66%)	**Ref.**	**Ref.**	Ref.	Ref.
Grade 12 or higher	27 (48%)	98 (34%)	**0.54**	**0.30, 0.97**	0.62	0.33, 1.17
Employment Status						
Unemployed	31 (55%)	172 (59%)	Ref.	Ref.		
Employed	25 (45%)	121 (41%)	0.87	0.49, 1.56	**--**	**--**
Household income (per month)						
Less than 3000 ZAR	44 (79%)	244 (83%)	Ref.	Ref.		
3,000 or more ZAR	8 (14%)	32 (11%)	0.72	0.31, 1.67		
DK	4 (7%)	17 (6%)	0.77	0.25, 2.39	**--**	**--**
Currently in a sexual relationship						
No	5 (9%)	23 (8%)	Ref.	Ref.		
Yes	51 (91%)	270 (92%)	1.15	0.42, 3.17	**--**	**--**

Table 5.4 (continued): Univariate and adjusted analyses of variables associated with contraceptive use among HIV-positive women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=349)

Variable	Contraceptive Use		Crude OR		Adjusted OR	
	No (%) (n=56)	Yes (%) (n=293)	OR	95% CI	OR	95% CI
HIV status of regular sexual partner/husband						
Don't Know	25 (45%)	126 (43%)	Ref.	Ref.		
HIV-negative	8 (14%)	44 (15%)	1.09	0.46, 2.60	--	--
HIV-positive	21 (38%)	107 (37%)	1.01	0.54, 1.91		
Single	2 (4%)	16 (5%)	1.59	0.34, 7.34		
Number of living children						
0	11 (20%)	27 (9%)	**Ref.**	**Ref.**	**Ref.**	**Ref.**
1	27 (48%)	87 (30%)	**1.31**	**0.58, 2.99**	**1.12**	**0.47, 2.65**
2+	18 (32%)	179 (61%)	**4.05**	**1.73, 9.50**	**3.07**	**1.18, 7.96**
Fertility Intentions						
Yes	30 (54%)	80 (27%)	**Ref.**	**Ref.**	Ref.	Ref.
No	26 (46%)	213 (73%)	**3.03**	**1.72, 5.56**	2.22	1.15, 4.35
Mean # of months since HIV dx [SD]	59.6 [SD=33.1]	59.8 [SD=35.9]	1.00	0.99, 1.01	--	--
Recent CD4						
< 200	8 (14%)	54 (19%)	Ref.	Ref.	--	--
200 to < 350	22 (39%)	88 (30%)	0.59	0.25, 1.43		
350 or greater	26 (46%)	148 (51%)	0.84	0.36, 1.97		

Table 5.4 (continued): Univariate and Adjusted analyses of variables associated with contraceptive use among HIV-positive women (aged 18-44 years, currently sexually active and non-pregnant) in Soweto, South Africa (n=349)

Variable	Contraceptive Use		Crude OR		Adjusted OR	
	No (%) (n=56)	Yes (%) (n=293)	OR	95% CI	OR	95% CI
Nadir CD4						
< 50	7 (13%)	36 (12%)	Ref.	Ref.	--	--
50 to < 200	22 (39%)	133 (46%)	1.18	0.47, 2.97		
200 to < 350	15 (27%)	63 (22%)	0.82	0.31, 2.19		
350 or greater	12 (21%)	58 (20%)	0.94	0.34, 2.61		
WHO Stage of Disease						
Stage I/II	55 (98%)	283 (98%)	Ref.	Ref.	--	--
Stage III/IV	1 (2%)	7 (2%)	1.36	0.17, 11.3		
Disclosed HIV status to anybody						
No	0 (0%)	16 (5%)	N/A	N/A	--	--
Yes	56 (100%)	277 (95%)				

Notes:

Ref. = Reference category

SD = Standard Deviation

N/A = Not applicable

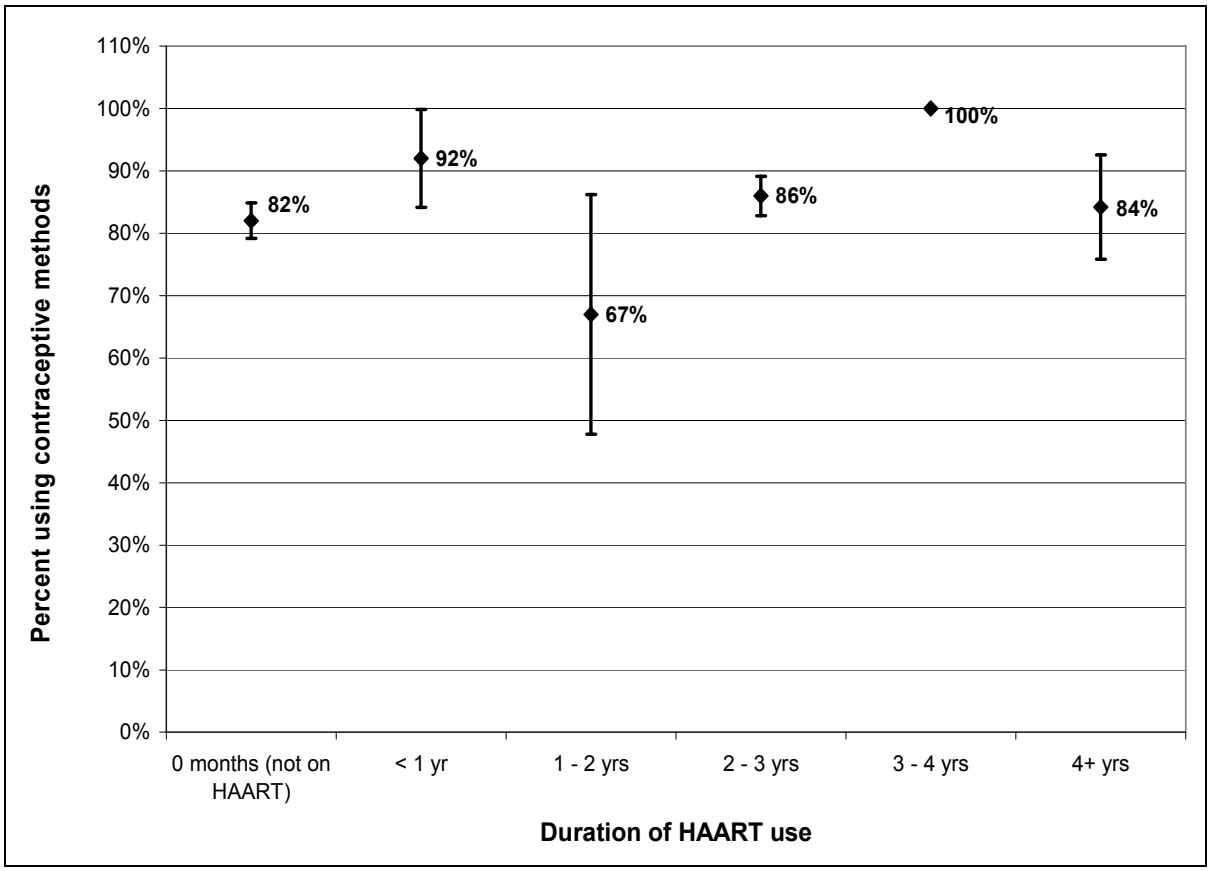

Figure 5.1: Percent of HIV-positive women (aged 18-44 years, currently sexually active and non-pregnant) using contraception by duration of HAART use in Soweto, South Africa (n=349)

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Fertility Intentions among HIV-Positive Women in Soweto, South Africa. *AIDS Behav* 2009.

CHAPTER 6[5]:

THE WHOMEN'S SCALE (WOMEN'S HAART OPTIMISM MONITORING AND EVALUATION SCALE V.1) AND THE ASSOCIATION WITH FERTILITY INTENTIONS AND SEXUAL BEHAVIOURS AMONG HIV-POSITIVE WOMEN IN UGANDA

6.1 INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) in 1996 heralded a new era of hope for people living with HIV/AIDS. Since then, a growing body of evidence has revealed that by suppressing HIV viral load, HAART has dramatically increased survival and decreased HIV/AIDS-related morbidity of individuals in both resource-rich [1, 2, 3] and resource-limited settings [4, 5, 6, 7].

Alongside the remarkable clinical benefits, early reports speculated that the availability of HAART would influence perceptions of HIV risk and sexual risk behaviour of both HIV-infected and uninfected individuals, thereby creating a potential for increased transmission of HIV and other sexually transmitted infections

[5] A version of this chapter has been published. Kaida A, Lima VD, Andia I, Kabakyenga J, Mbabazi P, Emenyonu N, Patterson TL, Hogg RS, Bangsberg DR. The WHOMEN's scale (Women's HAART Optimism Monitoring and EvaluatioN scale v.1) and the association with fertility intentions and sexual behaviours among HIV-positive women in Uganda. *AIDS and Behavior* 2009; Suppl 1:72-81.

[8, 9]. These perceptions, termed variably as 'HAART optimism' or 'HIV treatment optimism', reflected individuals' optimism about the use and efficacy of HAART and corresponding beliefs concerning the decreased need to engage in safer sexual behaviours [10]. These beliefs include two different but related aspects; namely, a belief that HIV-infected individuals on HAART are less likely to transmit HIV due to reduced viral loads and a belief that HIV infection is less of a threat to health and survival due to HAART availability [11, 12].

The concept of HAART optimism is important to HIV prevention efforts since higher levels have commonly been associated with lower rates of condom use, primarily among men who have sex with men (MSM) [13, 14, 15, 16, 17, 18]. While the association has not been entirely consistent [19], a meta-analysis reported that individuals with high levels of HAART optimism are significantly more likely to engage in unprotected sexual behavior, irrespective of their HIV status and actual HAART use status [20]. Based on the cross-sectional nature of these studies, however, we cannot conclude that HAART optimism is the causal factor for the risk, and not vice versa as shown elsewhere [21].

An important limitation of the published literature on HAART optimism to date is its near exclusive focus on sexual risk behavior among MSM populations in western country settings. No studies are available regarding the role of HAART

optimism in HIV endemic countries, owing in part to the recency of widespread HAART availability in these settings [22]. Limited findings are available concerning the prevalence and role of HAART optimism among women [23, 24], despite the fact that women comprise half of all people living with HIV/AIDS around the world [25]. Moreover, limited research has been conducted on the influence of HAART optimism on behaviours other than sexual risk-taking [10]. In particular, unlike MSM populations, HAART optimism may influence reproductive behaviors of HIV-positive women through changes in concerns about vertical transmission [26].

Uganda is an ideal setting to investigate issues related to women's HAART optimism since it is a country currently experiencing a generalized HIV epidemic, fueled primarily by heterosexual transmission [25]. HIV prevalence among adults aged 15-49 years in Uganda is estimated to be 6.3% and is higher among women (7.5%) than men (5.0%) [27]. HAART scale-up efforts in Uganda began in earnest in 2004 and recent government statistics estimate that approximately 120,000 Ugandans are currently on treatment, accounting for slightly more than one-third of those who need it [22]. At 6.6, Uganda has the second highest total fertility rate in Africa [28] and recent findings report that HIV-positive women on HAART are three times more likely to report fertility desires, compared with HIV-positive women not on HAART [29]. Previous research has demonstrated that self-reported fertility desires and intentions are strong predictors of future fertility [30, 31, 32, 33].

The purpose of this study was to develop a reliable HAART optimism scale for HIV-positive women in high prevalence settings and to test the scale's validity against a measure of fertility intentions and two measures of sexual behaviour (i.e., sexual abstinence and unprotected sex) among a sample of HAART-naïve and HAART-experienced women in Uganda.

6.2 METHODS

6.2.1 Study design

This analysis is based on data collected from a cross-sectional study of 540 HIV-positive women aged 18-50 years attending an HIV clinic in Mbarara, western Uganda.

6.2.2 Study setting

The study setting has been described in detail elsewhere [34]. Briefly, Mbarara Regional Referral Hospital (MRRH) is located in Mbarara district, in southwestern Uganda. Housed within the MRRH is the Mbarara University HIV treatment centre, the Immune Suppression Syndrome (ISS) clinic. The ISS clinic opened in 1998 and currently serves over 13,000 clients, 65% of whom are women.

The clinic offers comprehensive HIV care services, including HAART, free-of-charge. Approximately 35% of the clinic's population is currently receiving HAART.

6.2.3 Eligibility criteria

HIV-positive women aged 18-50 years, attending the ISS clinic, and competent to give consent were eligible to participate in the study.

6.2.4 Data collection

Women attending the ISS clinic were consecutively approached by a research assistant to assess eligibility and interest prior to requesting consent for participation in the study. Since non-HAART users attend the clinic less frequently than HAART users, non-HAART users were over-sampled.

Upon determining eligibility and consent, participants received a 20-30 minute interviewer-administered structured questionnaire in either English or Runyankole (the dominant regional language). The Runyankole questionnaire was translated from the original English version into Runyankole, and then back-translated into English to ensure consistency between the two versions. The questionnaire was piloted among 40 women and was administered either before or

after the patient's clinical encounter. Approximately 15 women were interviewed daily by three trained research assistants over eight months from November 2005 to June 2006.

The questionnaire assessed socio-demographic characteristics, HIV/AIDS history, diagnosis, and treatment, reproductive and sexual decision-making and behaviours, and HAART optimism. A medical record review was conducted to confirm HAART history and to obtain clinical data including WHO stage of disease [35] and CD4 cell count. The medical record was considered the referent measure for inconsistencies between self-reported and medical record data.

6.2.5 Instrument Development

The study questionnaire included 23 statements related to HIV and treatment with HAART, concern about horizontal and vertical HIV transmission, and concern about severity of HIV disease. Eleven statements were taken from Van de Ven et al's scale (2000), an existing and widely used HAART optimism scale validated for use among MSM populations [36]. While the Van de Ven scale is comprised of 12 statements, we excluded one item from our questionnaire because it was not relevant to our setting (i.e., "The availability of treatment (PEP) immediately after unsafe sex makes safe sex less important"). The remaining 11 statements were

subjected to focus group testing with ten Ugandan women to assess the interpretability of the scale statements in this setting. The statements were translated and back-translated from English to Runyankole, and were checked for cultural appropriateness and understanding by women of varying levels of formal education. After focus group testing, the language used for each statement from Van de Ven's scale was changed slightly to render it more understandable by women with lower levels of education. For instance, the term "undetectable viral load" was replaced with "a very small amount of virus". An additional 12 statements were developed from a literature review and from the results of related qualitative interviews with Ugandan women and three clinic staff members. These interviews were conducted to assess content and face validity.

The final list included 23 statements and incorporated a four-point response format. Respondents were asked to indicate how much they agreed or disagreed with each of the 23 statements. Responses to each statement were scored from 1 (Strongly Disagree) to 4 (Strongly Agree), with some questions requiring inversion. The complete list of statements is shown in Table 6.3.

Measuring fertility intentions and sexual behaviour

In order to assess the potential influence of HAART optimism on fertility intentions and sexual behaviours, the following three measures were included in the questionnaire.

The first outcome of interest was fertility intention. Fertility intention was assessed by answers to the question "Are you planning to have any (more) children in the future?''

The second outcome of interest was sexual activity/sexual abstinence in the previous three months. This variable was specific to vaginal intercourse.

The third outcome of interest was unprotected sexual activity (i.e., vaginal intercourse without a condom) in the previous three months. This analysis was restricted to women who reported being sexually active in the previous three months.

6.2.6 Data analysis

Univariate analyses of the baseline characteristics of the study population was conducted, including socio-demographic and clinical variables. Categorical

variables are presented as frequencies and percents while continuous variables are presented as medians and interquartile ranges [IQRs].

Factor analysis

The entire dataset was subjected to a principal components and factor analysis to identify which of the 23 statements best expressed the construct of HAART optimism. The principal components analysis served as a data reduction method (i.e., to reduce the number of variables in the scale) [37].

The principal components were extracted via variance maximizing (i.e., varimax) whereby the lines on which the variance was maximal was identified, with each line representing a factor. Because each consecutive factor was defined to maximize the variability not captured by the preceding factor, consecutive factors were independent of each other. However, each consecutive factor accounted for less and less variability. Extraction of factors was stopped when there was only very little random variability left. The assumptions of varimax rotation were assessed using a non-orthogonal rotation (i.e., oblimin) [37]. Items with loadings above 0.40, with no or few item cross-loadings, and no factors with fewer than three items were retained.

A correlation matrix was constructed where the variances of all items were equal to 1.0. In this way, the total variance in the matrix was equal to the number of

items (i.e., 23). Eigenvalues were calculated, representing the variance explained for each of the 23 items considered in the factor analysis. The eigenvalues were then expressed as a percent of the total variance. To select factors, the Kaiser criterion was applied, which states that only factors with eigenvalues greater than one are retained [38]. As the Kaiser criterion is a less conservative method for retaining factors, the scree test was also used to determine how many factors to maintain [39]. The scree test is a graphical method used to plot the eigenvalues. The point on the plot where the smooth decrease of the eigenvalues appears to level off was located. The "factorial scree" is found to the right of this plot, meaning that the primary factors are found to the left of that point. The information from both the Kaiser criterion and the scree test was combined and factor interpretability was also considered in indentifying which factors to maintain.

After identifying the primary factors, the squared multiple correlation of an item with all other items was used to estimate the communalities for each variable in the factor [37].

Cronbach's alpha (standardized) is reported to demonstrate the internal reliability of each of the identified factors. While a scale is generally considered reliable if the Cronbach's alpha coefficient is equal to or greater than 0.70 [40], for exploratory studies such as this one, a coefficient of ≥ 0.60 is considered acceptable

[41]. In addition, Pearson's correlation coefficient was used to calculate an item-specific correlation for each scale. A correlation exceeding 0.40 was considered satisfactory correlation of items within the scale [42]. We expected reliability coefficients (i.e., Cronbach's alpha) to exceed inter-scale correlations for the same scale.

For the factor of primary interest identified from this analysis (i.e., that identifying "HAART optimism"), the mean, standard deviation, median, and interquartile range of the scores were calculated for descriptive purposes.

Testing the association between the derived HAART optimism scale and fertility intentions and sexual behaviour outcomes

To assess scale validity, the association between the derived HAART optimism scale and fertility intentions, sexual activity, and unprotected sexual intercourse was tested using the Wilcoxon rank sum test. The associations are reported using a crude odds ratio (OR) with a 95% confidence interval (95% CI).

6.2.7 Ethical considerations

All participants provided informed consent and all procedures were approved by the *Faculty of Medicine Research and Ethics Committee* and the *Institutional Ethics Review Board* of Mbarara University, the Uganda National Council on Science and Technology, and the University of California, San Francisco Committee on Human Subjects. Study investigators only had access to de-identified data.

6.3 RESULTS

6.3.1 Recruitment

A total of 540 women completed the questionnaire. Of these, 49% were HAART users with a median duration of HAART use of 15 months [IQR: 11-25 months].

6.3.2 Baseline characteristics

Distributions of baseline characteristics are presented in Table 6.1. As shown, the median age was 34 years [29-39 years]. Overall, the majority of women had a primary school education or less (66%), belonged to the Kiga/Nkole tribe (81%), and

were Christian (88%). Only 39% of the women were married, 30% were widowed, 23% were separated or divorced, and 8% were single. Two-thirds (66%) had a monthly household income less than 80,000 UGX (approximately $50 USD). The median number of lifetime livebirths was 3.0 [IQR: 2-5]. Most of the women had advanced HIV disease with 62% presenting in WHO Disease Stage III or IV and 35% reporting a most recent CD4 cell count less than 200 cells/mm^3 (of those with non-missing responses).

6.3.3 Factor analysis

The eigenvalues of the correlation matrix for all 23 statements are shown in Table 6.2. The Kaiser criterion results revealed that seven factors (with eigenvalues greater than one) accounted for 55% of the cumulative variance. Figure 6.1 plots the results of the scree test. As shown, the factorial scree occurs at the third factor indicating that the analysis identified three primary and distinct factors. We used varimax rotation to assess the change in grouping of the loadings in each factor. The factorial scree identified factors that were each highly interpretable based on the contributing items. The variance accounted for by these three factors was 34%.

Based on the eight statements that comprised factor 1, the factor was labeled "HAART optimism". Included in this factor were statements about HAART-related

optimism/skepticism regarding HIV transmission to sexual partners and to unborn children through vertical transmission. The second factor comprised four items and was labeled "State of the epidemic". This factor included items related to changing opinions about the course of the HIV epidemic. The third factor was labeled "Trust of Information" about the epidemic from health care professionals and was made up of four items. Together, the communality between these three factors was 77%, with the first factor accounting for 32% of the communality, the second factor accounting for 25% and the third factor accounting for 20%. The total communality explained by these three factors did not change after varimax or oblique rotation.

The first factor, that identifying 'HAART optimism', was of primary interest to this study. This factor included eight statements (shown in Table 6.3), none of which were considered duplicates of one another. This factor, referred to as the derived HAART optimism scale, had moderately high internal consistency, with Cronbach's alpha = 0.70 in the overall sample. The item-total correlations ranged from 0.33 to 0.50 for the 8-item analysis (Table 6.4).

In the overall sample, the derived 8-item HAART optimism scale had a mean of 11.7 [SD=4.2] and a median of 11 [IQR: 8-13], with a possible range from 8 (indicating high skepticism) to 32 (indicating high optimism).

6.3.4 Association between the derived HAART optimism scale and fertility intentions

Overall, 14% of women reported that they intended to have (more) children. Women who intended to have (more) children had significantly higher HAART optimism scores (median=13.5 [IQR:12-16]) than women who did not intend to have (more) children (median=10.5 [IQR:8-12]) ($p<0.0001$).

6.3.5 Association between the derived HAART optimism scale and sexual activity in the previous three months

We found that overall, 45% of women reported being sexually active in the previous three months. Women who reported being sexually active in the previous three months had significantly higher HAART optimism scores (median=11 [IQR: 8-14]) than women who were sexually abstinent (median=11 [IQR: 8-13]) ($p=0.0206$).

6.3.6 Association between the derived HAART optimism scale and unprotected sexual activity in the previous three months

Of women who reported being sexually active in the previous 3 months (n=241), 49% reported practicing unprotected sex. Women who reported practicing

unprotected sex had significantly higher HAART optimism scores (median=12 [IQR: 9-15]) than women who practiced protected sex (median=11 [IQR:8-13]) (p=0.0157).

6.4 DISCUSSION

This study developed a culturally appropriate eight-item HAART optimism scale that demonstrated moderately high reliability when applied to HIV-positive women in Uganda. The new scale incorporates concerns related to pregnancy and vertical transmission, in addition to those related to HIV transmission risk to sexual partners and severity of HIV disease. We have termed this new scale the *Women's HAART Optimism Monitoring and EvaluatioN scale*, or the WHOMEN's scale, version 1.

As evidenced from the new scale, overall women expressed low HAART optimism with 75% reporting a HAART optimism score of 13 or lower, out of a possible range from eight (highly skeptical) to 32 (highly optimistic). This suggests that women are still very cautious about the use and effectiveness of HAART on lowering risk of HIV transmission and believing that HIV infection is less of a threat to their health and survival. This finding is consistent with other research which suggests that individuals with high HAART optimism tend to be a minority within the population under study [36, 12, 10, 24, 43].

There is evidence that the brief and reliable WHOMEN's scale has validity since women who report an intention to have (more) children have significantly higher HAART optimism than their counterparts who do not intend to have (more) children. Similarly, women who are currently sexually active and who practice unprotected sex have significantly higher HAART optimism scores than their counterparts who are sexually abstinent and who practice protect sex. It should be noted, however, that despite statistically significant differences between groups, the absolute difference in HAART optimism scores between groups was small.

Availability of HAART in Uganda has been relatively recent and it is unclear whether HAART optimism will change over time as HAART becomes more widely available. While a trend of increasing HAART optimism over time has not been noted in MSM populations [44], it remains to be seen whether the same trend will occur for women in terms of altering their reproductive intentions and sexual behaviour.

Fertility intentions and sexual behavior among HIV-positive women are, of course, mediated by a number of factors beyond simply HAART optimism [45, 24, 46]. From qualitative interviews with heterosexual women living with HIV and on HAART in Brazil, Kerrigan et al (2006) report that none of the women connected their recent sexual behaviors to HAART optimism [24]. Interestingly, heterosexual

men in the same study tended to report fertility intentions as a reason for not wanting to use condoms. No peer-reviewed studies were identified which have investigated gender differentials in HAART optimism and how this might influence reproductive and sexual behaviours. This type of research, explored in a longitudinal fashion, appears warranted.

It remains to be determined whether these findings are generalizable to women in other high HIV prevalence settings. Future studies should test the reliability and validity of the scale in other settings and construct multivariate analyses to determine the relative importance of HAART optimism vs. other factors (such as HAART use) in influencing fertility desires [29].

The limitations of this study must be acknowledged. First, the cross-sectional nature of this analysis precludes us from determining causality. The direction of causality should be interpreted with particular caution since it has been suggested that high HAART optimism may follow risky sexual behaviors, rather than precede them [21]. This finding may be of particular importance to women and fertility intentions since those who intend to have (more) children may be more likely to be optimistic about HAART. Despite the cross-sectional association, our findings offer important information on the association between HAART optimism and fertility intentions and sexual behaviours that may have important implications for HIV

prevention, family planning, and PMTCT programming, particularly as HAART access expands in high HIV prevalence settings. Second, there is a risk of social desirability bias whereby women may falsely report their optimism about HAART because they have been educated about HIV transmission and counseled to avoid pregnancy. If false reporting was differential, with those reporting fertility intentions, for instance, more likely to report falsely report HAART skepticism, then our effect estimates are likely somewhat inflated. During the data collection process we took precautions against reporting bias by including standardized questions and using non-clinic staff to conduct the interviews. Third, the associations provided here are crude. Future studies should investigate the reliability and validity of the WHOMEN's scale on different data sources and conduct multivariate analyses to assess the role of potential confounders in mediating the association between HAART optimism and women's fertility intentions and sexual behaviours.

Despite these limitations, our brief, reliable, and valid scale, termed the *Women's HAART Optimism Monitoring and EvaluatioN scale* (WHOMEN's scale), may be valuable to broader studies investigating the role of HAART optimism on reproductive intentions and sexual behaviours of HIV-positive women in high HIV prevalence settings.

Table 6.1: Characteristics of study population of HIV-positive women in Mbarara, Uganda (n=540)

Variable	N	%
Median Age [IQR]	34 [29-39]	
Education		
Primary school or less	356	66%
Secondary school and higher	184	34%
Tribe		
Kiga/Nkole	438	81%
Other	102	19%
Religion		
Christian	475	88%
Other	65	12%
Marital Status		
Currently Married	209	39%
Divorced/Separated	125	23%
Widowed	164	30%
Single	42	8%
Household Income (per month)§		
0 – 20,000 UGX	166	32%
20,001 – 80,000 UGX	178	34%
80,001+ UGX	181	34%
Median Lifetime livebirths [IQR]	3.0 [2.0-5.0]	
Most recent CD4 Count		
< 50	45	8%
50-199	91	17%
200-499	147	27%
500+	63	12%
Missing	155	29%
WHO Stage¥		
Stage 1 or 2	188	38%
Stage 3 or 4	313	62%
Current HAART use		
Yes	263	49%
No	277	51%

Notes: SD = Standard Deviation.
IQR = Interquartile Range.
§ 3% of participants did not report household income.
¥ 7% of participants did not have information on WHO Stage of Disease.

Table 6.2: Principal component Factor analysis of 23 statements about HAART

Factor	Eigenvalue	Difference	% of Total Variance	% Cumulative Variance
1	3.37	0.75	14.6	14.6
2	2.62	0.87	11.4	26.0
3	1.74	0.36	7.6	33.6
4	1.38	0.08	6.0	40.0
5	1.30	0.11	5.6	45.2
6	1.18	0.12	5.1	50.4
7	1.06	0.07	4.6	55.0
8	0.99	0.08	4.3	59.3
9	0.91	0.07	4.0	63.3
10	0.84	0.05	3.7	67.0
11	0.79	0.02	3.5	70.4
12	0.78	0.03	3.4	73. 8
13	0.74	0.02	3.2	77. 0
14	0.72	0.07	3.2	80.1
15	0.66	0.06	2.9	83.0
16	0.60	0.04	2.6	85.6
17	0.56	0.01	2.4	88.0
18	0.55	0.02	2.4	90.4
19	0.53	0.02	2.3	92.8
20	0.51	0.03	2.2	95.0
21	0.48	0.08	2.1	97.0
22	0.39	0.10	1.7	98.7
23	0.29		1.3	1.00

Table 6.3 Items with Principal Components Varimax Factor Loadings				
Item Number	**Item**	**Factor 1 (HAART optimism)**	**Factor 2**	**Factor 3**
21	It would be OK to stop HIV medicines if they made me sick, especially if I were pregnant.	**0.700**	0.057	-0.033
13	I believe that new drug therapies make people with HIV less able to pass the virus to other people.	**0.697**	0.100	0.054
19	If my partner and I were both on HIV treatments, it would be OK to stop using condoms.	**0.603**	0.121	0.074
1	A person with virus that has been turned off in the body (a very small amount of virus in the body) cannot pass the virus to someone else	**0.543**	-0.030	-0.077
7	People with a very small amount of virus in the body don't need to worry about infecting others with HIV.	**0.499**	-0.034	-0.195
6	If a cure for AIDS were announced, I would stop practicing safe sex (abstinence, being faithful, or using a condom).	**0.491**	-0.006	0.118
15	I am not worried about becoming pregnant because of available HIV treatments.	**0.460**	0.036	-0.120
22	Now that HIV medicines are available, I want to have a baby because I will live long enough to raise a child.	**0.448**	-0.058	0.062
10	HIV/AIDS is a less serious threat than it used to be because of new treatments.	0.102	**0.783**	0.218
9	HIV is less of a threat because the epidemic is on the decline.	0.196	**0.722**	0.095
14	I am less worried about HIV infection now that treatments have improved.	0.002	**0.720**	0.119
3	I'm less worried about HIV infection than I used to be.	-0.198	**0.570**	-0.181
18	I think the risks of HIV transmission with "safer sex" (using abstinence, being faithful, and using condoms) are less than what doctors say.	0.013	0.129	**0.751**
4	New HIV treatments will take the worry out of sex.	0.318	0.087	**-0.691**
17	I think the risks of HIV transmission in pregnancy are less than what doctors say.	0.206	0.136	**0.645**
2	A person's CD4 count will remain about 200 (at a safe level) if they stay on therapy.	-0.028	0.056	**0.463**
5	If every HIV positive person took the new treatments, the AIDS epidemic would be over.	0.231	0.252	0.076
8	Until there is a complete cure for HIV/AIDS, prevention is still the best practice. (reverse scored)	0.301	-0.382	0.053
11	It's never safe to have sex without a condom regardless of the amount of virus in the body. (reverse scored)	0.247	-0.243	0.143

12	Because of new treatments, fewer people are becoming infected with HIV.	0.316	0.369	0.253
16	If I become pregnant, I would be worried about passing HIV on to my baby, even if I were taking HIV treatments. (reverse scored).	0.104	0.112	0.017
20	HIV treatments/medicines could be harmful during pregnancy because of possible birth defects. (reverse scored).	-0.247	-0.028	0.257
23	I am worried that HIV medicines could cause AIDS. (reverse scored)	-0.273	-0.038	0.081

Table 6.4: Statements constituting the derived HAART optimism scale for use among HIV-positive women of reproductive age living in developing countries

Question: Considering the new medicines available to treat HIV, please tell me how much you agree or disagree with the statements I read to you. Do you Strongly Agree, Agree, Disagree, or Strongly Disagree with the statement?	
Statement	**Corrected item-total correlation**
It would be OK to stop HIV medicines if they made me sick, especially if I were pregnant. (inverted)	0.53
I believe that new drug therapies make people with HIV less able to pass the virus to other people.	0.50
If my partner and I were both on HIV treatments, it would be OK to stop using condoms.	0.45
A person with virus that has been turned off in the body (a very small amount of virus in the body) cannot pass the virus to someone else.	0.36
People with a very small amount of virus in the body don't need to worry about infecting others with HIV.	0.34
If a cure for AIDS were announced, I would stop practicing safe sex (abstinence, being faithful, or using a condom).	0.33
I am not worried about becoming pregnant because of available HIV treatments.	0.35
Now that HIV medicines are available, I want to have a baby because I will live long enough to raise a child.	0.35

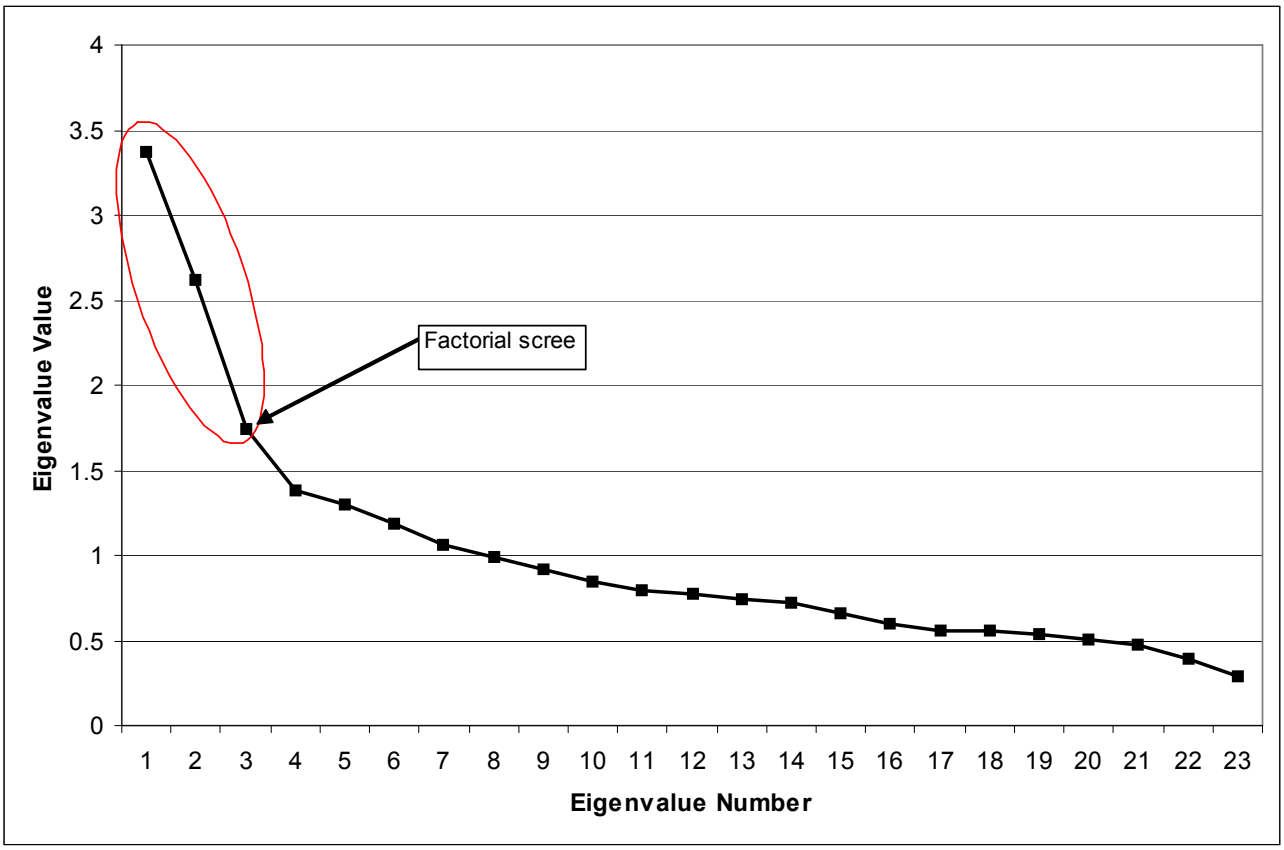

Figure 6.1: Results of the scree test

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CHAPTER 7:

SUMMARY, CONTRIBUTIONS, RECOMMENDATIONS, FUTURE RESEARCH, AND CONCLUSION

7.1 Summary of Objectives

The objectives of this thesis were: (1) to review the literature describing the potential impact of highly active antiretroviral therapy (HAART) on fertility in sub-Saharan Africa; (2) to assess whether the prevalence of recent sexual intercourse (and sexual abstinence) varied according to use of HAART among HIV-positive women of reproductive age from Brazil, South Africa, and Uganda; (3) to assess whether the prevalence of fertility intentions varied according to HIV status and use and duration of HAART among women in Soweto, South Africa; (4) to assess whether the prevalence of contraceptive use and method mix varied by HIV status and use and duration of HAART among women in Soweto, South Africa; and (5) to develop a reliable HAART optimism scale for use among HIV-positive women and to test the scale's validity against measures of fertility intention, sexual activity, and unprotected sexual intercourse among HIV-positive women in Mbarara, Uganda. All analyses were conducted within an over-arching framework that recognizes and supports the sexual and reproductive rights of people living with HIV [1].

7.2 Summary of Findings

My PhD dissertation research makes an important and lasting contribution to the emerging literature regarding the impact of expanding access to HAART on sexual and reproductive health decision-making and behaviours of HIV-infected and -affected women in high HIV prevalence settings in sub-Saharan Africa.

At the beginning of this thesis, I conducted a review of the available literature pertaining to the known and potential impacts of expanding access to HAART on the fertility of HIV-positive women in sub-Saharan Africa. As presented in **Chapter 2** (and published in *Current HIV/AIDS Reports* in 2006) [2], the review revealed that while a plethora of studies have examined the impact of HIV infection on fertility, there were limited empirical findings regarding the impact of increased HAART availability. Thus, the review was extended to use Bongaarts' proximate determinants of fertility framework (adapted for conditions of generalized HIV epidemics) [3, 4] to examine how use of HAART may mediate the impact of HIV infection on fertility through its biological and behavioural proximate determinants. Based on this examination, a conceptual framework (Figure 2.1) was proposed to guide hypothesis generation and subsequent investigations aimed at understanding how expanding access to HAART may impact the proximate determinants and ultimately fertility of HIV-positive women in sub-Saharan Africa. This published

framework formed the basis of the theoretical paradigm that I used to frame the objectives and hypotheses in the following chapters of my dissertation.

Chapters 3 to 6 examine relationships between receipt of HAART and several key determinants of fertility as outlined and prioritized in the conceptual framework including, sexual activity (Chapter 3), fertility intentions (Chapter 4), contraceptive use and method mix patterns (Chapter 5), and HAART optimism (Chapter 6).

Chapter 3, published in *AIDS Care* in 2008 [5], presents the results of a pilot study which examined the prevalence of recent sexual activity among cohorts of HIV-positive women in three global settings (Rio de Janeiro, Brazil; Soweto, South Africa; and Mbarara, Uganda) and whether sexual activity varied by current HAART use. The findings indicated that overall less than half (46%) of HIV-positive women reported recent sexual intercourse (defined as vaginal intercourse in the previous month). In adjusted analyses, sexual activity was not associated with receipt of HAART in the overall sample or in country-specific models. It was, however, positively associated with a measure of "HAART optimism", suggesting that being optimistic about the effect of HAART on reducing HIV transmission risks and reducing threats to health and survival may be a better predictor of sexual behaviour than actual receipt of HAART. This early finding prompted further

examination of HAART optimism among HIV-positive women and led to the development and testing of the HAART optimism scale presented in Chapter 6.

Chapter 3 also revealed that while HAART use wasn't associated with recent sexual activity, it was positively associated with other sexual behaviours including contraceptive use and practicing protected sex (i.e., consistent condom use). Despite a limited sample size, the findings from the pilot study highlighted the importance and feasibility of further investigating the role of receipt of HAART on sexual and reproductive behaviors among women in high HIV prevalence settings. Subsequently, larger fertility-related studies were developed and implemented in all three sites included in the pilot study. The analyses in Chapters 4 and 5 emerged from the study that I developed and led in collaboration with the Perinatal HIV Research Unit (PHRU) in Soweto, South Africa while the analyses in Chapter 6 emerge from a study led by investigators at Harvard Medical School and the Mbarara University of Science and Technology in Mbarara, Uganda.

Chapter 4, in press at the *American Journal of Public Health* [6], reveals that the adjusted odds of fertility intentions of HIV-positive women in Soweto are 60% lower than those of HIV-negative women, and this difference is largely irrespective of use and duration of HAART. This finding contrasts with those from other sub-Saharan African sites, which showed an increased likelihood of fertility intentions among

HIV-positive women receiving HAART compared with HAART-naïve women [7, 8]. The observed lack of association between HAART use and fertility intentions in Soweto may relate to the nature of HAART and HIV care services at the PHRU. Namely, HAART has been available at the PHRU since July 2004, nearly three years longer than at government clinics in South Africa [9] and at least two years longer than many sub-Saharan African settings [10]. The lack of association between HAART use and fertility intentions noted in this study may reflect an emerging reality that HIV-positive women who are not yet receiving HAART can be confident that treatment is available once they are medically eligible, thereby minimizing differences in fertility goals between groups.

This analysis also highlighted that while stated fertility intentions of HIV-positive women are significantly lower than HIV-negative women, they are not negligible. Nearly one-third of HIV-positive women reported intention to have (more) children, a proportion that increased significantly by younger age and fewer living children. These findings speak to the urgent need for policies and services that support HIV-positive women to achieve their reproductive goals in the healthiest and safest possible manner. It is similarly critical that effective, non-coercive, and non-judgmental family planning services be available to the 70% of HIV-positive women who reported that they do not intend to have (more) children.

The results in Chapter 4 also reveal that over two-thirds of HIV-negative women intend to have (more) children. In many regions of sub-Saharan Africa, HIV incidence and prevalence are highest among young women in their peak reproductive years. In South Africa in particular, HIV prevalence peaks among women in the 25-29 year age group among whom fully one-third have acquired HIV infection [11]. The substantial fertility intentions of HIV-negative women, viewed within the existing conflict between the unprotected sexual activity required for conception and the risk of HIV acquisition from sexual partners with unknown or known HIV-positive status, demands consideration of targeted reproductive health services to minimize their risks of HIV acquisition through realization of their reproductive goals.

Chapter 5, currently under review, describes the prevalence of contraceptive use and associations with HIV status and HAART use among sexually active women in Soweto, South Africa. Overall, a high proportion of women reported using contraception (78%) with significant variation by HIV status and use of HAART. In adjusted models, compared with HIV-negative women, women receiving HAART were significantly more likely to use contraception while HAART-naïve women were marginally more likely (AOR: 2.40; 95% CI: 1.25-4.62 and AOR: 1.59; 95% CI: 0.88-2.85, respectively). These findings are broadly consistent with the results from the pilot study presented in Chapter 3 and results

from a paper that I co-authored from the Mbarara study [12]. Although receipt of HAART was positively associated with contraceptive use, there was no association between increasing duration of HAART use and contraceptive prevalence.

Chapter 5 also highlights the important differences in the types of contraceptive methods used by women based on HIV status and receipt of HAART. Such data are severely lacking in the literature. The results show that not only were HAART users significantly more likely to use contraceptive methods overall, they were more likely than HAART-naïve and HIV-negative women to use dual protection (defined as use of both a barrier method (primarily the male condom) and a hormonal or permanent contraceptive method [13]). Women on HAART also reported the highest prevalence of consistent condom use (with or without other methods). Indeed much of the difference in contraceptive prevalence between the three groups was accounted for by the significantly lower prevalence of condom use among HIV-negative women. Compared with HAART-naïve women, HAART users were more likely to use hormonal contraception, and uptake of injectables exceeded oral contraceptive use. Collectively, these results suggest that the regular care, counseling and support associated with HIV care and treatment is contributing to contraceptive uptake among HIV-positive women in this setting. These findings highlight the great potential and on-going need for improved integration of HIV

testing, treatment, and care services with sexual and reproductive health services, including the provision of contraceptive options.

In **Chapter 6**, published in *AIDS and Behavior* in 2009 [14], I developed a reliable and culturally-appropriate HAART optimism scale among HIV-positive women in Mbarara, Uganda and tested the scale's validity against measures of fertility intentions, sexual activity, and unprotected sex. Uniquely, the scale incorporates measures of optimism about becoming pregnant and risks of vertical transmission of HIV, both of which are absent from previously validated and available HAART optimism scales. Overall, HIV-positive women in Mbarara expressed a low level of HAART optimism, with a median score of 11 [IQR: 8-13], out of a possible range from eight (highly skeptical) to 32 (highly optimistic). This suggests that women in this setting remain cautious about the use and effectiveness of HAART on lowering risk of HIV transmission and believing that HIV infection is less of a threat to their health and survival. Nonetheless, higher HAART optimism scores were positively associated with fertility intentions, recent sexual activity, and risky sexual behaviour. These findings constitute an important progression from the relationships explored in previous chapters and suggest that among HIV-positive women with access to HIV treatment services, optimism about the effect of HAART on improving health and reducing transmission risks may be as or more important than actual receipt of HAART. This scale was termed the Women's HAART

Optimism Monitoring and EvaluatioN scale (WHOMEN's scale v.1) and is currently being incorporated into other studies aimed at investigating the role of HAART optimism on influencing sexual and reproductive behaviours of HIV-positive women in settings with generalized HIV epidemics.

Together, the evidence provided here suggests that HIV-positive women receiving HAART are more likely to use contraception overall and dual protection in particular, with minimal differences in fertility intentions or rates of sexual activity, relative to their HAART-naïve counterparts. Indeed, optimism about the effects of HAART, rather than actual use or non-use, appears to be more strongly associated with fertility intentions and sexual activity of HIV-positive women. In addition, there remain important differences in sexual and reproductive decision-making and behaviours by HIV serostatus. Namely, HIV-positive women are significantly less likely to report fertility intentions and significantly more likely to use contraception (and condoms in particular) relative to HIV-negative women from the same community.

These empirical findings are at times inconsistent with the hypothesized effects of HAART described in the conceptual framework (Figure 2.1). It must be noted that the conceptual framework was developed by reviewing literature from the very early days of HAART scale-up initiatives in sub-Saharan Africa. Since then the scale-

up process has been dramatic; in 2008, an estimated 2.9 million people in the region were receiving antiretroviral therapy, a 30-fold increase since the end of 2003 [15]. Thus, early findings and initial hypotheses about the effects of HAART use on the proximate and underlying determinants of fertility may be incomplete, as they were indirectly predicated on the novelty and anticipated scarcity of HAART availability. Moreover, the role of increased regular contact with health care, support, and counseling services as a function of the clinical follow-up required to monitor the health of individuals receiving therapy was not adequately considered in the development of the conceptual framework. While the framework addressed the actual receipt or non-receipt of HAART at the individual-level, the findings presented here suggest the level of availability and accessibility of HIV treatment services in a given community and the role of HAART optimism may be additionally relevant variables. Thus, while the framework remains a useful tool to help guide future research regarding the impact of HAART on fertility and its determinants, current work is underway to update it to include recently available empirical findings.

Nonetheless, the findings of this thesis collectively reveal the critical need and great value of improved integration of HIV testing, treatment, and care services with reproductive and sexual health programming to address the diverse reproductive

and sexual needs of HIV-infected and affected women living in HIV endemic settings with expanding access to HAART.

7.3 Unique Contributions

The strengths and limitations of this research project have been detailed in each of the study chapters (2-6). However, taken collectively, the research papers yield several unique contributions to the literature worth highlighting.

An important and lasting contribution of this research lies in its assessment of the impact of HAART on the sexual and reproductive health of women in settings experiencing highly feminized, generalized epidemics. It has been argued that approaches to addressing the HIV epidemic in sub-Saharan Africa have been too heavily weighted on experiences and policies from countries where the disease affects particular "risk groups" [16]. The review in Chapter 2 also cautioned against generalizing findings about the impact of HAART on fertility in North American and European settings to sub-Saharan Africa given great differences in the epidemiology of the epidemic and the cultural, economic, social, and gender dynamics that influence the context of reproductive decision-making between the two settings. Fittingly, this thesis revealed novel patterns of the impact of HAART access on sexual and reproductive health that differed from those previously

described in settings not experiencing generalized HIV epidemics.

This thesis also yielded the first reliable and validated HAART optimism scale developed to measure HAART optimism among HIV-positive women in high HIV prevalence settings. Uniquely, the scale incorporated concerns related to pregnancy and vertical transmission of HIV, neither of which was included in previously validated scales. Among HIV-positive women higher HAART optimism was shown to be associated with fertility intentions and sexual behaviours, regardless of actual receipt of HAART. As HAART access continues to rapidly expand in high HIV prevalence settings, this finding suggests a critical need to address perceptions and beliefs about HAART within HIV prevention messaging in the general community, not just among those accessing treatment services.

Although the primary interest of this thesis was to investigate the impact of expanding access to HAART among HIV-positive women, this thesis included comparisons with HIV-negative women from the same community. No other published studies were identified that considered information across all three groups. The study findings revealed important differences and trends in reproductive and sexual health by HIV status and receipt of HAART. It was also possible to document the concerning context of reproduction for HIV-negative women in high HIV prevalence settings. As shown in Chapters 4 and 5, HIV-

negative women were unlikely to know the HIV status of their primary sexual partner, the most likely to report fertility intentions, and the least likely to use contraceptive methods overall, and condoms in particular (compared with their HIV-positive counterparts). This study highlighted the critical need to prioritize efforts to keep HIV-negative women negative and the important role of sexual and reproductive health programming in supporting HIV-negative women to safely fulfill their reproductive goals while minimizing their risks of HIV acquisition.

This thesis yielded an opportunity to incorporate findings across two diverse high-needs settings. South Africa and Uganda represent important and appropriate countries within which to investigate the impact of HAART on sexual and reproductive health. As one of the first countries to experience and document a high prevalence of HIV, Uganda is now one of few countries to have shown a sustained decreased HIV prevalence over the last decade from 18% in the mid 1990s to 6.7% today [17]. In contrast, HIV prevalence in South Africa remains stable at 19% [11]. The relative difference in HIV prevalence is also critical in absolute terms. There are an estimated 400,000 women living with HIV infection in Uganda compared with approximately 3.2 million in South Africa. Similarly, while antiretroviral coverage is currently comparable in the two countries (approximately one-third of HIV-positive individuals who need treatment are receiving it) [10], the scale of existing and required treatment services is markedly different. Recent estimates report that over

700,000 HIV-positive South Africans are receiving treatment compared with 140,000 Ugandans [10]. While fewer women are living with HIV in Uganda compared with South Africa, the total fertility rate of Uganda is over three times greater (TFR = 6.7 in Uganda; TFR = 2.0 in South Africa) [19].

These differences in HIV, HAART access, and fertility profiles enabled consideration of the relative ways in which HAART may influence sexual and reproductive health decision-making, behaviours, and outcomes and highlight the great differences in the nature and scale of required sexual and reproductive health programming for HIV-positive women in the two countries. In addition to the fertility intentions and contraceptive use papers presented in Chapters 4 and 5 based on data from Soweto, I co-authored two related papers on the impact of HAART among HIV-positive women in Mbarara, Uganda [8, 12]. While there was no HIV-negative comparison group in the Uganda study, we found that there were important differences in the overall prevalence of fertility intentions among HIV-positive women between the two sites (30% of HIV-positive women in Soweto expressed fertility intentions compared with 15% of women in Mbarara) yet similar rates of overall contraceptive use (84% and 85% of HIV-positive women in Soweto and Mbarara, respectively). In addition, receipt of HAART was associated with significantly increased fertility intentions in Mbarara but not in Soweto, and with contraceptive use in both settings. Engaging in investigations across these two sites

has offered a unique opportunity to highlight that sexual and reproductive decision-making and behaviours of HIV-positive women are likely to vary across settings and, to be effective, the required corresponding sexual and reproductive health programming must similarly consider these differences.

The opportunity to work with collaborators across sites yielded an additional unique contribution of this thesis with respect to knowledge translation and dissemination activities. Upon publication, the early findings of this research endeavour contributed to a growing interest in investigating the impact of HAART on sexual and reproductive health and fertility. Our group of research collaborators felt it was important to share these early research findings with a broader community of stakeholders such that more nuanced methodologies, analyses, and interpretations could be developed. As such, in collaboration with investigators from the Perinatal HIV Research Unit in Soweto, the BC Centre for Excellence in HIV/AIDS, Harvard Medical School, Simon Fraser University, and the University of British Columbia, I co-chaired a public forum and research conference held in Soweto between April 21st-23rd, 2008 entitled: *Switching gears in HIV research: Building an international agenda on the impact of highly active antiretroviral therapy (HAART) on fertility in sub-Saharan Africa* [20]. The purpose of the conference was to foster international knowledge exchange on emerging research and policy priorities related to reproductive and sexual health, fertility decision-making, and fertility of

HIV-positive individuals, during a time of expanding access to HAART. The event brought together internationally renowned HIV/AIDS and reproductive and sexual health stakeholders, including researchers, clinicians, policy-makers, community activists, and representatives of international development and health research funding agencies. The conference and the presented papers functioned to raise the profile of sexual and reproductive health issues in the context of expanding access to HAART and provided an opportunity to contribute to knowledge translation activities. Chapters 2 and 4 of this dissertation were shared at this conference to solicit feedback and to discuss implications of the findings.

As the conference drew to a close, it became clear that although exciting and important research was being conducted in the region, there was a dearth of published literature available. As such, a commitment was advanced to support local researchers and conference delegates to develop their research findings into manuscripts and to circulate a broader international call for related papers on the topic of HIV, HAART, and fertility in sub-Saharan Africa. The end result of this commitment was a published supplement edition of the journal *AIDS and Behavior* (published in print in July 2009) [21]. I was the lead Guest Editor for the supplement. The supplement provides an array of research findings from across the region to be used towards the design and implementation of evidence-based reproductive and sexual health policies and programs that support women, their families, and their

communities in reproductive decision-making in the context of HIV. The engagement of a larger community of stakeholders, particularly women living with HIV/AIDS in sub-Saharan Africa, greatly strengthened the interpretation and local relevance of the research findings presented here.

7.4 Recommendations

Each of the study chapters provides recommendations for policy and programming specific to each research finding; however, there are several recommendations worth highlighting upon considering the cumulative evidence presented here.

First, all women, including women living with HIV, should be supported to achieve their reproductive goals in the healthiest and safest possible manner [1]. Given the high prevalence of fertility intentions among HIV-positive women, it is critical that factual and non-stigmatizing information and support be incorporated into HIV treatment services to optimize sexual and reproductive outcomes for mother, father, and baby. This includes counseling services regarding use of HAART during pregnancy, safer labour options, accessible and comprehensive PMTCT services, antenatal and postnatal care, and support for safer infant feeding practices. No clear guidelines exist to support HIV-affected couples in limited-

resource settings who want to become pregnant to do so safely and this information is urgently needed. In particular, HIV-affected women require and have requested information regarding the ideal time for pregnancy with respect to CD4 level, stage of treatment, treatment regimen, viral load, and the HIV- and health-status of her sexual partner [22]. Without this information and support, HIV-affected couples may knowingly risk transmission in order to conceive, unaware that there are a range of strategies to mitigate the risk of infection. More must be done towards adopting a harm reduction approach to fertility counseling in resource-limited settings to minimize risk of HIV transmission between sero-discordant couples [23].

Since a substantial proportion of women do not want to have more children, it is also critical that effective, non-judgmental, and non-coercive family planning services (including access to termination of pregnancy services) are available to all women who need them. As shown in the contraceptive use paper, the higher prevalence of contraceptive use overall and dual protection methods in particular among women receiving HAART highlights a critical opportunity to assist women living with HIV/AIDS prevent unintended pregnancy and prevent HIV transmission. Overall, more work must be done on the provision of contraceptive options to close the gap between reported fertility intentions and fertility.

This work also highlights the great need for integration of HIV services with sexual and reproductive health services [24]. Integration is critical to support the clearly intertwined sexual and reproductive needs of HIV-affected women living in the context of generalized epidemics. Moreover, integration is also of operational value since it holds potential to reduce service duplication and could help reduce the stigma of accessing separate HIV services. Globally, an inspiring degree of effort and resources are currently being directed towards the critical need to expand access to HIV treatment services [10]. The additional expenditure associated with incorporating family planning services represents a highly cost-effective means of reducing unintended pregnancies and further minimizing vertical and horizontal HIV transmission, thus contributing to healthier individuals and families in HIV endemic regions [25].

Finally, the findings presented here have particular relevance to pioneering "Treatment as Prevention" strategies, which aim to curb HIV transmission through early, sustained, and successful antiretroviral treatment of people living with HIV [26]. As shown, expanding access to HIV treatment involves more than the provision of antiretroviral drugs; it can be an opportunity to address other aspects of health and well-being including sexual and reproductive health. In this study, women on HAART were more likely to use contraceptives overall, and barrier, permanent, and dual protection methods in particular. Of particular relevance to HIV prevention

efforts, 68% of sexually active HAART users reported consistent condom use, compared with 59% of HAART-naïve women, and 39% of HIV-negative women. Current models estimating the impact of expanding access of HAART on reducing HIV transmission assume rates of condom use reported in the general population [27]. However, the higher prevalence of condom use among HAART users suggests a further reduced risk of HIV transmission to discordant sexual partners than previously estimated given that 80% of women receiving HAART in our study are also virally suppressed. Explicitly incorporating sexual and reproductive health concerns of women into 'Treatment as Prevention' initiatives offers an opportunity to extend the value of HAART scale-up services to address the desperate state of maternal and child health in high HIV prevalence settings.

7.5 Future Research

Based on the findings presented here, there are a number of priority areas for future research on this topic. First, there is a great need for longitudinal data to monitor the ongoing impact of expanded access to HAART on the sexual and reproductive health of HIV-infected and –affected women. In particular, there is great value in conducting a large observational cohort study with an open recruitment strategy that enrolls women at various stages of their HIV disease and

reproductive lives. Such a study could be responsive to changes in HIV testing and incidence rates, changes in rates and strategies of HAART provision, and changes in the policy and programming environments that affect sexual and reproductive health of women living in conditions of generalized epidemics. It would be valuable to enroll both HIV-positive and HIV-negative women in such a cohort study as an important means of understanding systemic differences between groups that could not be fully accounted for in the analyses presented here. Moreover, a longitudinal assessment, which includes data pre- and post- HIV seroconversion and pre- and post HAART initiation, would be more appropriate to accurately assess a time-oriented potential impact of HAART access on sexual and reproductive decision-making and behaviors and ultimately, outcomes. For example, the systemic and genital tract changes associated with progesterone exposure have suggested a biological plausibility to increase risk of HIV acquisition [28-31], transmission [32-34], and disease progression [35] among oral contraceptive users. Although the epidemiologic evidence has yielded inconsistent findings in the general female population [36-40], it is possible that women using oral contraceptives may be at increased risk of HIV acquisition and disease progression, necessitating earlier receipt of HAART. The longitudinal cohort study proposed here would provide an opportunity to address this question of great public health priority.

It is acknowledged that women do not make reproductive decisions in

isolation. Thus, future research, including the cohort study described above, should include men both as individuals and as sero-concordant or discordant partners, as part of investigations investigating the impact of expanded access to HAART.

Another important future research direction is for a community-based study to complement the findings of clinic-based studies. Existing research has primarily enrolled HIV-positive and HIV-negative women from research-oriented clinical settings, which may limit the generalizability of the findings. Women who are actively seeking out HIV testing and treatment services may constitute a selective sample since most have disclosed their status and are seeking preventative health services. A community-based study of the potential impact of HIV status and HAART on sexual and reproductive health may yield more representative findings of the general population of women living with HIV in endemic settings.

Future research should utilize the WHOMEN's scale developed here to measure HAART optimism among HIV-positive women and to assess the role of optimism, versus actual receipt of HAART, on women's sexual and reproductive decision-making, behaviours, and outcomes. Use of the WHOMEN's scale would provide opportunities to investigate additional aspects of sexual and reproductive behaviour that may have implications for HIV transmission. In particular, it would

be of great value to use the scale to measure trends in HAART optimism corresponding with population-level changes in access to HIV treatment services.

Finally, despite the great value of epidemiologic analyses presented here, such quantitative data fails to capture the salient influence of cultural and gender dynamics on sexual and reproductive decision-making. As such, there is a great need for qualitative studies that explore the reasons and processes behind the outcomes measure here. Cultural beliefs and practices have often and consistently been discussed as critical determinants of sexual and reproductive behaviour [41, 42] and HIV status and HAART use alone are unlikely to be the sole or even primary drivers of reproductive decision-making [2]. Indeed, qualitative studies have highlighted the critical role of male partners, opinions and support of health care workers, and community and peer perceptions of positive parenting as critical factors influencing fertility decision-making of HIV-positive women [43, 44]. Additional such studies are desperately needed to provide a more complete and contextual picture of the impact of expanding access to HAART on sexual and reproductive decision-making and behaviours.

7.6 Conclusion

My PhD dissertation offers an important and lasting body of evidence pertaining to the role of expanding access to HAART in influencing sexual and reproductive decision-making and outcomes among women in two high HIV prevalence settings in sub-Saharan Africa. It has highlighted that HIV-positive women receiving HAART are more likely to use contraception overall and dual protection in particular, with minimal differences in fertility intentions or rates of sexual activity, relative to their HAART-naïve counterparts. Moreover, the findings reveal that optimism about the effects of HAART, rather than actual use or non-use, may be a more important predictor of fertility intentions and sexual activity of HIV-positive women. In addition, this thesis documents important differences in sexual and reproductive decision-making and behaviours by HIV serostatus. In particular, HIV-positive women are significantly less likely to report fertility intentions and significantly more likely to use contraception (and condoms in particular) relative to HIV-negative women from the same community. The findings have underscored the great value that integrated sexual and reproductive health services and HIV care and services can have towards improving HIV prevention efforts and supporting the rights of all women to be sexually active and achieve their fertility goals, while minimizing risks of HIV transmission.

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APPENDIX 1: HUMAN ETHICS APPROVAL CERTIFICATES

The University of British Columbia
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Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road,
Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL - FULL BOARD

PRINCIPAL INVESTIGATOR:	INSTITUTION / DEPARTMENT:	UBC BREB NUMBER:
Patricia Janssen	UBC/Medicine, Faculty of/Health Care & Epidemiology	H06-04019

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
N/A	N/A

Other locations where the research will be conducted:
Perinatal HIV Research Unit (PHRU) of the University of Witwatersrand's Chris Hani Baragwani Hospital in Soweto, South Africa

CO-INVESTIGATOR(S):
Angela Kaida
Deborah Money
Robert S. Hogg
Steffanie Strathdee

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Canadian Institutes of Health Research - "Measuring the impact of highly active antiretroviral therapy on HIV-positive women's sexual behaviour and fertility in a high prevalence setting"

PROJECT TITLE:
Investigating the impact of Highly Active Antiretroviral Therapy (HAART) on
sexual and reproductive behaviours and fertility among HIV-positive women in South Africa

REB MEETING DATE:	CERTIFICATE EXPIRY DATE:
January 25, 2007	**January 25, 2008**

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Document Name	**Version**	**Date**
Protocol:		
Research Proposal	N/A	December 15, 2006
Consent Forms:		
Revised consent form	4	March 21, 2007
Questionnaire, Questionnaire Cover Letter, Tests:		
Questionnaire_Gender, Fertility, HAART study_South Africa	N/A	December 1, 2006
Other Documents:		
Ethical Approval from the Human Ethics Research Board (Medical): University of the Witwatersrand	N/A	December 1, 2006

The application for ethical review and the document(s) listed above have been reviewed and the

procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board and signed electronically by one of the following:

Dr. Peter Suedfeld, Chair
Dr. Jim Rupert, Associate Chair
Dr. Arminee Kazanjian, Associate Chair
Dr. M. Judith Lynam, Associate Chair
Dr. Laurie Ford, Associate Chair

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa • Tel: +27-11-274-9200 • Fax: +27-11-274-9281

07 December 2006

FAXED & COURIE

Prof GE Gray,
Executive Director of the Perinatal HIV Research
Perinatal HIV Research Unit
PO Box 114
Soweto
Diepkloof
1034

Fax: 011 989 9762

Dear Prof Gray,

PROTOCOL: PHRU FERTILITY 001 - GENDER, HAART, AND FERTILITY: INVESTIGATING THE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON SEXUAL BEHAVIOUR AND FERTILITY AMONG HIV-POSITIVE WOMEN IN SOUTH AFRICA

ETHICS REFERENCE NO: 061112

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial was reviewed by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol Review Committee (PRC) on: 24 November 2006

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* A copy of the MCC Approval and/or MCC Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :
  - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (International and Local Reports).
  - Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - 011 274 9281 and a report of the final results, at the conclusion of the study.

4. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and it is planned that such analysis will be done outside Wits then the blood must be stored at Wits with release of sub-samples ONLY once projects have been approved by the local Research Ethics Committee applicable to where the research will be done, as well as by the Wits Human Research Ethics Committee: (Medical).

5. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) does not agree with the R150 reimbursement per visit as stipulated by the Medicines Control Council of SA but that reimbursement should be appropriate according to the situation.

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

7.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator /(s) per fax: 011 274 9281 for our records.

7.2 Protocol Review Committee Approval Signature page signed by the Chairperson of the PRC.

7.3 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM 2003

8. WE AWAIT YOUR RESPONSES AS REQUESTED:

* MCC Approval and/or Notification before the above study may commence.
* Copy of Approval Form signed by the Principal Investigator.
* Kindly forward the above to the undersigned at fax: 011 274 9281 at your earliest convenience.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards

PROF PETER CLEATON-JONES

For and on behalf of the Human Research Ethics Committee: (Medical)

INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

Ethics Reference No.	061112	Date of Meeting	24 November 2006
		Recertification Due	30 November 2006
Principal Investigators:		Investigators:	Prof GE Gray
			Dr R Hogg
			Dr A Kaida

Protocol Title:	Gender, HAART, and Fertility: Investigating the Impact of Highly Active Antiretroviral Therapy (HAART) on sexual behaviour and Fertility among HIV-Positive women in South Africa

DOCUMENTS REVIEWED				Tick As Appropriate Yes	No
Protocol Number	PHRU Fertility 001	Date:	05 November 2006		
Protocol	Protocol - PHRU Fertility 001	Date:	05 November 2006	☑	☐
Investigator's Brochure	N/A - Version: N/A - Dated:			☑	☐
Subject Information/Consent Form	Information Leaflet and Informed Consent - Version: 1.0 - Dated: 05/Nov/2006			☑	☐
Advertisements					
Questionnaires	HIV/HAART, and Fertility Survey in South Africa - Version: 1 - Dated: 11/May/2006			☑	☐
Insurance/Compensation	Valid From	To:		☐	☑
Synopsis of Study/Trial Summary	Gender, HAART, and Fertility			☑	☐
Other Documentation	Protocol Summary - Dated: 05/Nov/2006			☑	☐
	HREC Application Form - Dated: 07/Nov/2005			☑	☐
Relevant Trial Hospital/(s)	Perinatal HIV Research Unit - Baragwanath Hospital			☑	☐
Syndicate and/or Research Unit	Peri-Natal HIV Research Unit - PHRU			☑	☐

DETAILS OF COMMITTEE	
Name	University of the Witwatersrand Human Research Ethics Committee (Medical)
Address	Division of the Deputy Registrar (Research), Department of Research, Senate House University of the Witwatersrand , 1 Jan Smuts Avenue, BRAAMFONTEIN, Johannesburg, 2000

DETAILS OF MEETING	Yes	No
Is the Investigator a member of the committee ?	☐	☑
If "Yes" did he/she vote ?	☐	☑
Is the Committee organised and operated according to applicable laws and regulations together with ?	☑	☐
Local GCP requirements ?	☑	☐
ICH GCP requirements ?	☑	☐
FDA GCP requirements ? FWA Registered No. IRB00001223	☑	☐
Progress reports required either in March and September or six monthly from start of study ?	☑	☐

DECISION ON APPROVAL - Is approval given to conduct the trial ?	Tick As Appropriate
Yes - with no conditions	☑
Yes - with conditions	☐
Specify conditions :	
No	☐
Specify reasons	

SIGNATURES		
I confirm that the details on this form are correct:		Date
Name: Prof PE Cleaton-Jones Chair / Deputy Chair of Committee	Signature:	07 December 2006

DECLARATION OF INVESTIGATOR/(S)

To be completed and ONE COPY returned to the Secretariat for the HREC at Wits Health Consortium, 8 Blackwood Avenue, Parktown, 2193 or Fax To: 011 274-9281

I/We fully understand the conditions under which I am/we are authorised to carry out and complete the above-mentioned research and I/we agree to ensure full compliance with these conditions. Should any amendment, alteration or departure be contemplated from the research procedure methodology or manner of execution, I/we will communicate with the Chairman of the Human Research Ethics Committee (Medical) for approval prior to acting on any of the above mentioned proposed amendments, alterations or departures. I am/we are fully aware that any unauthorised amendment, alteration or departure as above will amount to misconduct and may lead to the institution of disciplinary procedures.

Any approval given by the HREC is conditional upon consent being obtained by the Investigator/s from the Superintendent (or equivalent official) of the Hospital, Clinic or Institution in which the research is, in part or full, to take place.

The Chairman may of course at his discretion place the matter t

DATE: 12 / 12 / 06 SIGNATURE: NAME: Dr R Panchia

PROTOCOL NUMBER PHRU Fertility 001 ETHICS REF.: 061112

Date Printe 07 December 2006

Attendance Register for the Ethics Meeting held on 24 November 2006 from 12:30 - 15:00

Venue: PPS BOARDROOM, Faculty of Health Sciences, University of Witwatersrand 7 York Road, Parktown

AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Bhagwanjee	S	Prof	Anaesthesia	MBBCh, FCA, DA (SA), FFA (SA)	M	Absent
Cleaton-Jones	PE	Prof	Medical Practitioner, Dental Practitioner, Syndicate Mailing List	BDS, MBBCh, PhD, DTM&H, DPH, DA (SA), DSc (Dent), Hon PhD, MASSAfr	M	Present
Connor	MD	Dr	Neurology	MBBCh, FCP (SA), FC Neurol (SA)	M	Absent
Cooper	PA	Prof	Paediatrics	MBBCh, PhD, DCH (SA), FCPaeds (SA)	M	Absent
Dhai	A	Prof	Biomedical Ethics	MBChB, FCOG, LLM; PGDip Int ResEthics	F	Present
Donde	B	Prof	Radiation Oncology	MBBCh, MMed Rad (T) FCP(SA)	M	Present
Drower	SJ	Prof	Social Worker	BSocSci (Hons), PhD, RSW	F	Absent
Feldman	C	Prof	Pulmonology, Syndicate Mailing List, GCP course attendee	MBBCh, PhD, FCP (SA) (Pulmonology), FRCP	M	Absent
Förster	OA	Dr	Cardiology	MEDC901, PHD Thesis	M	Absent
Langley	G	Dr	Nursing	MSc (Nursing), PhD	F	Present
Loram	L	Mrs	Physiology	MSc (Physio)	F	Present
Lownie	MA	Prof	Maxillo-Facial & Oral Surgery	BDS, BA (Hons), DipMFOS, FCMFOS (SA), M.ED	F	Absent
Mayekiso	TV	Prof	Psychology	PhD, BA (Hons), MA	F	Absent
McLean	GR	Prof	Philosopher and Ethicist	BA (Hons) MA B Phil DPhil	M	Absent
Mokhachane	M	Dr	Paediatrics	MBBCh, FCP (Paeds) SA, MMed (Wits), Neonatology (SA)	F	Present
Naidoo	S	Prof	Public Health	MBBcH, DGMTH, DHSM, DCH, MMED	M	Absent
Oettle	GJ	Prof	Surgery, Gastroenterology, Syndicate Mailing List	BSc (Hons), MBBCh, FRCS	M	Absent
Paizes	A	Prof	Lawyer	BCom, LLB, PhD	M	Absent
Patel	M	Prof	Clinical Medicine	MBChB, MMed, FCP (SA), FRCP, PhD	M	Absent
Penn	C	Prof	Speech Pathology	BA (S&HT), PhD	F	Present
Ross	E	Prof	Social Worker	BA, MA, PhD	F	Present
Ross	M	Prof	Public Health	FFCH(SA), MFAM, MFPH	F	Absent
Sanne	I	Dr	HIV, Infectious Diseases, Syndicate Mailing List	Wits MBBCh; FCP (SA), DTM&H; Reg MMED and PhD	M	Present
Szabo	CP	Prof	Psychiatry	MBBCh, MMed, PhD, FCPsych (SA)	M	Present
Thom	RGM	Dr	Psychiatry	MBChB, DCH, FCPsych	F	Present
Van Gelderen	CJ	Prof	Obstetrics & Gynaecology	MBBCh, FRCOG, FCOG(SA)	M	Present
Velaphi	S	Dr	Paediatrics, Neonatology, Syndicate Mailing List	MBBCh, FCPaeds, Mmed	M	Present
Vorster	M	Prof	Psychiatry, GCP course attendee, Syndicate Mailing List	BA, MBBCh, MMed, FCPsych(SA), PhD (Med), Dipl IRE	F	Present
Wadee	A	Prof	Immunology, Pathology, Syndicate Mailing List	BSc, MSc, PhD	M	Present
Woodiwiss	A	Prof	Cardiovascular Pathophysiology, Physiology, Syndicate Mailing List	BSc, MSc, PhD, BSc Physiotherapy	F	Present

NOT AFFILIATED TO THE UNIVERSITY OF THE WITWATERSRAND

Surname	Initials	Title	Discipline/s	Academic Qualifications	Gender	Present
Conradie	FM	Dr	Infectious Diseases	MBBCh, DTM&H	F	Present

Attendance Register for the Ethics Meeting held on 24 November 2006 from 12:30 - 15:00

Venue: PPS BOARDROOM, Faculty of Health Sciences, University of Witwatersrand 7 York Road, Parktown

Egan	A	Father	Theology	BA (HONS), MA, MDIV, STL, PhD	M	Absent
Khan	S	Dr	Governance		F	Present
Myburgh	C	Prof	Educationist	B.Sc (Hons), M.Com DEd NED	M	Present
Pantazis	A	Prof	Lawyer		M	Absent
Poggenpoel	M	Prof	Psychiatry Nurse	RN, PhD	F	Present
Stewart	A	Prof	Physiotherapy	BSc (Physio); MSc; PhD	F	Present
Tsotsi	NM	Dr	Dentistry / Community			Absent

Note 1: This committee has been in continuous operation since October 1966.
Note 2: The large committee size is to ensure a good attendance at meetings.
Note 3: A Quorum consists of 5 members, of which 1 non-affiliate and 1 non-medical member to be present.
Note 4: The following members alternate: Prof A S Skeen and Prof A. Pantazis
Prof C Penn and Dr E Ross
Prof C P. Szabo and Prof R Thom
Prof P A Cooper and Dr S Velenis

This is to certify that the Human Research Ethics Committee: (Medical) of the University of the Witwatersrand operates according to the following guidelines of good clinical practice:

1. ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996):
2. SA National Department of Health Guidelines for Good practice in the conduct of clinical trials in human participants in South Africa (2000):

The Committee's United States Federal Wide Assurance details are:

1. Country code SF:
2. University of the Witwatersrand: IORG0000862:
3. Human Research Ethics Committee (Medical): IRB00001223.

071364X

UNIVERSITY OF CALIFORNIA, SAN DIEGO
HUMAN RESEARCH PROTECTIONS PROGRAM

TO: Steffanie Strathdee Mailcode: 0622
RE: Project #071364X
Investigating the Impact of Highly Active Antiretroviral Therapy (HAART) on Sexual and Reproductive Behaviors and Fertility Among HIV-Positive Women in South Africa

Dear Dr. Strathdee:

The above-referenced project was reviewed and approved by one of this institution's Institutional Review Boards in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects (45 CFR 46 and 21 CFR 50 and 56), including its relevant Subparts. The review was conducted by expedited review procedures. This approval, based on the degree of risk, is for 365 days from the date of **IRB review and approval** unless otherwise stated in this letter. The regulations require that continuing review be conducted on or before the 1-year anniversary date of the IRB approval, even though the research activity may not begin until some time after the IRB has given approval.
The UCSD CFAR is not enrolling any subjects but only providing guidance and training for study personnel in Diepkloof, South Africa. This study was reviewed by the IRB through the expedited review procedure as authorized by 45 CFR 46.110 and 21 CFR 56.110 and falls under the following research category: (5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
Date of IRB review and approval: **7/19/2007**

/nm
Michael Caligiuri, Ph.D.
Director, Clinical Research Protections Program
Mailcode: 0052 Phone: 858-455-5050
E-mail: hrpp@ucsd.edu

Note: All Human Subject research conducted at the VA facility and/or utilizing VA/VMRF funds MUST BE APPROVED by the VA Research and Development Committee prior to commencing any research. In addition, please ensure that the clinical trial agreement or other funding is appropriately in place prior to conducting any research activities. IRB approval does not constitute funding approval. Approval release date: 7/31/2007

PROJECT: 071364X
Initial approval

UCSD HUMAN RESEARCH PROTECTIONS PROGRAM
VETERANS ADMINISTRATION SAN DIEGO HEALTHCARE SYSTEM

✓ CERTIFICATION of approval for the above-reference project is attached.

NB: (1) Modifications/Changes in this project must be received and approved by the appropriate HRPP Committee before they are initiated except where necessary to eliminate apparent immediate hazard to the subject.

(2) The Human Research Protections Program office should be notified immediately of any injuries to human subjects and/or any unanticipated problems that involve risks to human subjects or others.

_____ Because you have indicated that your research will involve VAMC patients and/or facilities, copies of approved documents have been forwarded to the VAMC Research Administration Office for processing.

_____ If you plan to use Clinical Research Center Facilities, Contact Cheryl Ward at UCSD Medical Center, Ext. 36180 for Specific Instructions.

_____ "Approved" consent forms are attached. Please ensure that subjects are given a copy of the most current, approved consent form on file.

_____ This project has been approved for Oral Consent. Please ensure the subject is presented with the approved oral script.

_____ All subjects must be given:

1. A copy of the consent form to keep and,
2. A copy of "The Experimental Subject's Bill of Rights" (sample enclosed)

✓ Please ensure that you submit a progress report for this study using the UCSD IRB PROTOCOL MONITORING FORM by the following date: 6.15.08

For studies that involve hospitalized patients, please ensure that the Medical Director and Nursing supervisor of the unit where the study will be conducted are aware of the study. Attached for your use is the UCSD RESEARCH SUBJECT INJURY REPORT FORM that may be found at our website: http://irb.ucsd.edu/ or you may photocopy the attached form. This form must be used to report all serious and unexpected, or unusual incidents of injury associated with an investigation drug/device/or procedure by UCSD/VASDHS subjects or others WITHIN 10 WORKING DAYS after first awareness of the problem.

CC: JLC _____ _____

UCSD Human Research Protections Program, 9500 Gilman Drive, La Jolla, CA 92093-0052
Ph. (858) 455-5050 Fax (858) 455-9540

(42)

MBARARA UNIVERSITY OF SCIENCE AND TECHNOLOGY
FACULTY OF MEDICINE

Ref: DMS 3/12a

31st May 2005

Dr. Andia Irene
Department of Internal Medicine

Re: RESEARCH PROPOSAL

Reference is made to your submitted research proposal titled "Impact of antiretroviral therapy on fertility of HIV positive women at MUTH"

The Faculty Research and Ethics Committee sitting on 20th May received and considered your research proposal and was satisfied that all ethical issues were addressed. However a few observations were made and need your attention.

i) Pg. 5 Protocol form last sentence "A thesis will be presented before the award of Masters of Medicine degree (anaesthesia) was misplaced.
ii) Pg 5 spelling of word fora
iii) Pg 8 5.3 There is no need of consulting the spouse
iv) Pg 5 proposal quote source of the figure (Fig.4)
v) The questions in the instrument are too many, could be reduced.

Subject to the above correction, your proposal is cleared and forwarded to institutional Ethics Committee for approval.

Please produce 10 copies of the revised copy for submission to institutional ethics committee.

Yours sincerely

Assoc. Prof. Nozmo Mukiibi
CHAIRMAN FREC

c.c. Secretary, FREC

APPENDIX 2: DATA COLLECTION TOOL FOR THE SOWETO, SOUTH AFRICA STUDY

Interviewer preamble and welcome:

Hi, my name is _____ and I am an interviewer for this research project. Your answers are very important to our research and will help us to develop better health programs in your community. I am not a doctor or a nurse. I want to assure you that anything you tell me will remain totally confidential and nothing you say here will affect the medical care you receive. Remember, there are no right or wrong answers. It is very important that you give the most honest answer that you can. You may stop at any time or refuse to answer any questions that you do not wish to answer. You are welcome to ask any questions before and after the interview. Do you have questions for me before we begin?

Section 1: Socio-Demographics
First, I would like to ask you questions about you and your family.

Section 2: HIV Status
Now I'd like to ask you some questions about your HIV-status.

Section 3: Fertility
Now I would like to ask you some questions about your pregnancy and sexual history. Some of these questions may be personal. If you feel embarrassed and don't want to continue, you can say so and we'll skip to other questions. I want to remind you that all your answers are confidential.

Section 4: Fertility Desires
Now I would like to ask you questions about your wishes to have (more) children.

Section 5: Use of prevention methods
In this section, I would like to ask you questions about your sexual activity and use of prevention.

Section 6: Sexual History
Now I'd like to ask you questions about your sexual partners and your sexual activity. Some of these questions might make you feel uncomfortable, however, it is really important that you answer the questions honestly. Please remember, that all your answers are confidential and no one will know your responses.

Before we begin, I want to define some terms. When I say "regular partner", I mean someone you have had sex with regularly in the past 6 months. When I say "casual sex partner", I mean someone who is not your husband or a regular sexual partner but you've had sex with them at least once in the past 6 months.

The number of sexual partners people have varies from person to person. There is no right or wrong number.

Section 7: HIV and HAART Optimism
In this final section, I would like to ask your opinions about HIV and treatment. Some of these questions will sound similar but each one is important.

Perinatal HIV Research Unit
Impact of ARVs on sexual and reproductive behaviours and fertility among women in South Africa

ARV-Impact: 011 Form Number: 001 Visit 001

Participant ID

1 – ___ ___ ___
Site Code Research Code

MPI # ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

Visit Date

___ ___ ___ ___ ___ ___
dd mm yy

Name of Interviewer _____

2. Start time of interview:..... ___ ___ : ___ ___ (24 Hours Clock)
HH MM

Screening Questions:

	yes	no	
1. Do you currently live in Soweto?.....	☐	☐	**Stop, not eligible**
2. Date of Birth.....	___ ___ dd	___ ___ mm	___ ___ yy
OR, please provide estimated age.....	___ ___ Years		
If younger than 18 or older than 49, **Stop, not eligible**.	☐ *Don't Know*		Tick only one
	☐ *Refused*		
3. Have you been diagnosed with HIV?.....	☐	☐	Invite to participate in HIV negative group. **Go to Section 1**
4. Are you currently on Antiretrovirals to treat your HIV Infection?.....	☐	☐	**Go to question 6**
5. Are you a patient in the PEPFAR Clinic?.....	☐	☐	**Stop, not eligible**
	↓ Invite to participate in ARV user group		
6. Are you a patient in the Wellness Clinic?.....	☐	☐	**Stop, not eligible**
	↓ Invite to participate in the non-ARV user group		

Version 1 . 0 MAY 7, 2007

☐ **Supervisor Reviewed**

_____
Staff Signature / Date

ARV-Impact: 011 Form Number: 002 Visit 001

Participant ID

1 – ☐☐☐

Site Code Research Code

Section 1: Socio-Demographics

1. What is the name of the township where you currently live?..._____

2. What is the highest level of schooling you have completed?.....
(Tick only one.)

- ☐ None
- ☐ Sub-Standard A/Grade 1
- ☐ Sub-Standard B/Grade 2
- ☐ Standard 1/Grade 3
- ☐ Standard 2/Grade 4
- ☐ Standard 3/Grade 5
- ☐ Standard 4/Grade 6
- ☐ Standard 5/Grade 7
- ☐ Standard 6/Grade 8
- ☐ Standard 7/Grade 9
- ☐ Standard 8/Grade 10
- ☐ Standard 9/Grade 11
- ☐ Standard 10/Grade 12
- ☐ Incomplete post-secondary training(University, College, Vocational)
- ☐ Complete post-secondary training(University, College, Vocational)
- ☐ Other, specify _____

3. What is your church denomination?.....
(Tick only one. If she says "Christian" probe further for denomination)

- ☐ Anglican
- ☐ Catholic
- ☐ Lutheran
- ☐ Methodist
- ☐ Seventh Day Adventist
- ☐ Born Again/Pentecostal
- ☐ Universal Church
- ☐ None
- ☐ Other, specify _____

_____
Staff Signature / Date

ARV Impact: 011 Form Number: 003 Visit 001

Participant ID

1 – ☐☐☐

Site Code Research Code

5. What is your current employment status?..... (*Tick only one. Read answers*)

- ☐ Full-time employed
- ☐ Part-time employed
- ☐ Self Employed
- ☐ Unemployed
- ☐ Student
- ☐ Refused to answer
- ☐ Other, specify _____

6. In the past 12 months, have you received any of the following sources of income..... (*Read each option. Tick all that are appropriate*)

- ☐ Social grant: disability
- ☐ Social grant: old age pension
- ☐ Social grant: child support
- ☐ Money from sexual partners, family members, and/or friends
- ☐ Refused to answer
- ☐ Other, specify _____

7. What is the range of your household's monthly income? Please include money received for work, government grants, other income and gifts..... (Tick only one. Read answers)

- ☐ 0 to 499 Rands
- ☐ 500 to 999 Rands
- ☐ 1,000 to 1,999 Rands
- ☐ 2,000 to 2,999 Rands
- ☐ 3,000 to 3,999 Rands
- ☐ 4,000 to 4,999 Rands
- ☐ 5,000 or more Rands
- ☐ Refused to answer
- ☐ Don't know

8. What is your current marital status?..... (Tick only one)

- ☐ Married (legal, traditional or common law) → **Go to question 9**
- ☐ Widowed → **Go to question 11**
- ☐ Divorced or separated → **Go to question 10**
- ☐ Single (never married) → **Go to question 12**

Version 1.0 MAY 7, 2007

_____
Staff Signature / Date

ARV-Impact: 011 Form Number: 004 Visit 001

Participant ID

1 – ☐☐☐

Site Code Research Code

9. If Married:

9.1 How old were you when you were first married?..... ☐☐ Years
☐ *Don't Know*
☐ *Refused*
→ Tick only one

9.2 Are you the only wife or does your husband have co-wives?.....
☐ I am the only wife
Go to question 12
☐ My husband has co-wives

9.2.1 How many wives does your husband have?..... ☐☐ # of wives
(Interviewer, please confirm number includes participant)

9.2.2 Are you the first, second, third, etc wife?.....
(Tick only one)
☐ First ☐ Third
☐ Second ☐ Other, specify _____

GO TO QUESTION 12

10. If Divorced or Seperated:

10.1 How old were you when you were first married?..... ☐☐ Years
☐ *Don't Know*
☐ *Refused*
→ Tick only one

10.2 When you were married, were you the only wife or did your husband have co-wives?.....
☐ I was the only wife
Go to question 12
☐ My husband had co-wives

10.2.1 How many wives did your husband have?..... ☐☐ # of wives
(Interviewer, please confirm number includes participant)

10.2.2 Were you the first, second, third, etc wife?.....
(Tick only one)
☐ First ☐ Third
☐ Second ☐ Other, specify _____

GO TO QUESTION 12

Version 1.0 MAY 7, 2007

_____
Staff Signature / Date

ARV-Impact: 011 Form Number: 005 Visit 001

Participant ID

1 – ☐☐☐

Site Code Research Code

11. If Widowed:

11.1 When did your husband die?..... ☐☐ ☐☐
mm *yy*

11.2 Please specify the cause of death..... _____

GO TO QUESTION 12

12. Do you currently have a sexual partner?..... *yes* ☐ *no* ☐ **Go to question 13**
(If married, ask "In addition to your husband")

12.1 Are you in a relationship? By this I mean, do you have a boyfriend?
(*If married, ask "In addition to* your husband")
yes ☐ *no* ☐
Go to question 13

13. Including yourself, how many people currently live in your house? By this I mean children and adults who sleep in the household at least two nights or more every week?.....

☐☐ Number of children aged 18 or younger
+
☐☐ Number of adults
=
☐☐ Total number of people

Go to Section 2: HIV Status

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Section 2: HIV Status

1. When were you first diagnosed with HIV?..... ☐☐ ☐☐ ☐☐ (dd mm yy) *Not Applicable (If HIV-Negative)* ☐

2. For what reason did you undergo HIV testing?..... (Tick only one)
- ☐ Pregnant/tested at antenatal clinic
- ☐ Insurance purposes
- ☐ Recommended by health care professional
- ☐ Was sick/having symptoms of HIV/AIDS
- ☐ Sexual partner got sick/had symptoms of HIV/AIDS
- ☐ Sexual partner asked that I get tested
- ☐ Just wanted to know status
- ☐ Sexual partner has risky behaviour
- ☐ Donated blood
- ☐ Sexual contact with a known HIV-positive individual
- ☐ Don't know
- ☐ Other, specify _____

3. Are you aware of medications to treat HIV/AIDS called antiretroviral therapy? Sometimes called HIV-drugs?..... *yes* ☐ *no* ☐ *unsure/DK* ☐

IF HIV-NEGATIVE THEN, GO TO SECTION 3

4. Are you currently taking ARV medications to treat your HIV infection? By currently, I mean ARVs that you have taken in the past 7 days..... *yes* ☐ *no* ☐ *unsure/DK* ☐ **Go to question 5**
(Interviewer: Please clarify that we are interested in ARV therapy ONLY and not Bactrin or similar drugs)

4.1 What type of ARV medication are you currently on? (*Interviewer: Please use ARV prompt card to help patient remember*)
- ☐ D4T (Stavudine)
- ☐ 3TC (Lamivudine)
- ☐ Efavirenz (Stocrin)
- ☐ Nevirapine (Viramune)
- ☐ Combivir (AZT & 3TC)
- ☐ AZT (ZDV, Zidovudine, Retrovir)
- ☐ ddI (Didanosine, Videx)
- ☐ Lopinavir/Ritonavir (Kaltera)
- ☐ Abacavir (ABC) (Ziagen)
- ☐ Tenofovir
- ☐ Nelfinavir (Viracept)
- ☐ Saquinavir (Invirase, Fortovase)
- ☐ Other, specify_____

4.2 When did you first start therapy?..... (*mm yy*) ☐☐ ☐☐ *unsure/DK* ☐

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5. Have you ever had your blood drawn to test your viral load? Viral load is the amount of HIV virus in your blood..... *yes* ☐ *no* ☐ *unsure/DK* ☐

6. Have you ever had your blood drawn to test your CD4 cell count? CD4 cell count is the number of cells your body has to fight the HIV infection..... *yes* ☐ *no* ☐ *unsure/DK* ☐ → Skip to question 7

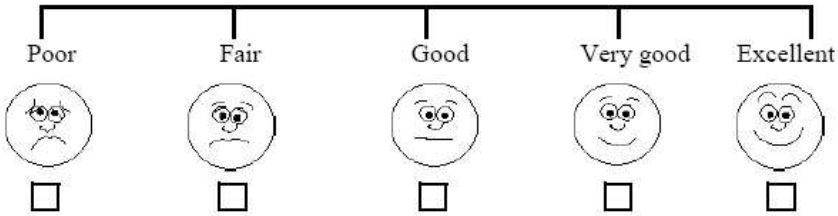
6.1 What was your most recent CD4 cell count?..... ☐☐☐☐ cells/absolute count

OR ☐ *unsure/DK*

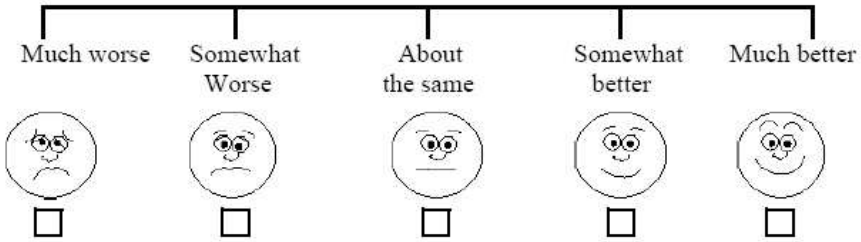
6.2 What was the date of your last CD4 cell count test?..... ☐☐ ☐☐ ☐☐ (*dd* *mm* *yy*)

OR ☐ *unsure/DK*

7. In general, how good or bad would you say your health is <u>now</u>? Please indicate on the diagram below by ticking the appropriate box.



8. Compared to now, how would you rate your health one year ago? Please indicate on the diagram below by ticking the appropriate box.



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9. Now we're going to talk about disclosure. Different people do different things when they find out the result of their HIV test. Some people tell their friends, families and sexual partners, while other people don't tell anyone. Please remember that I won't tell anyone what you tell me in this interview. Have you ever told anyone about your HIV status?

yes ☐ ↓ *no* ☐ → **Go to Section 3: Fertility**

9.1 Who have you told about your HIV status? Was the response from this person supportive, non-supportive or neutral? (*Please tick all that apply below and indicate responses for people told.*)

	Supportive	Non-Supportive	Neutral
☐ Husband →	☐	☐	☐
☐ Boyfriend →	☐	☐	☐
☐ Sexual partner →	☐	☐	☐
☐ Mother →	☐	☐	☐
☐ Father →	☐	☐	☐
☐ Sister →	☐	☐	☐
☐ Brother →	☐	☐	☐
☐ Cousins/Aunties/Uncles →	☐	☐	☐
☐ Friends →	☐	☐	☐
☐ Daughter/Son →	☐	☐	☐
☐ Other, specify → _____	☐	☐	☐

Go to Section 3: Fertility

_____
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Section 3: Fertility

1. How old were you when you had your first menstrual period?..... ☐☐ Years
   (Interviewer: Please obtain best estimate)

2. When did you have your last mentrual period?..... ☐☐ ☐☐ ☐☐
   (Interviewer: Please obtain best estimate)
   dd mm yy

3. How old were you when you first had vaginal sex? By vaginal sex, I mean when a man puts his penis in a woman's vagina..... ☐☐ Years
   (Interviewer: Please obtain best estimate if participant doesn't know exact age)

4. How many times have you been pregnant in your lifetime? Please include all pregnancies, whether the outcome was a live birth, miscarriage, stillbirth, or termination of pregnancy(T.O.P.)..... ☐☐

5. How many times have you given birth to a live baby in your lifetime?..... ☐☐

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6. Now, I'd like to ask you specifically about your previous pregnancies. For each one, I'm going to ask you the outcome of the pregnancy (born alive, stillbirth, miscarriage, or termination of pregnancy(T.O.P.)) and also the month and year of that outcome. You can start with either the most recent pregnancy or your first pregnancy.
(Interviewer: For each pregnancy please fill in the following information (see example below). Please also reconcile information provided in this question with questions 4 and 5)

Pregnancy	Date of pregnancy outcome		Pregnancy outcome								Alive today Yes or No		
			Live Birth		Stillbirth		Miscarriage		T.O.P.				
	MMM	YY	yes	no	yes	no	yes	no	yes	no	yes	no	na
e.g., 1	*N O V*	*0 5*	☒	☐	☐	☒	☐	☒	☐	☒	☒	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐☐☐	☐☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Go to Section 4: Fertility Desires

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Section 4: Fertility Desires

	yes	no	unsure/DK
1. Are you pregnant at the present moment?	☐	☐	☐
2. Do you wish to have (more) children in the future?	☐	☐	☐

→ **Go to question 4** (unsure/DK)

→ **Go to question 3** (no)

2.1 Why do you wish to have more children? _____

_____

2.2 How many more children would you like to have? ☐☐ **Go to question 4**

3. Why don't you want to have any more children? _____

_____

	POS	NEG
4. Participant's HIV status..... *(Interviewer: Do not ask participant. Just specify)*	☐	☐ → **Go to Section 5**: Use of Prevention Methods

	yes	no	unsure/DK
4.1 Have you ever been told by a health care worker that you should not become pregnant because of your HIV status?	☐	☐	☐

Go to Section 5: Use of Prevention Methods

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Section 5: Use of Prevention Methods

1. Have you had vaginal sex in the last 6 months? By vaginal sex I mean when a man puts his penis in a woman's vagina?..... *yes* ☐ *no* ☐

2. In the last 6 months, have you used anything to prevent becoming pregnant, such as, condoms, pills, injectables, loop, hysterectomy (removal of the uterus), vasectomy (man has his tubes tied), or other methods?..... *yes* ☐ *no* ☐ → **Go to question 3**
(*Interviewer:Probe for condoms*)

2.1 What type of prevention methods have you used in the last 6 months? Please select all that apply.
(Interviewer: If hysterectomy or sterilization, please note what month + year)

- ☐ Pill (Oral contraceptive)
- ☐ Injectables/Injection (Depo-Provera or Nuristerate)
- ☐ Loop/IUD
- ☐ Implant
- ☐ Diaphragm
- ☐ Condom (Male)
- ☐ Hysterectomy → ☐☐ *mm* ☐☐ *yy*
- ☐ Female sterilization → ☐☐ *mm* ☐☐ *yy*
- ☐ Male sterilization → ☐☐ *mm* ☐☐ *yy*
- ☐ Female Condom
- ☐ Other, specify _____

2.1.1 In the last 6 months, how frequently did you use a condom when having sex? Tick only one.
(Interviewer: Read options)

- ☐ Never, none of the time
- ☐ Rarely, once in a while
- ☐ Sometimes, about half of the time
- ☐ Frequently, more than half of the time
- ☐ Always, every time
- ☐ Refused to answer

2.2 What is the main reason you chose the method of prevention you use most consistently?_____
(specify method)

- ☐ It is easy to use
- ☐ It is convenient/more convenient
- ☐ It does not interfere with sexual activity
- ☐ It protects against transmission of sexual transmitted diseases and HIV/AIDS
- ☐ It is good at preventing pregancy
- ☐ My partner won't find out I'm using prevention
- ☐ My partner won't use birth control himself
- ☐ Other, specify _____
- ☐ I can use it only when needed
- ☐ It is cheap
- ☐ It has few or no side effects
- ☐ A doctor or nurse recommended it
- ☐ My friends use it
- ☐ My partner wants me to use this type of prevention
- ☐ I can decide when to use it and when not to

→ **Go to Section 6: Sexual History**

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3. Why haven't you used any prevention methods in the last 6 months?

- ☐ I am pregnant
- ☐ I am trying to become pregnant
- ☐ I can get an abortion if I become pregnant
- ☐ I don't think I will become pregnant
- ☐ I am not having sex
- ☐ I don't mind becoming pregnant
- ☐ I just had a baby
- ☐ Health related side effects of prevention methods (e.g. weight gain, abnormal periods, headaches, other health effects)
- ☐ I don't believe in using prevention
- ☐ I don't know why/No reason
- ☐ I cannot become pregnant (I am infertile)
- ☐ My partner will not use and/or will not let me use prevention
- ☐ Other, specify _____

Go to Section 6: Sexual History

_____
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Section 6: Sexual History

1. In your lifetime, with how many different men have you had vaginal sex? Again, by vaginal sex, I mean when a man puts his penis in a women's vagina. Please include your husband, regular partner and casual partners..... ☐☐ # of men ☐ Don't know

If zero, skip to question 3, otherwise continue to question 2.

2. In the past 6 months, with how many different men have you had vaginal sex? Please include your husband, regular partner and casual partners.... ☐☐ # of men ☐ Don't know

If zero, continue to question 3, otherwise skip to question 4.

3. Why haven't you had sex?_____

_____

After answering this question, please skip to Section 7: HIV and HAART Optimism

Question 4 appears on next page, page 15

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4. I'd like to ask you some questions about your male sexual partner(s). You mentioned that you had ☐☐ male sexual partners in the past six months. Please answer the following questions starting with your most recent partner.
(Interviewer: The following questions only apply to women who have had sex in the past 6 months.)

	Partner 1	Partner 2	Partner 3	Partner 4	Partner 5
a) What relationship do you have with this sexual partner? (Please refer to codelist below)	☐	☐	☐	☐	☐
b) Can you tell me the number of times you've had sex with this partner in the last 30 days?	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know
c) How many times have you used a condom with this partner in the last 30 days?	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know	☐☐ # of times OR ☐ Don't know
d) Do you know the HIV status of this partner?	Yes ☐ No ☐ DK ☐ Go to question F	Yes ☐ No ☐ DK ☐ Go to question F	Yes ☐ No ☐ DK ☐ Go to question F	Yes ☐ No ☐ DK ☐ Go to question F	Yes ☐ No ☐ DK ☐ Go to question F
d) What is your partner's HIV status?	Positive ☐ Negative ☐ Go to question F	Positive ☐ Negative ☐ Go to question F	Positive ☐ Negative ☐ Go to question F	Positive ☐ Negative ☐ Go to question F	Positive ☐ Negative ☐ Go to question F
e) Is your partner currently taking ARVs?	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐
f)Does your partner know your HIV status?	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐	Yes ☐ No ☐ DK ☐

Codes: 1 = Husband, 2 = Regular sex partner, 3 = Casual sex partner, 4 = Commercial sex partner, 5 = One time encounter, 6 = Other

	yes	no	DK/Refused
5. In the past 6 months, have you ever received any gifts or money in exchange for sex?	☐	☐	☐
6. In the past 6 months, has anyone ever physically forced you to have sex?	☐	☐	☐

Go to section 7: HIV and HAART Optimism

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Section 7: HIV and HAART Optimism

Considering the new medicines available to treat HIV, please tell me how much you agree or disagree with the statements I read to you. Do you Strongly Agree, Agree, Disagree or Strongly Disagree? You can use the face that best indicates your opinion.

	Strongly Agree 	Agree 	Disagree 	Strongly Disagree 
1. A person with a very small amount of virus in the body cannot pass the virus to someone else.	☐	☐	☐	☐
2. A person's CD4 count will remain above 200 (at a safe level) if they stay on therapy.	☐	☐	☐	☐
3. I'm less worried about HIV infection than I used to be.	☐	☐	☐	☐
4. New HIV treatments will take the worry out of sex.	☐	☐	☐	☐
5. If every HIV positive person took the treatment, the AIDS epidemic would be over.	☐	☐	☐	☐
6. If a cure for AIDS were announced, I would stop practicing safe sex (abstinence, being faithful, or using a condom)	☐	☐	☐	☐
7. People with a very small amount of virus in the body don't need to worry about infecting others without HIV.	☐	☐	☐	☐
8. Until there is a complete cure for HIV/AIDS prevention is still the best practice.	☐	☐	☐	☐
9. HIV is less of a threat because the epidemic is on the decline.	☐	☐	☐	☐
10. HIV/AIDS is a less serious threat than it used to be because of new treatments.	☐	☐	☐	☐
11. It is never safe to have sex without a condom regardless of the amount of virus in the body.	☐	☐	☐	☐
12. Because of new treatments, fewer people are becoming infected with HIV.	☐	☐	☐	☐

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	Strongly Agree 	Agree 	Disagree 	Strongly Disagree 
13. I believe that new drug therapies make people with HIV less able to pass the virus to other people.	☐	☐	☐	☐
14. I am less worried about HIV infection now that treatments have improved.	☐	☐	☐	☐
15. I am not worried about becoming pregnant because of available HIV treatments.	☐	☐	☐	☐
16. If I become pregnant, I would be worried about passing HIV on to my baby, even if I were taking HIV treatments	☐	☐	☐	☐
17. I think the risk of HIV transmission in pregnancy is less that what doctors say.	☐	☐	☐	☐
18. I think the risk of HIV transmission with "safer sex" (using abstinence, being faithful and using condoms) is less than what doctors say.	☐	☐	☐	☐
19. If my partner and I were both on HIV treatment, it would be ok to stop using condoms.	☐	☐	☐	☐
20. HIV treatments/medicines could be harmful during pregnancy because of possible birth defects.	☐	☐	☐	☐
21. It would be OK to stop HIV medicines if they made me feel sick, especially if I were pregnant.	☐	☐	☐	☐
22. Now that HIV medicines are available, I want to have a baby because I will live long enough to raise a child.	☐	☐	☐	☐
23. I am worried that HIV medicines could cause AIDS.	☐	☐	☐	☐

That was the final question. Thank you for participating in this study and for answering these questions. Do you have any questions for me?

Interview stop time: ☐☐:☐☐ (24 Hours Clock)
HH MM

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Perinatal HIV Research Unit
Impact of ARVs on sexual and reproductive behaviours and fertility among women in South Africa

ARV-Impact: 011 Form Number: 018 Visit 001

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Medical Record Review

MPI # ☐☐☐☐☐☐☐☐☐☐

Please extract the following information from the participant's medical record. HIV-negative women do not need to undergo medical record review.

1. Date of Record Review..... ☐☐ ☐☐ ☐☐ (dd mm yy)

2. Name of reviewer..... _____

3. Patient is a member of which clinic?..... ☐ PEPFAR ☐ WELLNESS

4. Date of first HIV diagnosis..... ☐☐ ☐☐ ☐☐ (dd mm yy) *Not available* ☐

5. Most recent CD4 count..... ☐☐☐☐ cells/absolute count *Unavailable* ☐ → **Go to question 6**

5.1 Date drawn..... ☐☐ ☐☐ ☐☐ (dd mm yy)

6. Lowest (nadir) CD4 count..... ☐☐☐☐ cells/absolute count *Unavailable* ☐ → **Go to question 7**

6.1 Date drawn..... ☐☐ ☐☐ ☐☐ (dd mm yy)

7. Most recent viral load measure..... ☐☐☐☐☐☐ cells/absolute count *Unavailable* ☐ → **Go to question 8**

7.1 Date drawn..... ☐☐ ☐☐ ☐☐ (dd mm yy)

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8. CDC staging.. ☐ A
☐ B
☐ C
☐ Not enough information

9. ARV History: ☐ *Not applicable (i.e. patient has never taken ARVs, END)*

ARV drug code	***Start date***	***Stop date***	***Ongoing***
[ ][ ]	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	☐
[ ][ ]	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	☐
[ ][ ]	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	☐
[ ][ ]	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	☐
[ ][ ]	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	☐
[ ][ ]	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	[ ][ ] *dd* [ ][ ] *mm* [ ][ ] *yy*	☐
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Study Drug Code:

01. = Stavudine (D4T, Zerit)
02. = Lamivudine (3TC, Epivir)
03. = Efavirenz (Stocrin)
04. = Nevirapine (Viramune)
05. = Nelfinavir (Viracept)
06. = Zidovudine (Retrovir,AZT)
07. = Didanosine (Videx,ddI)
08. = Lopinavir + Ritonavir (Kaletra)
09. = Ritonavir (Norvir)
10. = Saquinavir (Invirase, Fortovase)
11. =Combivir (AZT & 3TC, CBV)
12. Triomune
13. Tenofovir (TDF, Viread)
14. Abacavir (ABC, Ziagen)