Expanding access to antiretroviral therapy in southern Africa and India:

Implications for HIV prevention and care delivery in resource-limited settings

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A.B., Brown University, 2006

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This dissertation by Kartik K Venkatesh is accepted in its present form by the Department of Community Health as satisfying the dissertation requirement for the degree of Doctor of Philosophy.

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EDUCATION

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Undergraduate education:
Brown University: *Magna cum laude, phi beta kappa with double honors in Anthropology and Classics/Sanskrit in 2006*
- **Program in Liberal Medical Education (PLME):** 8-year continuum leading to both B.A. and M.D. degrees
- **Undergraduate concentration:** A.B. in Classics/Sanskrit; A.B. in Anthropology
Honors Theses:
"Tradition in Transition: Historical and Current Interpretations of *Puja*" in Sanskrit/Classics; and "The Gods come to America: Construction, Representation, and Reproduction of Real and Imagined Indian Diasporas" in Anthropology

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HONORS

Societies:
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Academic Honors:
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- 1st Place Graduate/Post Doctoral Fellowship Research, Brown Medical School Public Health Research Day (2010)
- Young Investigator Award, Conference on Retroviruses and Opportunistic Infections (CROI) (2010)
- Investigator Award, Brown University AIDS Program, Brown Medical School Public Health Research Day (2009)
- 2nd Place Graduate/Post Doctoral Fellowship Research, Brown Medical School Public Health Research Day (2007)
- Babette and Peter Stewart Scholarship for humanism in medicine, Brown Medical School (2006)
- Highest Achievement Honors Thesis Award in Anthropology, funded by the Albert Arnold Bennett Class of 1872 Award, Dept of Anthropology (2006)
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Community Honors:
- Honorable Mention, Community Contribution Award, Asian American Alumni Alliance (A4), Brown University (2006)
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- Sanskrit: Fluent in reading and writing in Vedic and Classical Sanskrit
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RESEARCH EXPERIENCE

Junior investigator and research assistant, Centers for AIDS Research (CFAR) (Dept. of Medicine, Brown Medical School) (6/06-Present)
- Examine primary and secondary prevention in the clinical care setting of YRG CARE, Chennai, India
- Study natural history of HIV disease in the era of antiretroviral therapy in South India

Research assistant, Childhood Asthma Research Program (CARP) (Dept. of Child and Family Psychiatry, Brown Medical School) (5/05-6/06)
- Examine healthcare disparities and psychosocial and cultural components of asthma among urban minority children
- Conduct interviews/protocols in English and Spanish; perform daily operations of running study and recruitment

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Global Frameworks Scholarship (08-09)
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David E. Rogers Fellowship Program, New York Academy of Medicine (07-08)
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Summer Scholarship for Medical Students, Infectious Diseases Society of America (07-08)
- To study the natural history of HIV disease, particularly AIDS defining illnesses and genotypic resistance, in South India

Foreign Studies Fellowship, International Health Institute, Brown University (09-10; 08-09; 07-08)
- To conduct gender-based studies of HIV natural history and prevention in South India and South Africa

International Health Travel Scholarship, Division of Biology and Medicine, Brown University (07)
- To examine different antiretroviral treatment strategies, including treatment switching and substitution, in South India

Jeanne Spurlock Minority Medical Student Clinical Fellowship in Child and Family Psychiatry, American Academy of Child and Adolescent Psychiatry (05-06)

Margaret B. Stillwell Prize in Book Collecting (John Carter Brown Library, Brown University) (05)

Research at Brown (RAB) Grant (Dean of the College) (8/04-12/04)

Research Grant, Office of the Vice President of Research (5/05-6/06)
Undergraduate Teaching Research Assistantship (UTRA) (6/04-8/04)
Royce Fellowship (Swearer Center for Public Service) (4/03-6/04)

TEACHING EXPERIENCE

Small group leader and guest lecturer in "Epidemiology and Biostatistics" as part of Year I and II of medical curriculum (09-present)
Guest Lecturer in "Introductory Methods in Epidemiologic Research" (09-present)
Graduate teaching assistant and guest lecturer in "Burden of Disease in Developing Countries" (09)
Teaching Assistant and guest lecturer in "AIDS in International Perspective" (05-09)
Lab Consultant, Computing and Information Services (10/04-Present)
  - Assist in technical problem solving for students/faculty; manage daily operations in campus computing clusters

LEADERSHIP

Scholarly Concentrations Working Group, Brown Medical School (1/07-Present)
Committee member, Rhode Island Medical Society (RIMS) (4/09-04/10)
Board member, Brown Medical School Alumni Association (5/08-5/10)
President, Brown Medical School Student Senate (5/08-6/09)
Treasurer, Brown Medical School Senate (5/07-5/08)
MD'10 Primary class advocate, Brown Medical School Senate (9/06-05/07)
Committee member, Medical Students, Residents, and Early Career Psychiatrists Committee (MRECP), American Academy of Child and Adolescent Psychiatry (11/05-11/08)

COMMUNITY SERVICE

Spanish Interpreter and medical volunteer, Rhode Island Free Clinic (10/04-Present)
  - Translator and interpreter at the state's only free clinic in South Providence
Brown University Community Council (BUCC) (4/08-6/09)
University Disciplinary Council (11/08-6/09)
Working Group on Global Health, Internationalization Initiative, Brown University (3/07-6/07)
Brown University Honorary Degrees Committee (5/04-5/06)
President, 7-9 Benefit Street Condominium Association, Providence, RI (9/06-Present)

BOOK CHAPTERS

1. S Solomon, **KK Venkatesh**. 2008. Structural Interventions in Societal Contexts. *HIV Prevention*. K Mayer, HF Pizer, eds. Elsevier. In press.

2. KH Mayer, HF Pizer, **KK Venkatesh**. The Social Ecology of HIV/AIDS. *Medical Clinics of North America*. ME Wilson, ed. Elsevier. 2008;Nov;92(6):1363-75, x.

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1. **KK Venkatesh**. 2006. HIPAA vs. Hippocrates. *Academic Medicine*. 2006 Oct;81(10):881.

2. **KK Venkatesh**. 2007. When the Gods Come to America: Constructing an Indian Diaspora through the Home and Temple. *Oriente* (European journal specializing in Asian Anthropology).

3. N Kumarasamy, **KK Venkatesh**, B Devaleenal, AJ Cecelia, T Yepthomi, S Saghayam, S Solomon, KH Mayer. Opportunities and options for the use of Protease inhibitors in a resource poor setting: Experiences from Southern India. *Journal of Acquired Immune Deficiency Syndrome*. 2007 Sep 1;46(1):119-21

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6. N Kumarasamy, **KK Venkatesh**, AJ Cecelia, B Devaleenal, AR Lai, S Saghayam, P Balakrishnan, T Yepthomi, S Poongulali, TP Flanigan, S Solomon, and KH Mayer. Spectrum of Adverse Events Following Generic HAART in Southern Indian HIV-Infected Patients. *AIDS Patient Care and STDs*. 2008 Apr;22(4):337-344.

7. **KK Venkatesh**, L Prasad, N Kumarasamy. HIV transmission transcends three generations: Can we prevent secondary transmission in India? *International Journal of AIDS and STDs*. 2008 Jun;19(6):418-420.

8. **KK Venkatesh**, J Biswas, N Kumarasamy. Impact of Highly active antiretroviral therapy (HAART) on Ophthalmic manifestations in HIV/AIDS. *Indian Journal of Ophthalmology*. 2008 Sep-Oct;56(5):391-3.

9. N Kumarasamy, P Balakrishnan, **KK Venkatesh**, AK Srikrishnan, AJ Cecelia, E Thamburaj, S Solomon, KH Mayer. Prevalence and incidence of sexually transmitted infections among South Indians at increased risk of HIV infection in press in *AIDS Patient Care and STDs*. 2008 Aug;22(8):677-82.

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born to HIV-infected women in South Africa: implications for child survival and health in resource-limited settings. *Journal of Tropical Pediatrics*. 2010 Jul.

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31. S Cu-Uvin, A DeLong, **KK Venkatesh**, J Hogan, J Ingersoll, J Kurpewski, MP De Pasquale, R D'Aquila, A Caliendo. Genital Tract HIV-1 RNA Shedding among Women with Below Detectable Plasma Viral Load in press in *AIDS*.

32. KH Mayer, **KK Venkatesh**. Antiretrovirals for HIV primary prevention: state of the science and the way in press in *Journal of Acquired Immune Deficiency Syndrome*.

33. **KK Venkatesh**, G de Bruyn, MN Lurie, L Mohapi, P Pronyk, M Moshabela, E Marinda, GE Gray, EW Triche, NA Martinson. Decreased sexual risk behavior in the era of HAART among HIV-infected urban and rural South Africans attending primary care clinics under review.

34. **KK Venkatesh**, MN Lurie, E Triche, G De Bruyn, ST McGarvey, GE Gray. Height, weight, and growth in children born to HIV-infected women in South Africa according to maternal and infant characteristics under review.

35. **KK Venkatesh**, A van der Straten, H Cheng, ET Montgomery, MN Lurie, T Chipato, G Ramjee, K Blanchard, NS Padian, KH Mayer, G de Bruyn. Biological and behavioral risk factors for HIV acquisition in southern African women in the MIRA study: implications for HIV prevention under review.

36. **KK Venkatesh**, AK Srikrishnan, KH Mayer, N Kumarasamy, S Raminani, E Thamburaj, L Prasad, EW Triche, S Solomon, SA Safren. Predictors of non-adherence to HAART among HIV-infected South Indians in clinical care: implications for developing adherence interventions in resource-limited settings under review.

37. **KK Venkatesh**, AK Srikrishnan, SA Safren, EW Triche, E Thamburaj, L Prasad, MN Lurie, M Suresh Kumar, N Kumarasamy, S Solomon, KH Mayer. Marriage, fertility intent, and unprotected sex among HIV-infected South Indians in primary care under review.

Preface and Acknowledgments

This doctoral dissertation represents research and training over the past five years through the MD/PhD program at Alpert Medical School, Brown University. I would like to thank my parents, Drs. Venki and Mangala Venkatesh, for instilling in me their immigrant ethic and commitment to education from a very young age. Perhaps as the son of an engineer father and neurologist mother, pursuing an MD/PhD was the "natural" career trajectory! I would also like to thank my older brother Dr Arjun Venkatesh for his ever optimistic mentorship and support.

At Brown, I must begin my thanking my two local anthropologist "mothers" who have always been ever ready to provide scholarly and personal guidance over the past eight, Drs. Lina Fruzzetti and Patricia Symonds. They instilled in me a commitment to looking at social science from subaltern and gendered perspectives. I would like to thank my chair of my dissertation committee, Dr Mark Lurie, who introduced me to conducting research in South Africa and opening a very fruitful research collaboration that has now developed at the University of the Witwatersrand/Chris Hani Baragwanath Hospital. Over the past five years, I have been able to execute my research and clinical training through the countless hours of thoughtful mentorship of Dr Kenneth Mayer. He has truly taught me what it means to be a physician-scientist. I have learned what it means to be a practicing epidemiologist from Dr Elizabeth Triche through our weekly memorable conversations on epidemiological methods, including the art of regression model construction. Dr Stephen McGarvey was always there to passionately advocate for my global research, and his keen observations and mentorship has provided me with the "survival skills" to navigate the halls of academia.

Table of Contents

CHAPTER 1: INTRODUCTION

Background

This background section highlights the major themes of the dissertation studies. The first section on HIV epidemiology provides an overview of the epidemic in the African and Indian settings of these studies. The following two sections then document the public health impact of expanding access to antiretroviral therapy (ART) on HIV natural history and the increasing debate about the use of ART as a means of HIV prevention. Since both viral and bacterial sexually transmitted infections (STIs) have been shown to be epidemiology synergistic with HIV, the next section provides an overview of STIs associated with HIV acquisition and transmission. There has also been growing concern of possible increases in risk behaviors following wider uptake of ART, and the next section reviews the relationship between treatment and sexual risk behaviors. Due to the continued high incidence of infant HIV infection in resource-limited settings due to lack of adequate maternal access to testing and treatment, the last section review the impact of HIV on maternal and child health.

Epidemiologic review of HIV/AIDS in sub-Saharan Africa and India

HIV continues to spread rapidly with over 2.5 million new infections globally each year [1], with the overwhelming majority of new cases occurring in resource-limited settings. It is estimated that globally 33 million individuals are currently living with HIV

[1], and increasingly the HIV epidemic has become feminized with almost half of all new HIV infections occurring among women [1]. Despite expanding access to voluntary HIV testing and counseling (VCT) and treatment, survey data from sub-Saharan Africa suggests that only 12-25% of individuals infected with HIV are aware of their status in that region [2]. At an individual level, HIV transmission remains a low probability but high consequence event, occurring in less than 1 in 100 contacts on average[3-5], but the global pandemic is potentiated by the frequency of humans having sexual intercourse and factors that amplify infectiousness and susceptibility in specific settings, such as sexually transmitted infections (STIs) and other risk taking behaviors (i.e. unprotected sex, multiple sex partners, substance use) [6]. The per contact calculation is based on composite data, and transmission probabilities vary considerably during the course of the disease, with higher transmission probability in the acute and late phases of HIV infection, as a reflection of plasma and genital HIV concentrations [7-11].

South Africa currently is home to the highest number of HIV-infected individuals in the world with an estimated 5.7 million individuals living with HIV/AIDS; HIV prevalence is near 20% among adults aged 15-49 years and 32% among pregnant women attending government antenatal services [12, 13]. The primary mode of HIV transmission in this generalized epidemic has been through heterosexual sex [14]. South Africa now faces a two-fold epidemic: one epidemic that has continued for over a decade is over 500,000 new infections per year, while the other epidemic is managing an ever-growing AIDS morbidity and mortality [15]. The high prevalence of HIV among young adults, which is likely linked to high risk sexual behaviors and a high prevalence of sexually transmitted infections (STIs), is cause for concern [16-18]. Possible behavioral

reasons for increased HIV risk in this region include inconsistent condom use within regular partnerships, risk profiles of male partners for married women, multiple sexual partnerships, and densely connected sexual networks in which few HIV individuals are aware of their infection [19-21]. All three thesis chapters involve data from South Africa.

After South Africa, India is likely home to the second largest population of HIV-infected individuals with about 2.5 million Indians currently infected with the virus and with a national prevalence among adults of 0.36% [22]. In India, the epidemic remains largely confined to individuals identified to be at high risk for HIV infection, including female sex workers (FSW), men who have sex with men (MSM), drug users, men who travel for work, and their primary sex partners [23]. Since the majority of the adult Indian population is married, for married monogamous women in this setting, sex with one's husband is the strongest risk factor for HIV [24, 25]. Chapter 2 includes data from South India.

The impact of antiretroviral therapy on HIV natural history

It has been close to 15 years since highly active antiretroviral therapy (HAART) was first introduced, and AIDS-related hospitalizations and death rates have been substantially reduced in both the developed and developing world [26-28]. Today ART continues to be made ever more sustainable, effective, and simpler, but the need for treatment on a global scale has grown with the continued rise in the number of HIV-infected individuals [29]. Over the past few years, the availability of fixed-dose generic therapy as a single combination for less than $1 a day had set the stage for the global expansion of ART across the developing world. However, any optimism generated by

the possibility of a global universal first-line treatment has now been tempered by the realities of treatment-associated toxicities [30]. A more promising first-line treatment option includes a fixed-dose combination containing tenofovir, which is a simple, safe, and well-tolerated regimen [31, 32].

About 3 million individuals were receiving ART by the end of 2007, but an estimated 6.7 million individuals were in need of treatment and an additional 2.7 million became infected with HIV in 2007. Despite the unprecedented gains in treatment access across the developing world through multilateral organization-based initiates, the number of individuals receiving ART must be put within the larger context of the estimated 38 million individuals who are currently living with HIV[10], and the reality that the number in need of treatment will now expand based on recently updated WHO treatment guidelines recommending treatment initiation at CD4 cell counts of 350 cells/ul or below [33].

Timely initiation of treatment suppresses viremia, increases CD4 cell counts, reduces the risk of drug-resistant virus, and improves general immune function in what is otherwise a progressive disease [34]. The CD4 cell count at the time of initiating therapy is the strongest predictor for risk of death and AIDS [35], and initiating ART at higher CD4 cell counts has been shown to decrease the risk of death, opportunistic infections, and of non-HIV related comorbidities [36, 37]. Although data from randomized controlled trials are not currently available to support initiation of ART at higher CD4 cell counts due to both ethical and logistical reasons, analyses of large observational cohort studies from diverse settings has guided our understanding of when to initiate ART. Treatment guidelines have been built around the evidence that sustained viral suppression is necessary to achieve a continued increase in CD4 t-lymphocytes, for an

optimal clinical response, and to minimize the development of drug resistant mutations. Observational data from North American and European cohorts have suggested that patients who begin ART at CD4 cell counts greater than 350 cells/ul have better immunological recovery and normalization of CD4 cell counts longitudinally compared to patients who delay treatment initiation [38-40]. In light of these emerging data, the WHO recently modified treatment initiation criteria recommending that those with a CD4 cell count at or below 350 cells/ul initiate therapy (the previous guidelines recommended a cut-off of 200 cells/ul) [33].

There is still considerable debate over what constitutes a public-health driven approach towards ART delivery [41]. The disheartening reality is that the number of new HIV infections each year remains more than double the number of HIV-infected individuals initiating therapy that year [1]. Due to the continued decline in CD4 cell counts in untreated individuals, the vast majority of currently HIV-infected individuals will be in need of treatment within the next decade. This means that by 2015 most of the 38 million currently HIV-infected individuals will be ART eligible based on the revised WHO treatment guidelines [42]. A growing public health concern is whether the current treatment strategy will be sustainable with the continued increase in the number of new HIV cases globally, coupled with increasing donor fatigue and changing global health priorities[43]. If universal treatment access is the ultimate goal, then the current provision of therapy must be viewed as a necessary but short-term emergency response [44].

Treatment as prevention

It is currently estimated that for every individual who received ART, an estimated four still require treatment [2]. The patient-centered approach to HIV management is based on the fact that ART can change the natural history of HIV into a manageable chronic medical condition. Beyond individual clinical benefits, by rendering an individual less infectious, treatment as prevention could also have the larger public health impact of curbing the growth of the epidemic [45-47]. The best evidence of the effect of ART on HIV prevention has come from the prevention of mother-to-child HIV transmission (PMTCT) [48, 49]. Further data about the role of ART in decreasing HIV sexual transmission from infected individuals has emerged from observational studies of serodiscordant couples [50-52], as well as the use of ARVs for post-exposure prophylaxis in occupational healthcare settings [53, 54].

At a biological level, the transmission dynamics of HIV-1 through body fluids, including seminal, vaginal, breast milk, and blood routes, have been well documented; ART has been shown to predictably decrease HIV-1 RNA levels in both plasma and genital compartments of treated individuals [55, 56]. The Rakai study from rural Uganda showed that plasma viral load (PVL) is the main predictor of HIV sexual transmission, and that transmission is rare when plasma HIV-1 RNA levels are below 1500 copies/ml [50]. No cases of HIV transmission occurred among couples in which the index partner had an HIV RNA level below 400 copies/ml. Another study among serodiscordant heterosexual couples in Thailand showed a dose-response effect between PVL and HIV transmission risk[51]. No cases of HIV transmission occurred below 1100 copies/ml. In

the era prior to ART, an Italian study of serodiscordant couples documented a 50%

reduction in HIV transmission attributed to the use of zidovudine monotherapy [57]. In

the ART era, a Spanish study of serodiscordant couples showed no HIV transmission in

the sexual partners of ART-experienced patients, and that ART was associated with a

substantial reduction (80%) in HIV transmission [52]. Recent data from southern Africa

has suggested that ART use was associated with substantially lower risk of HIV

transmission among heterosexual, HIV serodiscordant couples [58]. It has also been

recently reported from American and Canadian ecological studies that reductions in

community viral load via increased treatment access could decrease HIV incidence over

time, suggesting that wide-scale early treatment could have a preventive impact at a

population level [59, 60]. These observational studies among diverse patient populations

have provided further data both about the immune restorative effects of ART as well as

the role of ART in decreasing HIV transmission to uninfected individuals. Further

prospective data is needed to better understand the relationship between ART coverage,

plasma viral load, and HIV incidence, which is being examined currently in randomized

clinical trials.

Recent mathematical models have also highlighted the possible impact of wider

access to treatment on curbing HIV incidence. These models have suggested that the

more HIV-infected individuals treated at an earlier phase in the natural history of HIV in

a given population, the greater the preventive impact of expanded therapy in stopping

further infections, ultimately providing both individual and public health benefits [61].

Early models did show that the provision of ART could eradicate high-prevalence

epidemics, even with high levels of drug resistance and of high risk sexual behavior [62,

63]. A recent mathematical model using the South African epidemic as an example showed that the immediate commencement of ART following detection of all individuals found to be HIV infected through regular annual screening could dramatically reduce HIV incidence to less than one case per 1000 people per year [45]. In fact, in as little as five years this strategy could lead to the transition from the present epidemic phase in which most individuals with HIV are not receiving ART to the elimination phase in which most individuals with HIV are on ART. These model-based approaches raise many questions about feasibility and the ethical distribution of treatment in resource-constrained settings already unable to adequately provide treatment to HIV-infected individuals meeting treatment guidelines. However, these model-based approaches could potentially prove to be cost-effective in the long-term because the ART-induced reduction in infectivity should reduce further HIV transmission, resulting in fewer people needing to access ART. Chapter 2 examines the consequences of wider access to ART through determining whether sexual risk taking behaviors increase once HIV-infected individuals initiate treatment, which has implications for onward secondary transmission to sex partners. Chapter 3 emphasizes the need for greater and timely access to ART among HIV-infected mothers and their infants.

Sexually transmitted infections and HIV acquisition

Complicating HIV transmission dynamics is the fact that concurrent sexually transmitted infections (STIs) can increase HIV transmission probability [64]. Bacterial STIs have been shown to increase HIV-1 viral load in genital tract secretions [65], and interventions that provide treatment of these infections can decrease HIV-1 viral shedding [9, 66-68]. Despite observational epidemiologic data on viral STIs (primarily

HSV-2) as increasing the risk for HIV transmission and acquisition [69], clinical trials of acyclovir suppressive therapy were not associated with a decrease in HIV incidence [70]. A review of the seemingly contradictory findings of the impact of STI treatment on HIV incidence suggests that STI interventions initiated at early stages in an epidemic, and focused on tailored syndromic management, may have the greatest prospect of slowing down HIV transmission in specific environments [71, 72]. A limitation of many observational studies examining the association between STIs and HIV acquisition is that STI co-infections at the same time as the outcome are included in analyses, restricting the ability to assess exposure-outcome temporal causation. Additionally, both HIV and STIs result from the same sexual risk behaviors, so even after adjustment for sexual behaviors, remaining associations may still be an artifact of residual confounding. The current discordance between clinical trials of STI treatment and observational data documenting associations between STI exposure and HIV acquisition may be due to variety of factors, including limited power to detect a moderate effect, bias due to losses to follow-up, suboptimal treatment adherence, treatment doses were not sufficient to fully suppress STIs at the cellular level, lack of adequate STI exposure, and confounding as both STIs and HIV-1 were transmitted by the same sexual risk behaviors.

Longitudinal data from sub-Saharan Africa have suggested that STIs increase the infectiousness of HIV-infected individuals and the susceptibility of HIV-uninfected individuals [64, 73], and STI control has been recommended as an effective means of HIV prevention, particularly in the generalized HIV epidemics in this region [73, 74]. The role of *Herpes simplex* virus type 2 (HSV-2), which is one of the most common causes of genital ulcer disease, has increasingly been recognized as enhancing the risk of

HIV transmission and acquisition in sub-Saharan Africa [69, 75, 76]. HSV-2 acquisition is estimated to be 10-20% per year after sexual debut among South African young adults, and 20% of HIV seronegative and 80% of HIV seropositive teenagers are HSV-2 seropositive [77]. Other STIs, including *Trichomonas vaginalis* and *Neisseria gonorrhea*, have also been reported to increase the risk of HIV acquisition in sub-Saharan Africa [78]. Chapter 1 examines STI exposures in the context of HIV acquisition among young southern African women. Unlike many earlier studies, this study assesses the temporality of STI exposures in relation to HIV incidence.

Sexual risk behaviors and HIV transmission

As more individuals live with HIV and receive ART, there is a larger pool of individuals with HIV (ie higher prevalence) that could result in an increase in the number of new HIV infections (ie higher incidence). At the same time, ART also decreases plasma and genital tract HIV levels, and consequently reduces the risk of HIV transmission. Sexual risk behavior has generally been measured as multiple sex partners, substance use, and lack of consistent condom use [79]. Early data from high risk groups, such as MSM in the developed world, suggested that further access to ART could lead to increases in high risk behavior, often referred to as behavioral disinhibition or risk compensation, despite individual reductions in HIV-1 plasma viral load [80-82]. However, meta-analyses to date do not suggest increases in sexual risk taking behaviors among ART-experienced individuals from the developed world [83, 84].

Studies on the impact of ART on sexual behavior among HIV-infected individuals in resource-limited settings have been inconsistent, and it is not clear whether

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the provision of ART leads to an increase in high risk sexual behavior [79, 84]. Recent data from HIV-infected female sex workers in Kenya found that unprotected sex but not the number of sex partners decreased following ART initiation [85]. South African and Kenyan cohorts with 12 months of ART follow-up have also documented a decrease in the frequency of unprotected sex [86, 87]. A clinic-based cohort from Uganda found that while sexual activity increased following ART, condom use increased and the number of sex partners decreased [88], which was concordant with an earlier Ugandan cohort study [83]. Recent cross-sectional studies from African settings have also suggested that ART was not associated with increased sexual risk behaviors [89-92]. In contrast, a study from Cote d'Ivoire found that unprotected sex significantly increased during the first 6 months of treatment [93]. Differing results in these settings highlight the complexity of measuring the association between ART and sexual behavior and variations in study populations and treatment program characteristics. Further longitudinal data is needed to understand whether initial decreases in sexual risk behavior following ART initiation are sustained over time. Chapter 2 first includes two cross-sectional analyses of sexual risk behaviors and treatment adherence in relation to ART exposure from South India. Quantitative data from India examining these outcomes remains very limited, so these studies add substantively to our understanding of sexual behavior in the era of ART in this region. The second part of chapter 2 involves a large cohort study examining sexual risk taking behaviors in South Africa. This study represents the largest cohort to date conducted over a decade examining sexual risk behaviors from a resource-limited setting. Both the Indian and South African data are from observational cohorts in which HIV-infected individuals were enrolled in HIV care and prevention programs.

Impact of HIV on maternal and child health

HIV infection affects an estimated 2.3 million children worldwide, and the majority (>90%) live in sub-Saharan Africa [1]. It is estimated that in South Africa alone 300,000 children are HIV-infected [94]. Over a third of South African women of childbearing age are HIV-infected, and maternal HIV is likely a major component of elevated childhood mortality rates in both infected and uninfected children [95, 96]. Antiretroviral (ARV) prophylaxis during pregnancy and delivery has been shown to be an effective means of reducing the risk of mother-to-child transmission (MTCT) [97, 98]. Despite increasing access to MTCT, coverage remains low and disparate [99]. Continued HIV transmission to children results from lack of adequate maternal access to testing and prompt treatment initiation.

Postnatal transmission through breastfeeding remains an important source of possible infection [100, 101]. In sub-Saharan Africa, breastfeeding is widely practiced and can be prolonged beyond the first year of birth. The rate of breast milk transmission of HIV in sub-Saharan Africa is estimated to be at least 16% and is responsible for 40% of perinatally acquired HIV infections [101]. HIV-infected mothers face a dilemma regarding how to feed their newborn infants due to the competing risk of HIV transmission associated with breastfeeding and the risk of increased morbidity and mortality associated with formula-feeding [102-105]. Current global guidelines advise for exclusive breastfeeding for the first six months of life followed by the introduction of nutritious complementary foods, while breastfeeding continues up to two years or beyond when replacement feeding is not accessible, feasible, affordable, sustainable, or safe [106,

107]. Several African studies have suggested that exclusive breastfeeding could decrease the cumulative risk of HIV transmission while maintaining the benefits of breastfeeding [108-111], but the risk of HIV infection does not exist if breast exposure is completely avoided [112]. However, non-breastfed children can be at increased risk of hospitalization and dying from infectious diseases [113-115]. The risk of infant morbidity and mortality appears to be highest in the months after birth[112]. A pooled analysis from resource-limited settings had suggested that there is a protective effect of breast milk, particularly in the months after birth, against diarrhea and acute respiratory infections [113]. Another pooled analysis found no difference in infant mortality between breast-fed and formula-fed infants [95]. Data examining morbidity and mortality using validated clinical outcomes among HIV-exposed infants in Africa remains limited. Chapter 3 involves a cohort of HIV-exposed South African infants examining validated clinical outcomes, excluding morbidity and mortality events that were not related to maternal and infant HIV disease and feeding methods.

Pediatric HIV infection is also associated with growth retardation and is likely a significant contributor to infant malnutrition and morbidity [116]. Poor growth can be one of the first clinically recognized manifestations of HIV infection in children and has a significant impact on short-term survival [117, 118]. Disturbances in growth are likely to occur well before the onset of opportunistic infections or other HIV-related disease manifestations [119]. It has been suggested that over half of all HIV-infected children experience abnormal growth patterns [117, 120]. HIV-infected children have been shown to demonstrate stunting and wasting compared to HIV-uninfected children of the same age from diverse regional settings, and stunting and wasting can occur within the

first few months after birth [121, 122]. The degree to which maternal characteristics, vertically acquired HIV infection, or an adverse environment place children at increased risk for growth retardation remains to be fully elucidated in resource-limited settings [123, 124]. Studies conducted among infants born to HIV-infected mothers can provide insight into the nutritional implications of pediatric HIV infection. To date data on large cohorts of HIV-exposed infants from sub-Saharan Africa with a close frequency of anthropometric measurements during the first months of rapid growth after birth remains limited. Also, it remains to be fully elucidated the relative contribution of maternal relative to infant characteristics on growth among HIV-exposed infants. Chapter 3 examines growth parameters among a large cohort of South African HIV-exposed infants by isolating the relative contribution of both infant and maternal characteristics.

Study purpose

Overall aim: To understand risk factors associated with HIV acquisition in at risk women, sexual risk taking behaviors among HIV-infected individuals, and the impact of HIV on maternal and child health in resource-limited settings.

1. **Aim I (Chapter 2):** To determine biological, behavioral, and socio-demographic risk factors associated with HIV acquisition in sexually active young women at high risk for HIV infection in southern Africa.

2. **Aim II (Chapter 3):** To examine the relationship between sexual risk taking behaviors and ART among HIV-infected men and women enrolled in care programs in South India and South Africa.

3. **Aim III (Chapter 4):** To assess maternal and infant characteristics associated with infant morbidity, morality, and growth outcomes among HIV-exposed infants in South Africa.

Theoretical framework

Life-course perspective to HIV/AIDS

This dissertation examines the implications of HIV infection at the time of acquisition among at risk women, then when HIV-infected individuals receive care and treatment, and finally the impact of maternal HIV infection on infant health outcomes. Figure 1 summarizes this life-course perspective towards HIV-infection in terms of each of the dissertation chapters. The first chapter focuses on HIV acquisition in young, sexually active southern African women to tease out the temporal effects of prevalent and incident STI exposures, as well as other socio-demographic and behavioral covariates, on HIV incidence. Due to the continued high incidence of HIV in young sexually active women in this region, a better understanding of risk factors for HIV acquisition using timely data can inform future primary prevention interventions. Chapter 2 examines sexual risk behaviors, measured as being sexually active, unprotected sex, and multiple sex partners, among HIV-infected men and women in care programs in South India and South Africa. In light of increasing access to ART across resource-limited settings, data is needed to understand whether sexual risk behaviors increase once HIV-infected individuals are receiving treatment and enrolled in care and prevention programs. Potential increases in sexual risk behaviors could off-set the preventive impact gained through the wider roll-out of ART. Finally, Chapter 3 examines the relative contribution of maternal and infant characteristics on morbidity, mortality, and growth among HIV-exposed infants. The high incidence of HIV among infants in sub-Saharan Africa continues due to inconsistent coverage of PMTCT and lack of timely maternal access to ART.

Public health perspective to HIV/AIDS

Within a broader public health framework, chapter 1 on HIV acquisition among at risk women encompasses primary prevention, chapter 2 examining HIV transmission behaviors among already HIV-infected individuals encompasses secondary prevention, and chapter 3 focusing on the impact of HIV on infant health focuses on clinical outcomes (See Figure 1). Primary prevention based on biomedical and behavioral interventions remains an important strategy to curb the generalized HIV epidemics of southern Africa. The findings of chapter 1 can inform the future development of STI control programs and behavioral risk reduction strategies for young southern African women at risk for HIV infection. Due to the ever increasing number of HIV-infected individuals living longer and healthier lives due to the immune restorative effects of ART, understanding whether HIV-infected individuals on treatment engage in high risk sexual behaviors that could lead to further HIV transmission (i.e. secondary prevention) remains an important public health priority. The possible preventive effects of ART could be minimized if there is an upswing in HIV transmission behaviors among ART-experienced individuals with uninfected sex partners. Chapter 2 examines the relationship between treatment and sexual risk behaviors in two different regional settings, South India and South Africa. These studies conducted among HIV-infected men and women enrolled in care programs have greater generalizability than many earlier studies conducted among high risk groups. Increasingly the burden of HIV on mothers and infants has been recognized due to inadequate access to prompt testing and treatment. Despite the success of PMTCT and prompt treatment initiation of HIV-infected pregnant women in the developed world, the gap between the current level of knowledge and

public health implementation remains considerable across the developing world. Chapter 3 focuses on the implications of HIV exposure on infant health outcomes in South Africa.

Methodological framework

Figures 1-3 are diagrams (discrete acyclic graphs or DAGs) outlining the relationship between the different independent risk factors, confounding variables, and outcomes for each of the three chapters. Figure 1 corresponds to chapter 2 on HIV acquisition, figure 2 to chapter 3 on sexual risk behavior, and figure 3 to chapter 4 on maternal-infant health. These figures focus on the variables that were assessed in the studies, but also includes other relevant factors that were not measured in italics. Positive and negative signs are used to identify the projected direction of the association between variables based on prior studies (i.e. negative and positive confounding, effect modification) and do not necessarily reflect the association documented in the final analyses; a question mark reflects associations that could go in either direction or have not been fully elucidated in previous studies to date.

Within an exposure-outcome epidemiologic causal framework, all three chapters involve longitudinal data sets in which temporality between the exposure and the outcome can be assessed. In chapter 2, close follow-up visits generally at three month intervals in addition to PCR-based STI testing rather than antibody or symptomatic diagnosis allowed for assessing STI exposures that happened at the visit prior to HIV seroconversion. As expected, the associations documented for incident STI exposures and HIV acquisition were stronger than prevalent STI exposures. Many previous studies assessing STI exposures for incident HIV have often relied on STI exposures that were

diagnosed at the same time as the outcome, precluding assessment of the temporal

association [125]. Chapter 3 includes a longitudinal study spanning close to a decade

from primary care clinics in South Africa in which many patients transitioned from pre-

HAART to post-HAART status. Most studies to date from resource-limited settings that

have assessed sexual risk behaviors and ART have been cross-sectional analyses and

longitudinal data beyond 6 months of follow-up has been limited. Chapter 4 includes

longitudinal growth outcomes and incident morbidity and mortality events with time-

varying covariates when appropriate. To date data remains limited on morbidity and

mortality outcomes among HIV-exposed infants.

All three dissertation modules involve assessing a combination of socio-

demographic, behavioral, and biological/clinical exposures. Many of the same

exposures are examined in association with different study outcomes. For instance,

plasma viral load and CD4 cell count can be examined in the context of HIV acquisition,

sexual risk behavior, and infant health outcomes. When constructing regression models

to assess a variety of exposures, a proximate-determinants conceptual framework was

used in Chapter 2 [126, 127]. In this framework that has been extensively used in

demography but only as of late in epidemiology, socio-demographic factors are

considered distal predictors relative to more proximal behavioral and biological factors

(See Figure 2). So the association between socio-demographic risk factors and HIV

acquisition would be attenuated once more proximal factors, such as intercurrent STIs

and sexual risk behaviors, are added to the model. Chapter 3 first included two

exploratory cross-sectional analyses of socio-demographic and clinical factors associated

first with sexual risk behavior and then treatment adherence. In order to identify

independent risk factors for the outcome, a stepwise model was used. Then to assess

confounding, both *a priori* confounders identified from the literature as well as covariates

that modified the non log transformed beta coefficient of independent risk factors by at

least 0.10 were introduced into the model. The final part of chapter 3 was a longitudinal

analysis where the primary predictor was ART status. Generalized estimating equations

(GEE) with a logit link allowed for examining covariates that were constant as well as

those covariates that changed over time. In order to further elucidate the within

participant impact of ART on sexual behavior, fixed effects modeling was also utilized.

Chapter 4 involved a longitudinal analysis of infant health outcomes based on both

maternal and infant characteristics. Since a Cox proportional hazards model was

employed, time-varying covariates could be used. Also, in order to elucidate the impact

of maternal and infant characteristics, separate regression models were first run and then

a combined model including all characteristics.

Background research

Over the last four years as part of his seven year MD/PhD training program, Kartik has undertaken formative research on the natural history of HIV in the era of ART in South India, and more recently in South Africa, through over ten field-based experiences. A full listing of the manuscripts resulting from these observational clinical and epidemiologic studies is included in the curriculum vitae. These observational studies have provided Kartik with the formative research training and skills to execute the proposed PhD dissertation utilizing epidemiologic methods. Table 1 describes each of the data sets used in this dissertation in terms of time of data collection, region, sample size, method of enrollment, and type of study. In the case of observational studies assessing secondary aims of original randomized controlled trials (chapters 2 and 4), appropriate adjustment was made in data analysis, such as controlling for allocation to treatment vs. placebo study arms.

Kartik completed patient chart reviews at Chris Hani Bargwanath Hospital (Soweto, South Africa) in 2009 to complete chapter 4 through validating patient morbidity and mortality outcomes with the site principal investigator, Dr. Glenda Gray. Then in 2010, Kartik completed Chapters 2 and 3 while in South Africa working with the site principal investigators, Dr. Guy de Bruyn and Dr. Neil Martinson. Chapter 3 also involves primary observational data collection by Kartik between 2006 and 2008 in India, which was funded through a Brown/Lifespan/Tufts Centers for AIDS Research (CFAR) Grant and was the primary study funded through Kartik's six-year National Institutes of Mental Health (NIMH) MD/PhD Pre-doctoral National Research Service Award (NRSA).

Tables

Table 1. Description of data sets.

REGION	SAMPLE SIZE	TIME PERIOD	STUDY SITE	METHOD OF ENROLLMENT	TYPE OF STUDY
South Africa, Zimbabwe	4948 HIV-uninfected women at baseline aged 18-49 years with a healthy cervix	2003-2005	Urban clinics in Johannesburg and Durban, South Africa; Urban clinics in Harare, Zimbabwe	Women were recruited from family planning, well-baby, and general health clinics, and from community-based organizations, through printed media and radio; median 18 months follow-up per participant	Original study was an RCT to assess diaphragm/condoms (intervention) vs, condoms alone to prevent HIV acquisition; secondary case-control analysis of correlates of incident HIV acquisition
India	249 HIV-infected men and women	2007-2008	Outpatient tertiary care HIV clinic in Chennai	Consecutive clinic enrollment of HIV-infected patients receiving clinical care	Cross-sectional exploratory study
South Africa	6000 HIV-infected men and women	2002-2009	Outpatient HIV primary care urban and rural clinics	Consecutive clinic enrollment of HIV-infected patients receiving clinical care	Observational cohort study
South Africa	1051 mother-infant dyads; all mothers HIV-infected	2000-2002	3 urban hospital sites	Consecutive hospital enrollment of mothers giving birth who were unaware of their HIV status until delivery; Women enrolled within 24 hours of delivery for 6 month follow-up	Original study was an RCT to assess two ARV regimens to prevent mother-to-child HIV transmission; secondary cohort analyses examining infant morbidity and mortality and growth outcomes

Table 2. Overview of dissertation.

LIFE -CYCLE APPROACH TO HIV/AIDS

HIV acquisition: Women at risk for HIV infection	→	HIV-infected men and women in clinical care	→	Impact of maternal HIV on child health

PUBLIC HEALTH APPROACH TO HIV/AIDS

HIV primary prevention	→	HIV secondary prevention	→	Clinical outcomes

OUTCOME ASSESSMENT

Incident HIV-1 infection	→	Sexual behavior (being sexually active, unprotected sex, multiple sex partners)	→	ICD-9 morbidity and mortality

EXPOSURE ASSSESSMENT

Biological variables: N gonorrhea Herpes simplex 2 C trachomatis T vaginalis T pallidum ***Behavioral variables:*** Condom use Substance use Frequency and types of sex Number of sex partner Contraception status Individual and partner risk behaviors HIV and circumcision of primary partner ***SES variables:*** Age Education Occupation Income Marital status, Age at sexual début No. of live births	***Biological variables:*** CD4 cell count Opportunistic infections STI symptoms Highly active antiretroviral therapy (HAART) ***Behavioral variables:*** Condom use Substance use Number of sex partners Coital frequency Types of sex HIV status of primary partner Desire to have children Quality of life ***SES variables:*** Age Education Occupation Income Marital status No. of children Migrant status Urban/rural	***Biological variables:*** Plasma viral load CD4 cell count Antiretroviral prophylaxis Infant weight Infant height Premature birth Infant HIV infection Premature birth ***Behavioral variables:*** Feeding method ***SES variables:*** Age Infant gender Maternal death

STUDY DESIGN

Nested, matched case-control study with risk-set sampling	→	Cross-sectional study Open prospective cohort study	→	Prospective cohort study

↓ (left column) ↓ (right column)

STATISTICAL METHODS

Conditional logistic regression using proximal determinants conceptual framework	→	Logistic regression modeling Generalized Estimating Equations (GEE) with logit link and fixed effects modeling	→	Cox proportional hazards modeling with time-varying covariates

↓ (left column) ↓ (right column)

PATIENT POPULATION

Sexually active women at risk for HIV infection at three sites (Johannesburg, Durban, and Harare) in South Africa/Zimbabwe, (N=5020)	→	HIV-infected men and women enrolled in clinical care for ≥6 months in Chennai, South India (N=249) HIV-infected men and women enrolled in primary care in urban and rural South Africa (N=6263)	→	HIV-infected women enrolled at time of delivery in South Africa and their infants (N=840 mother-infant dyads)

Figures

Figure 1. Conceptual framework of socio-demographic, behavioral, and biological risk factors and HIV acquisition.


```
┌──────────┐      ┌─────────────────┐              ┌──────────────┐
│ Proximal │  {   │ STIs (+)        │ ◄──────────► │ Outcome:     │
│ biological│     │ T vaginalis     │              │ HIV-1        │
│ exposures │     │ N gonorrhea     │              │ acquisition  │
└──────────┘      │ C trachomatis   │              └──────────────┘
                  │ HSV-2           │
                  │ T palidum       │
                  └─────────────────┘
```
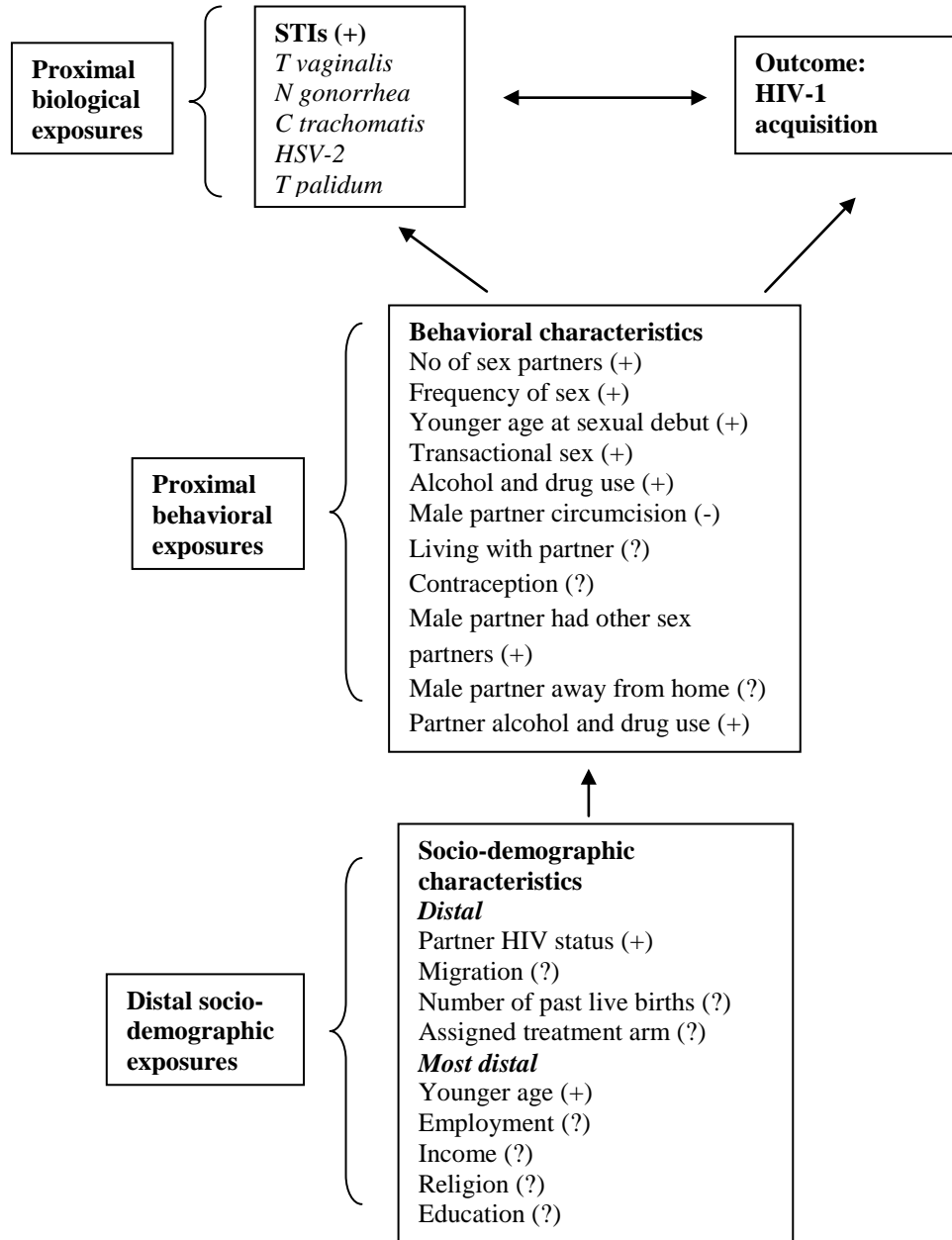
```
┌──────────┐      ┌──────────────────────────────┐
│ Proximal │  {   │ Behavioral characteristics    │
│ behavioral│     │ No of sex partners (+)        │
│ exposures │     │ Frequency of sex (+)          │
└──────────┘      │ Younger age at sexual debut (+)│
                  │ Transactional sex (+)          │
                  │ Alcohol and drug use (+)       │
                  │ Male partner circumcision (-)  │
                  │ Living with partner (?)        │
                  │ Contraception (?)              │
                  │ Male partner had other sex     │
                  │ partners (+)                   │
                  │ Male partner away from home (?)│
                  │ Partner alcohol and drug use (+)│
                  └──────────────────────────────┘
```

```
┌──────────────┐   ┌──────────────────────────────┐
│ Distal socio-│ { │ Socio-demographic            │
│ demographic  │   │ characteristics              │
│ exposures    │   │ Distal                       │
└──────────────┘   │ Partner HIV status (+)       │
                   │ Migration (?)                │
                   │ Number of past live births (?)│
                   │ Assigned treatment arm (?)   │
                   │ Most distal                  │
                   │ Younger age (+)              │
                   │ Employment (?)               │
                   │ Income (?)                   │
                   │ Religion (?)                 │
                   │ Education (?)                │
                   └──────────────────────────────┘
```
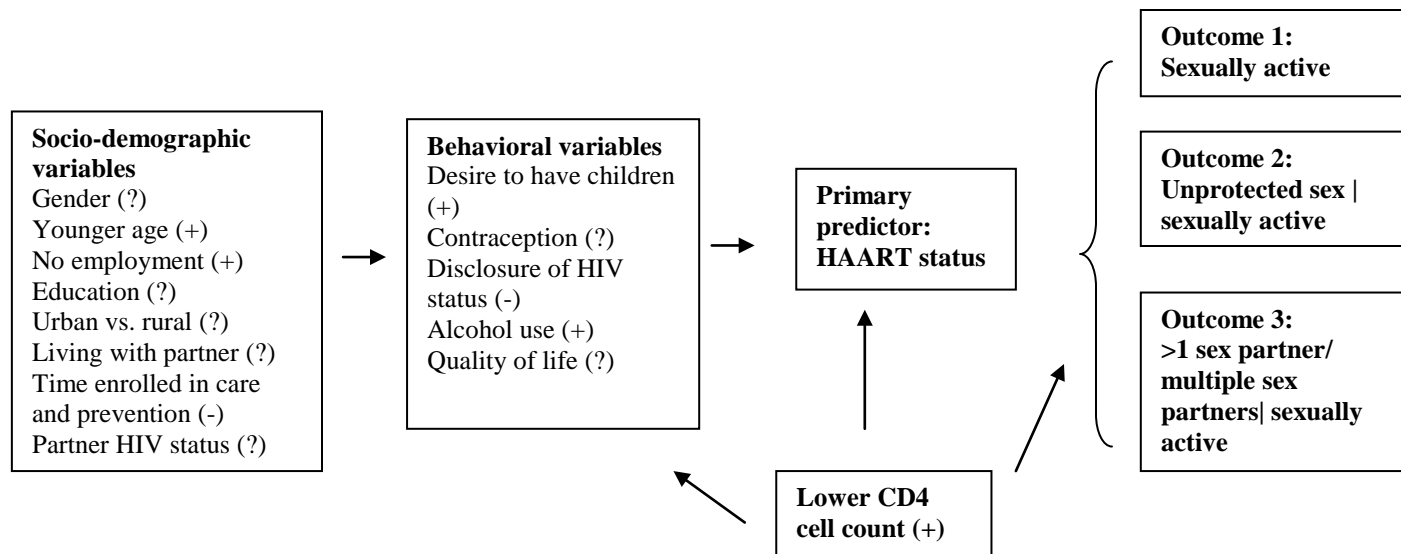
Unmeasured biological variables: Primary male partner HIV and STI status (+), Primary partner CD4 cell count (low=+), plasma viral load (high=+), and treatment status (-) if HIV infected

Unmeasured behavioral variables: Condom use (-), desire to have children (+)

Direction of projected association: + = positive; - = negative; and ? = unclear to date
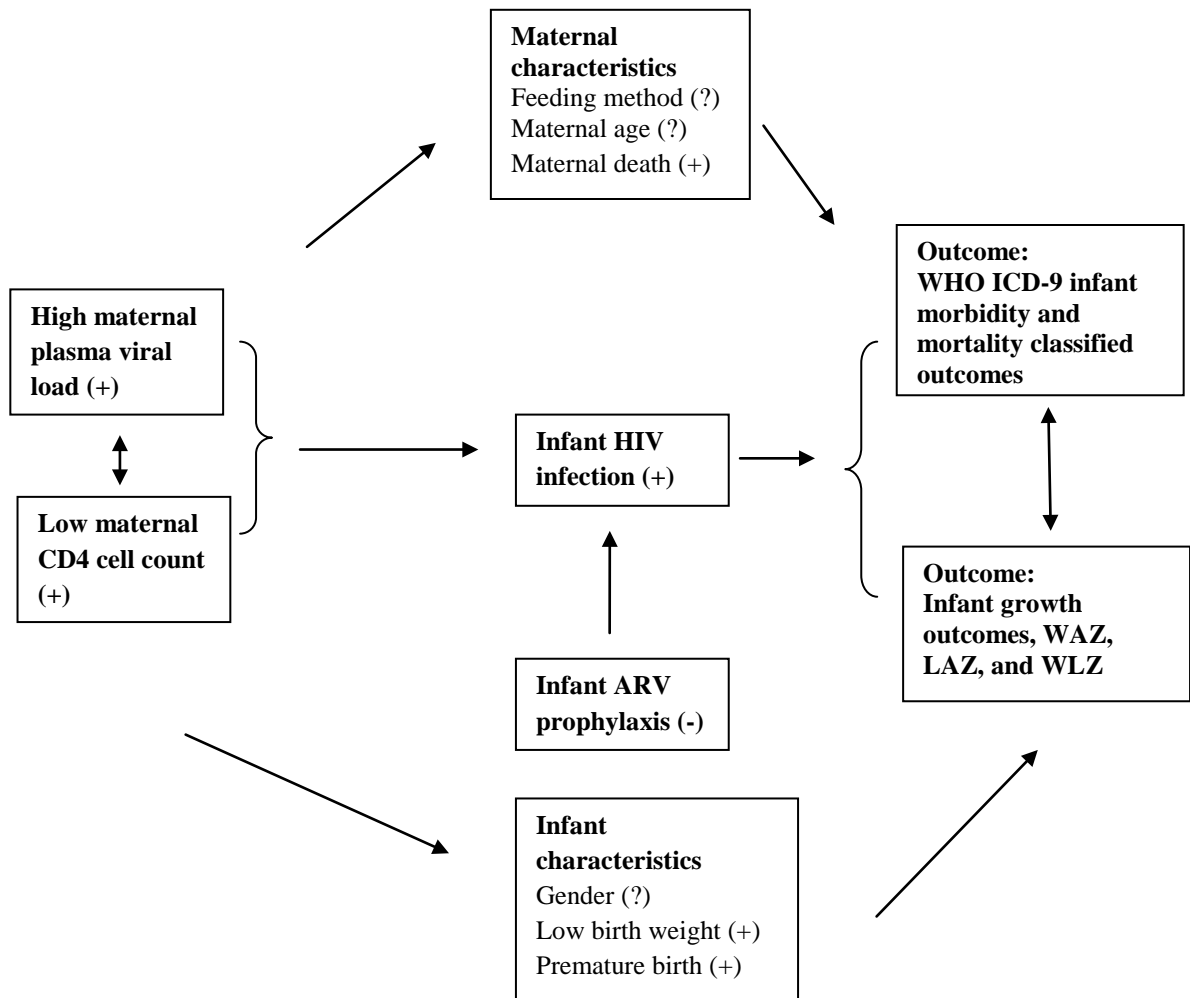
Figure 2. Conceptual framework of ART and sexual risk behaviors

Socio-demographic variables
Gender (?)
Younger age (+)
No employment (+)
Education (?)
Urban vs. rural (?)
Living with partner (?)
Time enrolled in care and prevention (-)
Partner HIV status (?)

Behavioral variables
Desire to have children (+)
Contraception (?)
Disclosure of HIV status (-)
Alcohol use (+)
Quality of life (?)

Primary predictor: HAART status

Lower CD4 cell count (+)

Outcome 1: Sexually active

Outcome 2: Unprotected sex | sexually active

Outcome 3: >1 sex partner/ multiple sex partners| sexually active

Unmeasured behavioral variables: Transactional sex (+), drug use (+)
Direction of projected association: + = positive; - = negative; and ? = unclear to date

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Figure 3. Conceptual framework of maternal and infant characteristics and infant health outcomes

Unmeasured biological variables: Infant plasma viral load and CD4 cell count if HIV-infected (+)
Unmeasured behavioral variables: Maternal psychosocial status (?)
Unmeasured socio-demographic variables: Lower maternal socio-economic status (+)
Direction of projected association: + = positive; - = negative; and ? = unclear to date

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CHAPTER 2: HIV ACQUISITION

"Biological and behavioral risk factors for HIV acquisition in southern African women in the MIRA study: implications for HIV prevention"

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Abstract

Background: Risk factors influencing the incidence of HIV infection were examined in a nested case-control study within the MIRA study, an open-label randomized controlled trial of the female diaphragm to prevent HIV infection among at risk women, in two southern African countries with high HIV prevalence, South Africa and Zimbabwe.

Methods: Cases were women who became HIV-infected after study enrollment; controls were HIV-uninfected at the time of case seroconversion selected in a 1 to 3 case to control ratio (risk-set sampling), matched on study site and time of follow-up. Conditional logistic regression models were used to calculate adjusted odds ratios (AORs) and population-attributable fractions (PAFs). Effect modification was examined through stratified multivariable analyses.

Results: We analyzed 309 case and 927 control women. Women who were older (>35 years of age AOR: 0.49; 95% CI: 0.29-0.83); p=0.008), currently living with their primary partner (AOR: 0.55; 95% CI: 0.36-0.84; p=0.006), and who had a past live birth (2 or more births AOR: 0.48; 95% CI: 0.27-0.86; p=0.013) were less likely to seroconvert. Women who had 4 or more lifetime male partners (AOR: 1.85, 95% CI: 1.16-2.95; p=0.010), who had ever used recreational drugs (AOR: 2.99, 95% CI: 1.28-6.98; p=0.012), and who used long-term contraception (AOR: 2.22 [95% CI: 1.06-4.64]; p=0.034) and injectable hormonal contraception (AOR: 1.95 [95% CI: 1.20-3.17]; p=0.007) were more likely to seroconvert. The incidence of HIV infection was higher in women who had prevalent *Herpes simplex* type 2 (HSV-2) (AOR: 2.14; 95% CI: 1.55-

2.96; p<0.0001), incident HSV-2 (AOR: 4.43; 95% CI: 1.77-11.05; p=0.001), and incident N *gonorrhea* (AOR: 6.92; 95% CI: 3.01-15.90; p<0.0001).

Conclusions: Women's greatest risk factors for HIV acquisition were incident bacterial and viral STIs. Women-centered interventions aimed at decreasing HIV incidence in young African women may need to address these common co-morbid conditions.

Background

Of the estimated 40 million individuals living with HIV globally, more than 65% reside in sub-Saharan Africa, with heterosexual intercourse as the primary mode of HIV transmission [1]. In southern Africa, women have twice the risk of HIV infection compared to their male counterparts [2, 3]. Despite the increasing availability of highly active antiretroviral therapy (HAART) in this region, effective HIV prevention must remain a priority to stem the continued spread of the epidemic. Risk factors for HIV acquisition may change over time as regional epidemics evolve, social mores and economic circumstances change, and prevention efforts underway possibly impact on behavioral and biological factors. Continuous refocusing of prevention efforts on the most critical socio-demographic, behavioral, and biomedical risk factors influencing HIV acquisition in women can assist in the development of counseling and care models in the increasingly generalized and feminized epidemic of southern Africa and can be important for planning, executing, and interpreting HIV prevention clinical trials.

Multiple studies conducted in different African settings have reported on the aspects of sexual behavior and biomedical cofactors that influence HIV acquisition [4-7]. The incidence of HIV infection in sub-Saharan Africa has been shown to be higher in women who reported multiple sexual partners and who were younger in age [8-10]. Longitudinal data in this region have suggested that sexually transmitted infections (STIs) increase the infectiousness of HIV-infected individuals and the susceptibility of HIV-uninfected individuals [11, 12]. The role of *Herpes simplex* virus type 2 (HSV-2), which is one of the most common causes of genital ulcer disease, has increasingly been recognized as enhancing the risk of HIV transmission and acquisition in sub-Saharan

Africa [13-15]. HSV-2 acquisition is estimated to be 10-20% per year after sexual debut among South African young adults, and 20% of HIV seronegative and 80% of HIV seropositive teenagers are HSV-2 seropositive [16]. Other STIs, including *Trichomonas vaginalis* and *Neisseria gonorrhea*, have also been reported to increase the risk of HIV acquisition in sub-Saharan Africa [17].

The current case-control study using risk-set sampling, nested within the randomized controlled Methods for Improving Reproductive Health in Africa (MIRA) trial, examines risk factors influencing HIV acquisition in at-risk women in two high HIV prevalence southern African countries. We examine the association of socio-demographic, behavioral, and biomedical risk factors with HIV acquisition after adjusting for confounding factors, estimate population-attributable fractions (PAF), and assess effect modification.

Methods

Participants, study design, screening, and enrollment procedures: The MIRA study was a phase III randomized, controlled, open-label trial of the effectiveness of the diaphragm and lubricant gel to prevent heterosexual HIV/STI acquisition in women, conducted at 3 study sites in southern Africa: Harare, Zimbabwe and Durban and Johannesburg, South Africa. These sites spanned semi-rural, peri-urban, and urban settings. Women were enrolled between September 2003 and September 2005, and follow-up concluded in December 2006. Further details about the methods, study procedures, and eligibility criteria can be found elsewhere [18-20]. Briefly, to be eligible for the study, women had

to test negative (or be treated in the case of *C trachomatis* and *N gonorrhea*) for HIV, *C trachomatis*, *N gonorrhea*, and pregnancy; be sexually active (defined as an average of at least four sex acts per month); be aged 18-49 years; have no allergy to latex or history of toxic shock syndrome; have a healthy cervix; and be willing and able to correctly insert and remove the diaphragm at the clinic. Women enrolled in the study received a state of the art HIV prevention package consisting of risk reduction counseling, pre- and post-test HIV counseling and testing in accordance with US Centers for Disease Control and Prevention (CDC) guidelines, and diagnosis and treatment of curable STIs. Women were given male condoms at clinic visits and were counseled to use condoms for each sexual act.

At screening, consenting women received HIV counseling and testing. Women were also tested for *N gonorrhea*, *C trachomatis*, and *T vaginalis* and treated if found to test positive. At enrollment, participants had a pelvic exam, were tested for syphilis, HSV-2, and pregnancy. Women were randomized into two arms, provision of latex diaphragm, lubricant gel, and condoms (intervention) compared with condoms alone (control). Participants completed an Audio Computer Assisted Self-Interviewing (ACASI) baseline questionnaire in their native language, including demographics and sexual behavior.

All women provided written informed consent at screening and enrollment into the study. The study protocol was reviewed and approved by the ethics review committees at all participating institutions.

Follow-up schedule: Participants were followed quarterly for 12-24 months (median 21 months), depending on how late in the accrual period they were enrolled. Follow-up counseling and testing for HIV, *C trachomatis*, *N gonorrhea*, and *T vaginalis* occurred at each quarterly visit. *T pallidum* was tested at enrollment, exit, and if clinically indicated. HSV-2 was tested at exit for those who were negative or indeterminate at enrollment. Among women who tested positive for HSV-2 at exit, stored sera was retrospectively tested to determine date of HSV-2 seroconversion. At each visit, participants were notified of available test results and received risk-reduction counseling, referral to necessary support services, treatment for laboratory diagnosed curable STIs (if applicable), and a resupply of gel (intervention arm) and condoms (both arms).

Measures: The following socio-demographic variables were assessed at screening: age, education, language, religion, earned income in the last 12 months, employment, currently living with primary partner, current contraception status, and number of past live births. We created a hierarchical variable for current contraception status based on method effectiveness, defined as long-term (includes tubal ligation, vasectomy, intrauterine device, and implants such as Jadelle and Norplant), injectable hormone consisting of progestin-only depot-medroxyprogesterone acetate (DMPA), pill (includes combined oral contraceptive and progesterone only pills), and barrier (includes male and female condoms). The following behavioral variables about participant risk behavior were assessed at enrollment: number of male partners in lifetime, age at sexual debut, frequency of sex in the last three months, exchange of sex for money, food, drugs, or shelter in the last three months, number of sexual partners in the last three months, alcohol use in the last three months, and ever used recreational drugs. The following

behavioral variables about the sexual partners of participants were also assessed: having any sexual partners ever test positive for HIV; suspect or know that regular partner had other sex partners in the last three months; ever had vaginal sex when a partner was under the influence of drugs or alcohol in the last three months; and primary partner was away from home for one or more months in the last year. A composite index of partner risk was constructed using the above variables about the sexual partners of the participant. High risk was defined as having at least one of these indicators of partner risk present, and low risk was defined as having none of these indicators present. We also created a single baseline non-viral STI prevalence indicator variable consisting of prevalent *C trachomatis*, *T vaginalis*, *T pallidum*, or *N gonorrhea*.

Laboratory assessments: At each study visit, participants provided a urine specimen for Polymerase Chain Reaction (PCR) testing for *N gonorrhea*, *C trachomatis*, and *Trichomonas vaginalis* (Roche Pharmaceuticals, Branchburg, NJ, USA). Participants provided blood samples to be used in tests for syphilis, rapid plasma reagin (RPR) and *T pallidum* hemagglutinin (TPHA) (Randox Laboratories, Crumlin, UK), and HSV-2 (HSV2; ELISA, FOCUS Diagnostics, Cypress, CA, USA). Two HIV rapid tests were done on whole blood samples from finger-prick or venipuncture by use of Determine HIV-1/2 (Abbott Laboratories, Tokyo, Japan) and Oraquick (OraSure Technologies, Bethlehem, PA, USA). Confirmatory laboratory testing was done for women with double-positive or inconsistent HIV rapid results with HIV ELISA (Vironostika, Biomerierux, Durham, NC, USA; BioRad, Redmond, WA, USA; or AxSYM HIV Ag/Ab Combo assay, Abbot Laboratories, Abbot Park, IL, USA). In cases of weakly reactive

ELISA results, Western Blot (BioRad Laboratories, Hercules, CA, USA) was used to corroborate ELISA test results.

Statistical analysis: The primary outcome variable was incident HIV infection, defined as time from enrollment to seroconversion using discrete quarterly visits. To confirm that participants with HIV infection identified during follow-up were negative at enrollment, we tested for viral nucleic acid by HIV DNA PCR (Amplicor HIV-1 DNA v1.5, Roche Molecular Systems, Branchburg, NJ, USA) from stored dried blood spot samples. At the South African sites, HIV RNA PCR tests (Amplicor HIV-1 MONITOR, v1.5, Roche Molecular Systems) were also done on stored plasma from the enrollment visit. Participants with a positive test for HIV DNA PCR, HIV RNA PCR (>400 copies per ul), or both, were classified as having prevalent HIV infection at enrollment, and were excluded from the current analysis. For participants who seroconverted, the date of seroconversion was defined as the date of first positive antibody-based HIV test results. In the case of missed interval visits, the date of seroconversion was assumed to be the visit containing the midpoint between these two time points.

Prevalent STI infections were defined as a positive test result at either screening or enrollment. Incident STI infections were defined as STIs occurring after enrollment and up to the visit prior to detecting HIV seroconversion for cases and up to the visit prior to censoring for controls, which allowed for assessing temporality between STI exposure and HIV seroconversion. Since syphilis was only tested at enrollment and closing and we were particularly interested in assessing the temporality of STI exposures in relation to HIV acquisition, we were unable to assess incident syphilis in the current analysis.

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A nested case-control study design was employed to examine risk factors associated with HIV acquisition. Cases were defined as those women who became HIV infected, and control participants, matched on study site and follow-up time, were selected at the time of case seroconversion among participants who were HIV-uninfected (risk-set or incidence-density sampling) [21]. We employ risk-set sampling, which allows for estimated odds ratios to be interpreted as risk ratios without the rare disease assumption and is generally a more accurate estimate of the risk ratio than the odds ratio obtained from conventional cumulative incidence (survival) sampling [22, 23]. We used the *sttoc* command in STATA to randomly select 3 controls for each case.

Hierarchical conditional logistic regression was used to estimate odds ratios (OR) for socio-demographic, behavioral, and biomedical factors, using a proximate-determinants conceptual framework [24, 25]. Significance was assessed using the likelihood ratio test (LRT). Colinearity of included covariates was examined. All models included age and treatment arm, included *a priori* as potential confounders. Baseline socio-demographic factors whose association reached significance (p<0.20) were first examined in a multivariable model. Those socio-demographic factors independently associated with HIV seroconversion (p<0.10) were retained in the core model. Next, behavioral and then biomedical factors whose association reached significance (p<0.20) were examined and those associated with HIV seroconversion (p<0.10) in a multivariable model were added to the core model. While individual prevalent *C trachomatis*, *T vaginalis*, *T pallidum*, and *N gonorrhea* were not significant risk factors, the baseline STI prevalence indicator variable as having one or more of these infections present was significant (p<0.05). The final model included the following

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socio-demographic factors: age, currently living with partner, number of past live births, contraception status, and treatment arm; the following behavioral factors: number of male partners in lifetime; exchange of sex for money, food, drugs, or shelter in the last three months, ever use of recreational drugs, and partner risk behavior indicator; and the following biomedical factors: prevalent HSV-2, baseline STI prevalence indicator, incident *T vaginalis*, incident HSV-2, and incident *N gonorrhea*.

The population attributable fraction (PAF) of incident HIV infection associated with select risk factors in the final model was estimated using the formula $PAF=p_c (RR-1)/RR$, where p_c is the proportion of cases exposed and RR was estimated by the adjusted OR [26]. The PAF and its confidence intervals (CI) were obtained using the *aflogit* command in STATA [27]. To assess whether the impact of significant STIs, namely *N gonorrhea* and HSV-2, varied by age (>25 years vs. ≤ 25 years), cohabitation status (living with primary partner vs. not living with primary partner), and HSV-2 infection (prevalent or incident HSV-2 vs. persistently HSV-2 negative), we also assessed effect modification (multiplicative interaction) through conducting multivariable stratified analyses. All data analyses were conducted using STATA (STATACORP, version 10.0, College Station, TX) software. When interpreting our statistical findings, we used 95% confidence interval (CI) and a 5% level of significance to assess statistical significance. All statistical tests were two-tailed.

Results

As previously described [18], among 5039 enrolled women in the MIRA trial, 19 women tested positive for HIV at baseline, and an additional 72 women tested HIV negative at baseline but did not have any follow-up visits. After excluding these participants and among the remaining 4948 women (total of 7655 women-years of follow-up), the current nested study included all 309 participants with incident HIV infection and 927 matched controls. The overall HIV incidence rate was 4.0 per 100 women-years.

Socio-demographic risk factors: Table 1 presents univariate odds ratios of baseline socio-demographic risk factors. Due to the matched study design, cases and controls were selected in the same proportion of the three study sites and period of study follow-up. Women > 35 years had the lowest incidence of HIV infection (OR: 0.44 [95% CI: 0.30-0.64]; p<0.0001) compared to women who were < 25 years. Women who were currently living with their primary partners were at lower risk of HIV infection compared to non-cohabiting women (OR: 0.59 [95% CI: 0.45-0.76]; p<0.0001). Women who had given birth were also at less risk of HIV infection, and the risk decreased from one birth (OR: 0.63 [95% CI: 0.40-1.00]; p=0.0390) to two births (OR: 0.43 [95% CI: 0.27-0.68]; p=0.0001). There was no significant association between incident HIV infection and education, religion, income, employment, or treatment assignment.

Behavioral risk factors: Table 2 presents univariate odds ratios of behavioral risk factors for participants and their sexual partners. Women who had multiple lifetime male partners were at increased risk of HIV seroconversion, which increased from having 2-3 partners (OR: 1.35 [95% CI: 1.01-1.81]; p=0.043) to 4 or greater partners (OR: 1.60 [95% CI: 1.13-2.28]; p=0.009). Women who had sex in exchange for money, food, drugs

or shelter in the last three months (OR: 1.67 [95% CI: 1.02-2.69]; p=0.0258), and those women who had ever used recreational drugs (OR: 3.47 [95% CI: 1.44-8.42]; p=0.0011) were also at increased risk of seroconversion. Women who currently used injectable hormone-based contraception were at increased risk of HIV infection (OR: 1.56 [95% CI: 1.00-2.47]; p=0.0431). There was no significant association between incident HIV infection and age at sexual debut, frequency of sex in the last three months, and number of men had sex with in the last three months.

Women who reported having vaginal intercourse with male partners who were under the influence of alcohol or drugs in the last three months (OR: 1.31 (95% CI: 1.00-1.71]; p=0.046) as well as women who reported that their male partners had other sexual partners in the last three months (OR: 1.65 [95% CI: 1.15-2.39]; p=0.0046) were at increased risk of HIV seroconversion. In terms of the partner risk behavior indicator, women who reported high risk partners were at increased risk of HIV seroconversion (OR: 1.59 [95% CI: 1.16-2.18]; 0.003). Knowledge of primary partner circumcision status, whether any past partners were HIV-infected, and primary partner being away from home for more than one month per year were not significantly associated with seroconversion.

Biomedical risk factors: Table 3 presents univariate odds ratios of biomedical risk factors. Women who were infected with prevalent HSV-2 were more likely to seroconvert (OR: 1.55 [95% CI: 1.17-2.04]; p=0.002). Women who tested positive for either prevalent

N gonorrhea, *C trachomatis*, *T vaginalis*, or *T pallidum* were at increased risk (albeit non-significant) of HIV acquisition (OR: 1.40 [95% CI: 0.99-1.99; p=0.057). Women who tested positive for incident *T vaginalis* (OR: 1.74 [95% CI: 1.03-2.95]; p=0.040), incident HSV-2 (OR: 3.66 [95% CI: 1.62-8.25]; p=0.002), or incident *N gonorrhea* (OR: 8.20 [95% CI: 3.75-17.93]; p<0.0001) were at significantly increased risk of HIV acquisition. Incident infection with *C trachomatis* was not significantly associated with seroconversion.

Multivariable analysis of socio-demographic, behavioral, and biomedical risk factors:
Table 4 presents the final multivariable model including selected socio-demographic, behavioral, and biomedical factors associated with HIV acquisition. HIV risk was lower in women who were older (>35 years: adj OR: 0.49 [95% CI: 0.29-0.83]; p=0.008), who lived with their primary partner (adj OR: 0.55 [95% CI: 0.36-0.84]; p=0.006), and who reported an increasing number of past live births (2 or greater live births adj OR: 0.48 [95% CI: 0.27-0.86]; p=0.013). Women who used long-term contraception (adj OR: 2.22 [95% CI: 1.06-4.64]; p=0.034) and injectable hormone-based contraception (adj OR: 1.95 [95% CI: 1.20-3.17]; p=0.007) were at increased risk of HIV acquisition. HIV risk was higher in women who reported four or more lifetime male partners (adj OR: 1.85 [95% CI: 1.16-2.96]; p=0.010, and ever using recreational drugs (adj OR: 2.99 [95% CI: 1.28-6.98]; 0.012).

Women with prevalent HSV-2 infection at enrollment were at over twice the risk of HIV acquisition compared to HSV-2 uninfected women (adj OR: 2.14 [95% CI: 1.55-2.96]; p<0.0001). Women who were diagnosed with incident HSV-2 (adj OR: 4.43 [95%

CI: 1.77-11.05]; p=0.001) and incident *N gonorrhea* (adj OR: 6.92 [95% CI: 3.01-15.90]; p<0.0001) were at markedly increased risk of HIV acquisition.

The adjusted PAF of HIV incidence for prevalent HSV-2 was 29% (95% CI: 16.9-39.4), for incident HSV-2, it was 2.2% (95% CI: 0.01-0.04), incident *N gonorrhea* 4.2% (95% CI: 0.03-0.06), and prevalent infection with either *N gonorrhea*, *C trachomatis*, *T vaginalis*, or *T pallidum* 12.5% (95% CI: 0.19-0.36).

Multivariable analysis stratified by age, cohabitation status, and HSV-infection:

Women >25 years of age vs. women ≤ 25 years of age: The risk of HIV acquisition associated with incident HSV-2 was more than 4 times greater among women > 25 years (adj OR: 15.68 [95% CI: 2.46-100.03]; p=0.004) compared to women ≤ 25 years (adj OR: 3.28 [95% CI: 1.06-10.08]; p=0.039). Similarly, the risk of HIV acquisition associated with incident *N gonorrhea* was almost 2 times greater among women > 25 years (adj OR: 9.86 [95% CI: 2.42-40.21]; p=0.001) compared to women ≤ 25 years (adj OR: 5.80 [95% CI: 1.88-17.85]; p=0.002).

Women living with primary partner vs women not living with primary partner: The risk of HIV acquisition associated with incident HSV-2 was over 2 times greater among cohabiting women (adj OR: 7.70 [95% CI: 2.26-26.27]; p=0.001) compared to non-cohabiting women (adj OR: 2.37 [95% CI: 0.56-10.04]; p=0.241), and also for prevalent HSV-2 between cohabiting women (adj OR: 3.05 [95% CI: 1.87-4.96]; p<0.0001) compared to non-cohabiting women (adj OR: 1.55 [95% CI: 0.99-2.44]; p=0.058). Similarly, the risk of HIV acquisition associated with incident *N gonorrhea* was greater

among cohabiting women (adj OR: 8.37 [95% CI: 2.26-30.96]; p=0.001) compared to non-cohabiting women (adj OR: 5.84 [95% CI: 1.93-17.64]; p=0.002).

Women infected with prevalent or incident HSV-2 vs women who were persistently HSV-2 negative: The risk of HIV acquisition associated with incident *N gonorrhea* was over 2 times greater among persistently HSV-2 seronegative women (adj OR: 13.89 [95%CI: 2.94-65.75]; p=0.001) compared to women with prevalent or incident HSV-2 (adj OR: 5.09 [95% CI: 1.86-13.90]; p=0.002).

Discussion

The current study presents socio-demographic, behavioral, and biological risk factors influencing HIV acquisition in at risk women in urban and semi-urban regions of two high-prevalence southern African countries, South Africa and Zimbabwe. Women with prevalent HSV-2 and incident STIs, namely *N gonorrhea* and HSV-2, were at markedly increased risk of HIV acquisition. Also, women who reported multiple lifetime sexual partners, having ever used drugs, and use of injectable hormone- and long-term barrier-based contraception at enrollment were at increased risk of acquiring HIV. However, women who were older, who had given birth, and who lived with their primary partners were at decreased risk of HIV infection. Due to the sustained prevalence of HIV infection in younger women in southern Africa [3], the findings of the current study are timely in reinforcing the need for more women-centered STI/HIV prevention interventions.

Prevalent HSV-2 infection doubled the risk of HIV acquisition and incident HSV-2 more than quadrupled the risk, after adjusting for socio-demographic and behavioral risk factors and other STIs. HSV-2 seropositivity at enrollment was high in this population (>60%), and a third of HIV infections in this population of women were attributable to prevalent and incident HSV-2.   The strongest observed effect of HSV-2 was in older women, which has been reported in data from Tanzania [4], as well as women who lived with their primary partner. The biological mechanism for an increased risk of HIV due to HSV-2 likely results from the disruption of the genital epithelium during HSV-2 reactivation and recruitment of activated HIV target cells (i.e. CCR5 positive CD4 cells and immature dendritic cells) to the genital tract [28, 29], as well as via up-regulation of HIV replication [30]. Previous meta-analyses of longitudinal data have also concluded that prevalent HSV-2 doubled the risk of acquiring HIV across all populations [15, 31]. Additionally, incident HSV-2 may be more strongly associated with HIV acquisition relative to prevalent HSV-2 because HSV-2 reactivation, which is associated with an increase of HIV target cells in the genital tract, is likely to be most severe close to the time of infection [32]. A recent prospective cohort study among high risk Kenyan women found an increased risk of HIV infection with incident HSV-2 [33], as did another cohort study among women seeking clinical and reproductive services in Zimbabwe and Uganda [34]. Studies among men who have sex with men in the United States and patients attending STI clinics in India have also documented an elevated risk of HIV infection associated with incident relative to prevalent HSV-2, but both studies included incident HSV-2 infections that were diagnosed concurrently with HIV, precluding examination of temporality between both infections [35, 36].

It had been postulated that treating individuals with acyclovir as HSV-2 suppressive therapy could decrease the incidence of HIV infection among HIV seronegative and HSV-2 seropositive women, but two recently completed randomized controlled studies, one in Tanzania and the other a multicenter trial (HPTN 039), did not demonstrate that acyclovir decreases the incidence of HIV-1 infection [37, 38]. Acyclovir had an impact on suppressing HSV-2 shedding in the genital tract but did not impact chronic inflammation. Further biomedical interventions will need to be explored, such as an HSV-2 vaccine, as a means of primary prevention that could be delivered prior to sexual debut in populations with a high burden of HSV-2 infection.

Previous data has also suggested that STIs other than HSV-2 also can increase the risk of HIV acquisition [7, 17]. It has been postulated that reducing the population level of STIs could reduce HIV susceptibility and infectiousness of HIV-1 infected individuals, and may thus serve to decrease the continued spread of HIV-1 at the population level [12]. While a decrease in population HIV-1 incidence was associated with improved STI case management in Mwanza, Tanzania [5], it was not associated with STI mass treatment in Rakai, Uganda [6]. In the current study, incident *N gonorrhea* substantially increased the risk of HIV acquisition, which is different than findings from earlier studies in Africa [39, 40]. However, concordant with the current study, a randomized controlled trial examining antibiotic prophylaxis among Kenyan sex workers found that HIV incidence was associated with *N gonorrhea* [17]. We found that the impact of *N gonorrhea* on HIV acquisition was over two-fold greater among persistently HSV-2 negative women compared to HSV-2 positive women. Individuals with untreated HSV-2 experience chronic inflammation and intermittent shedding in the absence of symptoms

[13], so the addition of *N gonorrhe*a may be less likely to alter the genital mucosa due to a pre-existing inflammatory milieu. However, incident *N gonorrhea* in HSV-2 negative women may likely have a more dramatic effect on altering the genital mucosa. While the current study did not document a statistically significant association between incident *T vaginalis* and HIV infection, the documented adjusted odds ratio (1.58 [95% CI: 0.89-2.92]) is concordant with the estimates of other studies that have found a non-significant elevated risk [41]. In a survival analysis of the full cohort used in the current study, the adjusted relative risk was 2.05 (95% CI: 1.05-4.02) [42]. Recent prospective analyses conducted among both female sex workers in Kenya and a general population of women in Uganda and Zimbabwe demonstrated a significant association between *T vaginalis* and HIV acquisition [43, 44].

Women living with their primary partners were less likely to become HIV-infected, suggesting that exposure from the primary partner may not be the main source for HIV-infection. The risk of HIV acquisition associated with STIs, namely HSV-2 and incident *N gonorrhea*, was greater among women who lived with their primary partners. It has been suggested that early in an epidemic, most HIV infections are attributable to extra-marital relationships [4], and that as an epidemic matures with a greater number of discordant couples, a higher proportion of infections are attributable to transmission within stable partnerships [45, 46]. The current study was conducted within a population of at-risk women within a generalized regional epidemic. Women who had multiple lifetime sex partners were at increased risk of HIV infection, which is in accordance with earlier data from rural Uganda [8, 9]. Also, women who had given birth were at decreased risk of HIV acquisition. A case-control study nested in the community-

randomized trial of syndromic STI treatment in Mwanza, Tanzania found that women who had never given birth were more likely to become HIV infected [4]. Fertility pressures may increase the risk of engaging in unprotected intercourse [47], and prevention interventions that address broader reproductive health issues (i.e. family planning) may be warranted for at risk women in high prevalence HIV regions.

Injectable hormonal contraception, consisting of the progestin-only depot-medroxyprogesterone acetate (DMPA),was associated with an increased risk of HIV acquisition, which is concordant with some recent studies in Africa [33, 37]. However, we did not find an association with pill-based contraception. A cohort analysis among women in Uganda and Zimbabwe and another study in South Africa found no association between hormonal contraceptive use (neither pill nor DMPA) and HIV acquisition [48, 49]. We also found that women who used long-term contraception were at increased risk of HIV acquisition. Almost all women (98%) who used long-term contraception already had two or more prior live births, suggesting that further prevention efforts may be warranted in these women who may not use condoms due to long-term contraception but are still at risk for HIV acquisition. In the current study, we did not control for condom use as in previous analyses of this data, including using both a direct effect approach with time-dependent condom use and an intent to treat approach with baseline condom use, there was a very weak (if any) effect between condom use and HIV incidence[18, 50]. We also did not show an association with male circumcision [51], which may be because many women were unable to confirm the circumcision status of their primary male sexual partner.

Unlike earlier studies that have often assessed STI and HIV seroconversion concurrently, making it impossible to rule out co-transmission [52], in the current study we were able to assess the temporality of STI exposures prior to HIV seroconversion. Incident STI diagnoses were taken up to the visit prior to seroconversion for cases and up the visit prior to censoring for controls. Also, the current study collected sexual behavior data via ACASI, to minimize social desirability bias. Earlier studies have generally relied on interviewer-administered questionnaires that are more susceptible to misreporting of sexual behavior. Additionally, participants were asked to complete the ACASI before any adherence or risk-reduction counseling. While many studies in sub-Saharan Africa have investigated the presence of various behavioral risk factors, the majority of these studies have measured exposure to various behaviors retrospectively among prevalent cases of HIV. In the current study, we have prospectively evaluated several self-reported risk behaviors. The relatively high number of HIV seroconversions (309 in total) coupled with risk-set sampling, which to date has not been widely reported in infectious disease epidemiology [53], allowed for greater precision in the measures of effect and for assessment of relatively less common exposures. A limitation of the current study is we did not have diagnostic data on the HIV status of primary partners, which is likely an important determinant of an individual's risk for HIV infection [25]. Many women were unaware of the HIV status of their sexual partners. The current study uses data from a randomized controlled trial with stringent entry criteria and hence the findings may not be fully generalizable to the wider population.

The PAF for STIs likely vary with the stage of the HIV epidemic; as HIV prevalence rises with more infections in the general population, it has been suggested the

PAF associated with STIs decreases as fewer HIV infections take place in the presence of

STIs [54]. Although the current study was conducted within a generalized HIV epidemic

with higher population prevalence than earlier studies in Uganda and Tanzania [55, 56],

our population consisted of at risk women in whom a relatively high proportion of HIV

cases were attributable to STI exposure. While the PAF for prevalent HSV-2 was the

largest, curative treatment is not available, and hence prevention efforts must center on

initial acquisition or the development of new biomedical interventions. It is possible that

in the sub-population of women who remain HSV-2 negative, proactive diagnoses and

treatment of curable STIs, such as *N gonorrhea*, could be the most beneficial short term

strategy to reduce enhanced vulnerability to HIV. Multiple STIs are likely responsible

for a large proportion of new HIV infections, and future STI prevention efforts should

target young women in these populations.

Tables

Table 1. Unadjusted socio-demographic risk factors influencing HIV incidence in participants in the MIRA trial (N=1236)

Characteristic	Participant response (%)		Unadjusted odds ratio (OR) (95% CI); p-value
	Cases (N=309)	Controls (N=927)	
Age, years			
<= 24 years	51.1	38.1	1.00
25-34 years	35.0	23.5	**0.68 (0.51-0.90); 0.008**
>=35 years	13.9	38.4	**0.44 (0.30-0.64); <0.0001**
Education			
Less than High school	56.8	60.4	1.00
High school or greater	43.2	40.9	1.10 (0.85-1.43); 0.478
Religion			
Christian	94.5	93.9	1.00
Other	5.5	6.1	0.89 (0.51-1.55); 0.678
Earned income from work in the last 12 months			
Yes	52.8	50.2	1.00
No	47.2	49.8	0.90 (0.70-1.17); 0.429
Current employment status			
Employed	18.6	22.9	1.00
Unemployed	81.4	77.1	1.30 (0.94-1.80); 0.115
Currently lives with primary partner			
No	54.0	40.9	1.00
Yes	46.0	59.1	**0.59 (0.45-0.76); <0.0001**
Number of past live births			
0	13.6	7.4	1.00
1	41.7	36.0	**0.63 (0.40-1.00); 0.0390**
2 or greater	44.7	56.5	**0.43 (0.27-0.68); 0.0001**
Treatment arm			
Control arm (condoms only)	48.9	50.2	1.00
Intervention arm (diaphragm/gel/condoms)	51.1	49.8	1.05 (0.81-1.37); 0.69

Table 2. Unadjusted behavioral risk factors influencing HIV incidence in participants in the MIRA trial (N=1236)

Characteristic	Participant response (%)		Unadjusted odds ratio (OR) (95% CI); p-value
	Cases (N=309)	Controls (N=927)	
Current contraception status			
None	11.7	15.1	1.00
Long term	5.5	6.8	1.05 (0.51-2.09); 0.8842
Injectable hormone	34.3	28.6	**1.56 (0.99-2.47); 0.0431**
Pill	25.6	27.4	1.21 (0.76-1.95); 0.4016
Barrier	23.0	22.1	1.35 (0.84-2.19); 0.1987
Number of lifetime male partners			
1	35.6	44.1	1.00
2-3	42.1	38.6	**1.35 (1.01-1.81); 0.043**
4 or greater	22.3	17.3	**1.60 (1.13-2.28); 0.009**
Age at first vaginal sex			
<16	35.6	32.5	1.00
16-20	52.8	54.8	0.88 (0.66-1.16); 0.364
>20	11.7	12.7	0.83 (0.54-1.29); 0.413
Number of times had sex in the last three months			
3 times per week or less	67.3	68.0	1.00
More than 3 times per week	32.7	32.0	1.03 (0.77-1.37); 0.833
In the last three months, exchanged sex for money, food, drugs or shelter			
No	89.9	93.7	1.00
Yes	10.1	6.3	**1.67 (1.02-2.69); 0.0258**
Number of male sex partners in the last 3 months			
0	5.2	6.2	1.00
1	81.4	84.8	1.14 (0.63-2.16); 0.6559
>1	13.4	9.0	1.76 (0.86-3.69); 0.0957
In the last 3 months, consumed alcohol			
No	81.1	84.9	1.00
Yes	18.9	15.1	1.31 (0.92-1.86); 0.1144
Ever used recreational drugs			
No	95.8	98.7	1.00
Yes	4.2	1.30	**3.47 (1.44-8.42); 0.0011**
Regular partner has been circumcised			
No	51.8	55.9	1.00
Don't know	26.7	25.3	1.18 (0.86-1.62); 0.2840
Yes	20.5	18.9	1.17 (0.82-1.66); 0.3561
Any sexual partners tested positive for HIV			

No	67.8	71.3	1.00
Don't know	28.9	25.8	1.18 (0.87-1.59); 0.2588
Yes	3.3	2.8	1.21 (0.51-2.66); 0.6085
Partner has had other sexual partners in the last 3 months			
No	19.2	26.2	1.00
Don't know	38.1	38.5	1.35 (0.94-1.96); 0.0936
Yes	42.7	35.2	**1.65 (1.15-2.39); 0.0046**
Primary partner was away from home for 1 or more months			
No	62.4	67.4	1.00
Yes	37.6	32.6	1.25 (0.94-1.64); 0.1086
During the last 3 months, did you ever have vaginal sex when your partner was under the influence of alcohol or drugs			
No	59.3	65.6	1.00
Yes	40.7	34.4	**1.31 (1.00-1.71); 0.046**
Partner risk behavior			
Low risk	20.2	28.7	1.00
High risk	79.8	71.2	**1.59 (1.16-2.18); 0.003**

Table 3. Unadjusted biomedical risk factors influencing HIV incidence in participants in the MIRA trial (N=1236)

Characteristic	Participant response (%)		Unadjusted odds ratio (OR) (95% CI); p-value
	Cases (N=309)	Controls (N=927)	
Prevalent *C trachomatis*			
No	92.9	94.3	1.00
Yes	7.1	5.7	1.26 (0.76-2.11); 0.372
Incident *C trachomatis*			
No	92.9	95.1	1.00
Yes	7.1	4.9	1.50 (0.89-2.54); 0.130
Prevalent *T vaginalis*			
No	94.5	95.6	1.00
Yes	5.5	4.4	1.26 (0.70-2.25); 0.438
Incident *T vaginalis*			
No	92.6	95.6	1.00
Yes	7.4	4.4	**1.74 (1.03-2.95); 0.040**
Prevalent *T pallidum*			
No	94.8	96.0	1.00
Yes	5.2	4.0	1.31 (0.72-2.40); 0.374
Prevalent *N gonorrhea*			
No	98.4	99.1	1.00
Yes	1.6	0.9	1.89 (0.61-5.82); 0.268
Incident *N gonorrhea*			
No	92.6	99.1	1.00
Yes	7.4	0.9	**8.20 (3.75-17.93); <0.0001**
Prevalent HSV-2			
No	30.4	40.3	1.00
Yes	69.6	59.7	**1.55 (1.17-2.04); 0.002**
Incident HSV-2			
No	95.8	98.8	1.00
Yes	4.2	1.2	**3.66 (1.62-8.25); 0.002**
Tested positive for prevalent *C trachomatis*, *T vaginalis*, *T pallidum*, or *N gonorrhea*			
No	82.2	82.5	1.00
Yes	17.8	13.4	**1.40 (0.99-1.98); 0.057**

Table 4. Adjusted risk of HIV incidence for selected socio-demographic, behavioral, and biomedical factors in participants in the MIRA trial (N=1236)

Characteristic	Adjusted Odds ratio (95% CI); p-value
Demographic risk factors	
Age, years	
< 24 years	1.00
25-34 years	**0.69 (0.49-0.98); 0.038**
>35 years	**0.49 (0.29-0.83); 0.008**
Currently lives with partner	
No	1.00
Yes	**0.55 (0.36-0.84); 0.006**
Number of past live births	
0	1.00
1	0.62 (0.37-1.02); 0.061
2 or greater	**0.48 (0.27-0.86); 0.013**
Treatment arm	
Control arm (condoms only)	1.00
Intervention arm (diaphragm/gel/condoms)	0.96 (0.73-1.27); 0.805
Behavioral risk factors	
Current contraception status	
None	1.00
Long term	**2.22 (1.06-4.64); 0.034**
Injectable hormone	**1.95 (1.20-3.17); 0.007**
Pill	1.29 (0.74-2.26); 0.368
Barrier	1.19 (0.71-1.97); 0.510
Number of male partners in lifetime	
1	1.00
2-3	1.32 (0.92-1.88); 0.131
4 or greater	**1.85 (1.16-2.96); 0.010**
In the last three months, have had sex in exchange for money, food, drugs or shelter	
No	1.00
Yes	1.55 (0.94-2.56); 0.085
Ever used recreational drugs	
No	1.00
Yes	**2.99 (1.28-6.98); 0.012**
Partner risk behavior	
Low risk	1.00
High risk	1.35 (0.96-1.88); 0.080
Biomedical risk factors	
Prevalent HSV-2	
No	1.00
Yes	**2.14 (1.55-2.96); <0.0001**
Tested positive for prevalent *C trachomatis*, *T*	

vaginalis, *T pallidum*, or *N gonorrhea*	
No	1.00
Yes	1.18 (0.81-1.74); 0.387
Incident *T vaginalis*	
No	1.00
Yes	1.58 (0.89-2.82); 0.118
Incident HSV-2	
No	1.00
Yes	**4.43 (1.77-11.05); 0.001**
Incident *N gonorrhea*	
No	1.00
Yes	**6.92 (3.01-15.90); <0.0001**

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CHAPTER 3: ART AND SEXUAL RISK BEHAVIORS

"Marriage, fertility intent, and unprotected sex among HIV-infected South Indians in primary care"

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Abstract

Background: The current study examines sexual behavior among HIV-infected Indians in primary care, where access to highly active antiretroviral therapy (HAART) has recently increased.

Methods: Between January to April 2008, the sexual behavior of 247 HIV-infected South Indians in care was assessed. Multivariable logistic regression models were used to determine predictors of being in a seroconcordant primary relationship, being sexually active, and unprotected sex.

Results: Over three-fourths (80%) of participants were HAART-experienced, and among the 58% who were in a HIV-seroconcordant relationship, one-third of the couples were serodiscordant when first tested. Two-thirds (63.2%) of the participants were sexually active; 9.0% reported unprotected sex. In the multivariable analyses, participants who were in a seroconcordant primary relationship were more likely to have children, use alcohol, report unprotected sex, and have been enrolled in clinical care for greater than 12 months. Participants who reported to be sexually active were more likely to be on HAART, have a prior tuberculosis diagnosis, test *Herpes simplex* type 2 antibody seropositive, and have low general health perceptions. Participants who reported unprotected sex were more likely to be in a seroconcordant relationship, be childless, want to have a child, and use alcohol.

Conclusions: Among HIV-infected Indians in primary care, predictors of unprotected sex included alcohol use and desire for children. Prevention interventions for Indian

couples should integrate reproductive health and alcohol use counseling at entry into

care.

Background

In both the developed and developing world, increased access to highly active antiretroviral therapy (HAART) has extended life and reduced morbidity and mortality [1, 2], and has enabled HIV-infected individuals to resume behaviors, including sexual activity [3, 4]. As HAART significantly reduces plasma HIV RNA levels and improves physical health, HIV-infected individuals may engage in unsafe sex [5-8]. However, increased access to clinical care via HIV prevention counseling and receiving HAART could also encourage decreases in sexual risk behavior. Data from the developed world has suggested that HAART initiation is not necessarily associated with increased sexual risk taking behaviors[3].

The effect of HAART on sexual behavior may differ in resource-constrained settings due to difficulties accessing clinical care, differences in cultural and gender norms, and less familiarity with treatment benefits[9]. In India, condom use remains relatively low and serostatus disclosure is uncommon [10]. Despite the increasing availability of generic HAART in India through the government National AIDS Control Program[11], the impact of treatment on preventing secondary transmission remains to be fully elucidated. An increase in unprotected sex following the introduction of HAART could have unintentional consequences on the future spread of the HIV/AIDS epidemic if not appropriately addressed via prevention interventions for HIV-infected individuals[12]. Limited data from Sub-Saharan Africa has suggested that HAART is not associated with an increase in sexual risk taking behavior, [13-17] but has not been fully explored in India, the home of the largest population of people living with HIV outside of Africa [18].

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The current study examines socio-demographic, behavioral, and clinical factors associated with being sexually active and engaging in unprotected sex among HIV-infected South Indians in clinical care. We also examine differences between HIV-concordant relative to serodiscordant primary relationships.

Methods

Setting and study population: Between January and April 2008, 247 HIV-infected patients receiving outpatient HIV clinical and preventive care at YRG Center for AIDS Research and Education (YRGCARE), a large community-based HIV care facility in Chennai, India were enrolled in this study. All participants were HIV-infected, > 18 years of age, and had been enrolled in care there for at least 6 months. Participants who had initiated HAART had to have been on therapy for at least 3 months. The study sample was selected to match the larger population of patients receiving HIV clinical care at YRGCARE based on gender, age, CD4 cell count at enrollment into care, and HAART status.

Services at YRG CARE include integrated medical services for the treatment of HIV and related illnesses, prevention programs, and nutrition counseling. YRGCARE has clinical protocols for HIV treatment, which are consistent with World Health Organization (WHO) treatment guidelines [19]. Patients are seen every 3-6 months or as clinically indicated, and undergo laboratory monitoring every 3-6 months. Standard of care at YRGCARE also includes voluntary counseling and testing (VCT) program of partners of HIV-infected individuals receiving care[20], in which patients testing for HIV

undergo pre- and post-test counseling. As part of this VCT program, couples are

counseled together about sexually transmitted infections (STI) and risk reduction

strategies. Patients and their partners are provided with free condoms at each clinic visit.

Patients are strongly encouraged to disclose their HIV status to their sex partners at

enrollment to care and to attend clinic visits with their primary partner. Uninfected

primary partners are assessed for their HIV status at follow-up visits, which occurs every

3-6 months.

Data was collected under the approval of the Institutional Review Boards (IRBs)

at YRGCARE, Brown University, and the Miriam Hospital.

Survey assessment of socio-demographic and behavioral data: After identification and

consent, participants completed a structured interviewer-administered survey. The

survey was delivered in either Tamil or English; the Tamil survey was translated from the

original English version and then back-translated into English to ensure consistency

between the two versions. The survey was originally piloted among twenty participants,

after which the survey was revised. Interviewers were trained in eliciting information on

sensitive topics in a non-judgmental manner.

Participant demographics included age, sex, residential status (urban vs rural),

education, employment, marital status, cohabitation status, number of children, and

migrant worker (defined as whether one travels regularly for employment or is a truck

driver). Fertility intent was defined as whether the participant was interested in having a

child. Alcohol use, as drinking frequency over the past month, was measured with a

frequency scale [21]. General health perceptions were measured by asking participants

"How do you feel about your current health?" to indicate their overall health using a percentage scale from 0 (worst) to 100 (best)[22]. An overall general health perceptions score, ranging from 0 to 100, was divided into low and high categories based on the distribution of individual scores.

Sexual behavior over the past 3 months was assessed by inquiring about frequency of sex (regardless of the number of partners) and frequency of condom use for each sex act. Among sexually active participants who did not use condoms, we asked further questions about type of sex acts for which condoms were not used with primary and non-primary sexual partners. "Sexually active" was defined as having engaged in anal or vaginal sex either with a primary or non-primary partner in the last three months. Among those participants who were sexually active, "unprotected sex" was defined as having engaged in at least one act of sex without a condom with a primary or non-primary partner in the last three months, which is in accordance with indicators used in other studies [15, 17]. An HIV-concordant relationship was defined as the participant and his/her primary partner were both HIV-infected, and a discordant relationship was defined as the primary partner of the participant had tested HIV-negative up to the study date.

Clinical and laboratory assessments via medical record review: Medical record reviews were also conducted to confirm HAART history and to obtain relevant clinical data, including CD4 cell count at time of enrollment to care and at the time of the survey (measurement within 6 months of the date of survey) and STI and opportunistic infections diagnoses, which was a part of the YRG CARE Chennai HIV Natural History Study Observational Database[23]. This database, updated daily, collects information on

patient demographics, including probable route of HIV infection, date of HIV diagnosis, and prior antiretroviral treatment; clinical status, including data related to the occurrence of new opportunistic infections, current treatment regimens, and adverse events (AEs); and laboratory data. The medical record was considered the referent measure for inconsistencies between participant self-report and medical record data documented by a clinic physician.

For all participants and for their primary partners as part of standard clinical care, blood specimens were tested for HIV by an enzyme-linked immunosorbent assay rapid HV antibody test (ABBOTT Determine HIV-1/2, ABBOTT Laboratories, IL, USA; HIV TRI-DOT, BIOMED Industries, India), and reactive sera were confirmed by Western blot analysis (Bio-Rad Laboratories, Hercules, CA) or by 2 different HIV antibody tests. *Herpes simplex* type 2 was diagnosed as any clinically identifiable genital outbreak of vesicular or mucosal inflammation and/or Herpes Select 2 ELISA IgG (Focus Diagnostics, Cypress, CA). Tuberculosis (TB) diagnosis was based on consistent history and physical exam and culture yielding *Mycobacterium* tuberculosis or positive sputum or aspirate tests for acid-fast bacilli, radiological features suggestive of TB, or clinical and radiological improvement in response to anti-tuberculosis treatment.

Statistical analysis: Descriptive statistics were calculated with mean and standard deviation for variables that were normally distributed; and the median and interquartile range (IQR) were calculated for variables influenced by extreme values. Chi square tests were used to compare categorical variables and student t-tests were used with continuous variables. We first calculated demographic, behavioral, and clinical predictors of being in a HIV concordant primary relationship. We then examined variables associated with

being sexually active, and then among participants who were sexually active, we examined variables associated with reported unprotected sex. Multivariable logistic regression models were used to assess selected socio-demographic, behavioral, and clinical factors associated with being in a HIV concordant primary relationship, being sexually active, and reported unprotected sex. Independent risk factors were accessed using a stepwise regression model (cutoff p-value of 0.20). After introducing independent risk factors into the models, each covariate was introduced into the models to assess confounding. Confounding was assessed based on a change of at least 0.10 or 10% of the non-log transformed beta coefficient of independent risk factors. The following variables were included in the adjusted model of predictors of being in a HIV concordant primary relationship: sex, residential status, has children, alcohol use, reported unprotected sex, and time in clinical care. The following variables were included in the adjusted model of predictors of being sexually active: sex, age, residential status, HAART status, CD4 cell count at the time of the study, HSV-2 antibody positive, prior tuberculosis diagnosis, general health perceptions, and time in clinical care. The following variables were included in the adjusted model of predictors of reported unprotected sex: residential status, HAART status, primary partner HIV status (concordant vs discordant), number of children, desire to have children, general health perceptions, and alcohol use. All data analyses were conducted using STATA (STATACORP, version 10.0, College Station, TX) software. A 95% confidence interval (CI) and a 5% level of significance were used to assess statistical significance. All statistical tests were two-tailed.

Results

Among the 247 study participants (>95% heterosexual HIV transmission), a third were women, 64% were urban residents, and 84% were > 30 years old. Almost three-fourths of participants (70%) had been enrolled in the HIV care program for over 24 months. Most participants (80%) were HAART-experienced. The median CD4 cell count at the time of the current study was 402 cells/ul (IQR: 263-568). Most participants (>90%) were married/currently living with their primary partner and 81% already had a child.

The majority (58%) were in a HIV concordant primary relationship. Among participants currently in a HIV concordant primary relationship, a third (32.6%) seroconverted following their partners' enrollment in care, and the median time to HIV seroconversion was 119 days. Two-thirds (63.2%) of participants reported being sexually active in the last three months, and 9.0% of them reported unprotected sex during that time.

Demographic, behavioral, and clinical predictors of being in a HIV concordant primary relationship: Table 1 presents univariate and multivariable analyses of predictors of being in a HIV concordant primary relationship. In the univariate analysis, participants who were female, not employed, urban residents, had a child, wanted to have a child, used alcohol, reported unprotected sex, and had been in clinical care for greater than 12 months were significantly more likely to be in a HIV concordant primary relationship (p<0.05). Participants who were migrant workers were significantly less likely to be in a HIV concordant relationship (p<0.05). Participants in discordant and

concordant relationships did not vary by age, education, cohabitation status, general health perceptions, being sexually active, HAART status, HSV-2 antibody positivity, prior tuberculosis diagnosis, and current CD4 cell count.

In multivariable analysis, participants in concordant relationships were more likely to be women (adj OR: 3.82; 95% CI: 1.94-7.50; p<0.0001), to be urban residents (adj OR: 2.12; 95% CI: 1.16-3.87; p=0.014), and to have children (OR: 2.28; 95% CI: 1.07-4.86; p=0.031) compared to discordant participants. Concordant participants were more likely to report alcohol use (adj OR: 3.05; 95% CI: 1.36-6.81; p=0.006) and be in clinical care for a longer period of time (adj OR for 12-24 months: 7.75; 95% CI: 2.53-23.75; p<0.0001 and adj OR for >24 months: 5.08; 95% CI: 2.20-11.68; p<0.0001) compared to discordant participants.

Patterns of sex across concordant and discordant couples: Table 2 summarizes the frequency of reported sex, and the proportion of sex acts that were protected by condoms. Similar proportions of participants in concordant (65.3%) and discordant (60.2%) relationships reported to be currently sexually active. The median number of sex acts with primary partners in the last three months was slightly lower among concordant participants (median: 6; IQR: 3-10) than discordant participants (median: 9; IQR: 4-12). However, the proportion of sex acts that were protected by condoms was lower among concordant participants (88%) compared to discordant participants (99.2%).   Two participants, one who was concordant and the other discordant, reported having had sex with a non-primary partner in the last three months. Out of a total of 65 reported sex acts with a non-primary partner, all were protected by condoms.

Multivariable analysis of predictors of being sexually active: Table 3 presents univariate and multivariable analyses of predictors of being sexually active. Participants who were sexually active were less likely to be HAART-experienced (adj OR: 0.31; 95% CI: 0.13-0.74); p=0.009), to have lower general health perceptions (adj OR: 0.41 (0.23-0.75); p=0.004), and to have a prior diagnosis of tuberculosis (adj OR: 0.40; 95% CI: 0.20-0.80); p=0.009), and were more likely to be *Herpes simplex* type 2 antibody positive (adj OR: 2.16; 95% CI: 1.01-4.59); p=0.045) compared to participants who were currently not sexually active. Though not statistically significant, participants who were sexually active were more likely to be urban residents (adj OR: 1.80; 95% CI: 0.99-3.28); p=0.054). Participant gender, age, current CD4 cell count, and time enrolled in clinical care were not associated with being sexually active.

Multivariable analysis of predictors of reported unprotected sex: Table 4 presents univariate and multivariable analyses of predictors of reported unprotected sex among participants who were sexually active. Participants who reported unprotected sex were more likely to be in a HIV concordant primary relationship (adj OR: 17.37; 95% CI: 1.66-180.82); p=0.017), to not have any children (adj OR: 13.10; 95% CI: 2.20-77.81; p=0.005), to want to have children (adj OR: 11.75; 95% CI: 1.25-110.07); p=0.031), and to use alcohol (adj OR: 5.77; 95% CI: 1.13-29.52); p=0.035). Though not statistically significant, HAART-experienced participants were more likely to report unprotected sex compared to HAART-naïve participants (adj OR: 2.70; 95% CI: 0.48-15.15); p=0.258).

Discussion

Among South Indian HIV-infected patients enrolled in clinical care, unprotected sex was being driven by fertility concerns. Further efforts will be needed to integrate reproductive health programs into HIV clinical and preventive care in pronatal societies, such as India, where the societal and familial obligation is to get married and to have children is strong [24]. Participants who used alcohol were also more likely to report unprotected sex, as has been seen in other settings [25, 26], suggesting the need to develop targeted interventions focused on substance use for patient sub-populations.

We found that among concordant participants, a third had been in a discordant relationship at the time of entry into care and then consequently transmitted HIV to their primary partner[27]. Concordant participants were more likely to report unprotected sex, to have children, and to be enrolled in care longer than their discordant counterparts. Due to the cross-sectional design of the current study, we are unable to ascertain correlates of unprotected sex at the time of seroconversion. Our findings do suggest that timely prevention counseling that integrates reproductive health delivered soon after enrollment into care could be an effective means of secondary prevention, and could decrease HIV transmission within couples.

In the current study, the desire to have children was an important predictor of reporting unprotected sex, and the fewer number of children participants had, the more likely they were to report unprotected sex. Though HAART decreases the risk of sexual transmission of HIV through decreasing viral levels in blood and plasma[28, 29], HAART-experienced individuals could still be at risk of transmitting HIV, especially in resource-limited settings without adequate viral load monitoring. Data from Uganda has suggested that HAART-experienced women are more likely to report wanting children or

wanting more children [30] . However, another study from Uganda found that HAART-experienced women were more likely to use contraceptives compared to HAART-naïve women[31]. In a recent clinic-based study among Spanish heterosexual discordant couples, sexual risk behavior was strongly associated with recent pregnancy [32]. In India, condoms have traditionally been considered as a part of family planning rather than as means of preventing HIV/STI transmission[10, 33]. Unprotected sex to procreate remains an important limitation of condom-based HIV prevention interventions for couples trying to fulfill their reproductive goals.

The data in the current study underscore the need for further research regarding the cost-effectiveness and cultural acceptability of biomedical interventions that could address the needs of Indian couples seeking to procreate, including viral suppression of the HIV-infected partner via prompt initiation of HAART[34], assisted reproduction after sperm washing [35, 36], and antiretroviral chemoprophylaxis, including pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) [37, 38] [39]. Given the close link between heterosexual HIV transmission and the incidence of pregnancy, future studies will be needed to examine the impact of HAART on fertility in resource-limited settings so that couples can be sexually active, achieve their reproductive goals, and minimize the risk of HIV transmission.

The current study is broadly consistent with earlier data emerging from sub-Saharan Africa that HAART is not associated with an increase in sexual risk taking behaviors[15-17, 40, 41]. Recent studies from ART treatment programs in Kenya and South Africa have documented a decrease in unprotected sex following ART initiation [42-44]. Though early studies from the developed world had found an increase in sexual risk

taking behavior following the introduction of HAART [5, 6, 8], a later meta-analysis did not find that HAART was associated with behavioral disinhibition[3]. Since participants in the current study received regular prevention counseling about initiating HAART if they wanted to engage in unprotected sex for the purpose of having a child, it is possible that the slight elevation we documented in HAART use among those reporting unprotected sex may be connected to wanting to have a child. Participants in the current study generally reported to only be sexually active with their primary partner. A recent population level analysis from Rwanda and Zambia found that most heterosexual HIV transmission occurs within the context of marriage or cohabitation[45]. Data from other African settings have suggested that unprotected sex occurs mainly with primary partners[13, 15]. These data from differing social milieus do suggest the possible difficulty of negotiating safe sex with primary partners. Further studies are needed to examine barriers to condom use among couples.

Although earlier studies have examined sexual behavior in the context of HIV transmission and acquisition in India[46], to date this is the first study examining the association between treatment and sexual behaviors among HIV-infected Indians receiving clinical care. A strength of the current study is data was available on the HIV status of the primary partner, which has not been available in many studies assessing the impact of HAART on sexual behavior in resource-limited settings. As part of standard of care, participants received risk reduction counseling and free condoms at each clinic visit and it is not possible to disentangle the contribution of various prevention activities (ie counseling, condom provision, VCT) on risk behavior. Because participants were regularly receiving prevention messages from counseling personnel, it is possible that

participants may have under-reported sexual behaviors due to socially desirable responding[47]. We utilized non-clinic based interview staff who had undergone cultural sensitivity training and a variety of measures to assess risk taking behaviors. Further research in this setting evaluating new data collection techniques, such as ACASI that are less susceptive to social desirability bias, will need to be investigated. Participants in the study may be a self-selected sample and may not be representative of the HIV-infected population in need of treatment, but we attempted to ensure that the study sample matched the wider clinic patient population during the study period on important clinical and demographic variables.

Increasing calls have been made to rapidly expand the provision of HAART in resource-limited settings, and it has been suggested that treating all HIV-infected patients could have a major impact on HIV transmission[48]. Proactive risk reduction strategies targeted towards discordant couples, including prompt treatment initiation of the HIV-infected partner and empirically developed culturally-relevant couples prevention interventions, delivered promptly after enrolling into clinical care could be particularly efficacious[49-51]. These findings suggest the need for continued prevention counseling that integrates reproductive health within the context of primary marital relationships as part of the roll-out of HAART programs in India.

Tables

Table 1. Demographic, behavioral and clinical predictors of being in a HIV concordant primary relationship among HIV-infected participants in clinical care in South India (N=247)

Characteristic	Proportion, % by partner HIV status		Univariate odds ratios, OR (95% CI); p-value	Multivariable odds ratio, OR (95% CI); p-value*
Demographic characteristics	**Concordant couple (N=144)**	**Discordant couple (N=103)**		
Sex*				
Male	59.0	79.6	1.00	1.00
Female	40.1	20.4	**2.71 (1.51-4.85); 0.001**	**3.82 (1.94-7.50); <0.0001**
Age, years				
<30	17.4	14.6	1.00	
>30	82.6	85.4	0.81 (0.40-1.62); 0.557	
Education				
Secondary or below	86.8	80.6	1.00	
University or greater	13.2	19.4	0.79 (0.56-1.11); 0.188	
Current employment				
Employed	72.9	85.4	1.00	
Not employed	27.1	14.6	**1.29 (1.04-1.61); 0.021**	
Residential status*				
Rural	29.2	44.7	1.00	1.00
Urban	70.8	55.3	**1.96 (1.12-3.44); 0.013**	**2.12 (1.16-3.87); 0.014**
Migrant worker				
No	92.4	84.5	1.00	
Yes	7.6	15.5	**0.45 (0.18-1.09); 0.0499**	

Lives with spouse				
No	13.9	22.3	1.00	
Yes	86.1	77.7	1.78 (0.87-3.65); 0.0845	
Has children*				
No	14.6	25.2	1.00	1.00
Yes	85.4	74.8	**1.97 (1.04-3.75); 0.037**	**2.28 (1.07-4.86); 0.031**
Behavioral characteristics				
Wants to have a child				
No	35.6	37.9	1.00	
Yes	74.3	62.1	**1.76 (1.00-3.04); 0.042**	
Alcohol use*				
No	77.8	87.4	1.00	1.00
Yes	22.2	12.6	**1.98 (0.98-3.99); 0.057**	**3.05 (1.36-6.81); 0.006**
General health perceptions				
High	44.4	36.9	1.00	
Low	55.6	63.1	0.73 (0.43-1.22); 0.235	
Sexually active				
No	34.3	39.8	1.00	
Yes	65.7	60.2	1.26 (0.75-2.14); 0.374	
Reported unprotected sex*				
No	91.0	99.0	1.00	1.00
Yes	9.0	1.0	**10.12 (1.30-78.64); 0.027**	**17.95 (1.64-196.31); 0.018**
Clinical characteristics				
HAART-experienced				
No	19.4	19.4	1.00	
Yes	80.1	80.6	1.00 (0.50-1.98); 0.996	
CD4 cell count (cells/ul)				
≤350	12.7	11.8	1.00	
350-500	29.6	28.4	0.96 (0.40-2.30); 0.937	
>500	57.7	59.8	0.89 (0.40-1.99); 0.789	

Prevalent HSV-2 positive				
No	75.7	84.5	1.00	
Yes	24.3	15.5	1.75 (0.87-3.61); 0.095	
Prior tuberculosis diagnosis	31.9	42.7	1.00	
No	68.1	57.3	1.59 (0.91-2.78); 0.084	
Yes				
Time in clinical care*				
<12 months	7.6	61.2	1.00	1.00
12-24 months	**16.0**	**12.6**	**4.34 (1.48-12.98); 0.003**	**7.75 (2.53-23.75); <0.0001**
>24 months	**76.4**	**26.2**	**4.29 (1.89-10.19); <0.0001**	**5.08 (2.20-11.68); <0.0001**

*Variables included in multivariable model: sex, residential status, has children, alcohol use, reported unprotected sex, and time in clinical care.

Table 2. Patterns of reported sexual intercourse by primary partner HIV status (N=247)

	Total , % (N=247)	Concordant , % (N=144)	Discordant, % (N=103)
Sexually active (%)	156 (63.2%)	94 (65.3%)	62 (60.2%)
Median number of sex acts with primary partner (IQR)	7 (3-10)	6 (3-10)	9 (4-12)
Proportion of sex acts protected with primary partner (%)*	1291/1392 (92.7%)	704/800 (88%)	587/592 (99.2%)

*Two participants reported having had sex with a non-primary partner, one who was concordant and the other discordant. Out of a total of 65 reported sex acts with a non-primary partner, all were protected.

Table 3. Selected predictors of being sexually active among HIV-infected participants in clinical care in South India (N=247)

	Proportion who were sexually active		Univariate odds ratios, OR (95% CI); p-value	Multivariable odds ratios, OR (95% CI); p-value
	Yes (%) N=156	No (%) N=91		
Sex Male Female	68.6 31.4	65.9 34.1	1.00 0.88 (0.51-1.53); 0.667	1.00 0.57 (0.28-1.13); 0.111
Age, years <30 >30	16.7 83.3	15.4 84.6	1.00 0.91 (0.44-1.84); 0.792	1.00 0.74 (0.31-1.75); 0.500
Residential status Rural Urban	67.3 32.7	40.7 59.3	1.00 1.41 (0.82-2.41); 0.208	1.00 1.80 (0.99-3.28); 0.054
HAART experienced No Yes	25.0 75.0	9.9 90.1	1.00 **0.32 (0.15-0.71); 0.005**	1.00 **0.31 (0.13-0.74); 0.009**
CD4 cell count, cells/ul ≤350 350-500 >500	9.0 30.1 59.6	17.6 26.4 54.9	1.00 2.23 (0.93-5.34); 0.069 2.12 (0.95-4.70); 0.063	1.00 1.63 (0.65-4.10); 0.295 1.39 (0.658-3.32); 0.455
Prevalent HSV-2 positive No Yes	23.1 76.9	83.5 16.5	1.00 1.52 (0.77-2.96); 0.219	1.00 **2.16 (1.01-4.59); 0.045**

Prevalent tuberculosis				
No	41.7	24.5	1.00	1.00
Yes	58.3	72.5	**0.53 (0.30-0.93); 0.026**	**0.40 (0.20-0.80); 0.009**
General health perceptions				
High	48.7	28.6	1.00	1.00
Low	51.3	71.4	**0.42 (0.24-0.73); 0.002**	**0.41 (0.23-0.75); 0.004**
Time in clinical care				
<12 months	16.0	14.3	1.00	1.00
12-24 months	16.0	12.1	1.18 (0.44-3.13); 0.737	1.93 (0.65-5.71); 0.232
>24 months	67.9	73.6	0.82 (0.39-1.71); 0.604	1.05 (0.46-2.41); 0.894

Table 4. Selected predictors of reported unprotected sex among sexually-active HIV-infected participants in clinical care in South India (N=156)

	Proportion reporting unprotected sex		Univariate odds ratios, OR (95% CI); p-value	Multivariable odds ratios, OR (95% CI); p-value
	Yes (%) N=14	No (%) N=142		
Residential status				
Rural	57.1	31.7	1.00	1.00
Urban	42.9	68.3	0.61 (0.20-1.88); 0.399	0.41 (0.11-1.57); 0.198
HAART experienced				
No	14.3	26.1	1.00	1.00
Yes	85.7	73.9	2.11 (0.45-9.89); 0.342	2.70 (0.48-15.15); 0.258
Partner HIV status				
Discordant	7.1	43.0	1.00	1.00
Concordant	92.9	57.0	**9.79 (1.24-76.88); 0.030**	**17.37 (1.66-180.82); 0.017**
# of children				
2 or more	35.7	54.9	1.00	1.00
1	28.6	33.8	1.30 (0.33-5.08); 0.706	1.69 (0.37-7.64); 0.492
0	35.7	11.3	**4.87 (1.26-18.82); 0.022**	**13.10 (2.20-77.81); 0.005**
Wants to have a child				
No	14.3	31.0	1.00	1.00
Yes	85.7	69.0	2.69 (0.57-12.54); 0.207	**11.75 (1.25-110.07); 0.031**
General health perceptions				
High	35.7	50.0	1.00	1.00
Low	64.3	50.0	1.80 (0.57-5.63); 0.313	3.08 (0.78-12.10); 0.106
Alcohol use				
No	64.3	81.7	1.00	1.00
Yes	35.7	18.3	2.47 (0.76-8.01); 0.129	**5.77 (1.13-29.52); 0.035**

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"Predictors of non-adherence to HAART among HIV-infected South Indians in clinical care: implications for developing adherence interventions in resource-limited settings"

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Abstract

Background: In light of the increasing availability of generic highly active antiretroviral therapy (HAART) in India, further data is needed to examine variables associated with HAART non-adherence among HIV-infected Indians in clinical care.

Methods: We conducted a cross-sectional analysis of 198 HIV-infected South Indian men and women between January-April 2008. Non-adherence was defined as taking <95% of HAART doses in the last 1 month, and was examined using multivariable logistic regression models.

Results: Half of the participants reported <95% adherence to HAART, and 50% had been on HAART for >24 months. The median CD4 cell count was 435 cells/ul. An increased odds of non-adherence was found for participants with current CD4 cell counts >500 cells/ul (adj OR: 2.22 [95%CI: 1.04-4.75]; p=0.038), who were on HAART for >24 months (adj OR: 3.07 [95%CI: 1.35-7.01]; p=0.007), who reported alcohol use (adj OR: 5.68 [95%CI: 2.10-15.32]; p=0.001), who had low general health perceptions (adj OR: 3.58 [95%CI: 1.20-10.66]; p=0.021), and high distress (adj OR: 3.32 [95%CI: 1.19-9.26]; p=0.022).

Conclusion: This study documents several modifiable risk factors for non-adherence in a clinic population of HIV-infected Indians with substantial HAART experience. Further targeted culturally-specific interventions are needed that address barriers to optimal adherence.

Background

For over a decade, increasingly well-tolerated highly active antiretroviral therapy (HAART) has dramatically changed HIV-associated morbidity and mortality and has improved the quality of life of HIV-infected individuals [1, 2]. Recent global initiatives have concentrated on expanding access to HIV treatment in resource-limited settings [3]; so, by the end of 2008, close to 4 million people were receiving HAART [4]. In India, it is estimated that 2.47 million individuals are currently living with HIV [5]. In 2004, the Indian government began providing HAART, consisting of an initial regimen of stavudine or zidovudine, lamivudine, and nevirapine, free of charge as part of its National AIDS Control Program, with the objective of initiating 100,000 people on treatment by 2007 [6]. The government had aimed to provide HAART to 300,000 adults and 40,000 children over the next five years as part of its second phase.

However, the success of HAART, associated with viral suppression, immunologic recovery, and avoiding the development of resistant virus, depends on optimal medication adherence [7-9]. Hence promoting optimal adherence is necessary for the success of HAART. Treatment non-adherence can also overlap with other self-care behaviors, such as continued unsafe sexual practices; and the co-occurrence of non-adherence and HIV transmission risk behavior could lead to the spread of drug-resistant virus [10, 11]. Data from the developed world has suggested an association between treatment non-adherence and continued HIV transmission risk behavior [12-14]. Studies conducted in resource-limited settings have shown that HIV-infected individuals can maintain high levels of adherence to HAART [15-23]. Despite expanding access to HAART in India, quantitative studies examining behavioral correlates of adherence

remain limited [24]. We had earlier undertaken one qualitative study [25] and one chart review study [26] to assess barriers and facilitators of HAART adherence in South India, which were conducted before the further reduction in cost and roll-out of subsidized HAART. However, these studies were limited in that the qualitative study was hypothesis generating, and the chart review was limited to data that was in patients' medical records. Further quantitative data from India is needed in light of the expanded access to HAART through the government roll-out and to examine whether associations of non-adherence found in other settings apply to this social context.

In the current study, we examined socio-demographic, behavioral, and clinical risk factors of HAART non-adherence among 198 HIV-infected South Indians in clinical care. We also estimated population attributable fractions and assessed effect modification (interaction) associated with significant potentially modifiable risk factors for non-adherence. The findings of the current study can inform the development of further culturally-tailored adherence interventions for HIV-infected Indians in clinical care.

Methods

Setting and study population: Between January and April 2008, we enrolled 247 HIV-infected patients receiving outpatient HIV clinical care at YRG Center for AIDS Research and Education (YRG CARE), Voluntary Health Services (VHS),a large community-based HIV care facility in Chennai, India. Among these 247 participants, 198 were prescribed HAART for at least 3 months, and the current analysis is only on

these 198 participants. All participants were HIV-infected, greater than 18 years of age, and had been enrolled in HIV clinical and preventive care for at least 6 months prior to the date of study enrollment. We attempted to select the current study sample to match the larger population of patients receiving HIV clinical care at YRGCARE in 2008 on gender, age, current CD4 cell count, and HAART status.

Services at YRGCARE include integrated medical services for the treatment of HIV and related illnesses, prevention programs, and nutrition counseling. YRGCARE has clinical protocols for treatment, which are consistent with World Health Organization (WHO) treatment guidelines [27], consisting of first-line non-nucleoside reverse-transcriptase inhibitor (NNRTI) containing regimens. Patients were generally advised to initiate HAART before CD4 cell counts fell below 200 cells/µL or when CD4 cell counts ranged between 200-350 cells/µL with an AIDS-defining illness. Standard of care involved seeing providers every 3-6 months or as clinically indicated and adherence and risk reduction counseling at each clinic visit following initiation of HAART.

Data was collected under the approval of the Institutional Review Boards (IRB) at YRGCARE, Brown University, and the Miriam Hospital.

Data collection: HIV-infected patients completed a structured interviewer-administered questionnaire about demographics, psychosocial status, sexually transmitted infections (STI) symptoms, and behavioral practices. After determining eligibility and consent, the questionnaire was delivered in either Tamil or English; the Tamil questionnaire was translated from the original English version and then back-translated into English to ensure consistency between the two versions. The questionnaire was piloted among

twenty patients to assess cultural suitability. Interviewers received training in eliciting

information on sensitive topics in a non-judgmental manner. Additional clinical data and

information of primary partner's HIV status (concordant vs. discordant) were obtained

via an observational database.

Behavioral measures: Patient demographics included age, gender identification, sex,

residential status (urban vs. rural), education, employment, marital status, number of

children, and migrant status (defined as whether travels regularly for employment or is a

truck driver). General health perceptions were measured by asking participants "How do

you feel about your current health?" to indicate their overall health using a percentage scale

from 0 (worst) to 100 (best) [28]. Scores were then divided into three categories—low,

intermediate, and high—such that approximately 25% of participants were grouped in the

low and high categories and about 50% were grouped in the intermediate category. The

split yielded ranges of 0-70 for low, 70-90 for intermediate, and 90-100 for high.

Distress was measured using a visual analog scale (ie distress thermometer) by asking

participants "how much distress you have been experiencing in the past week. By

distress, I am referring to any pain and suffering that you have been feeling during this

past week. . . ."[29] The 10-point distress visual analog scale was split into three

categories—low, intermediate, high—such that approximately 25% of the participants

were grouped in the low and high categories and about 50% into the intermediate

category. The split yielded ranges of 0-1 for low, 1-6 for intermediate, and 6-10 for high.

Sexual behavior over the past 3 months was assessed by inquiring about sexual frequency

(regardless of the number of partners), and frequency of condom use for each sex act.

Among sexually active participants who did not use condoms, we asked further questions

about type of sex acts for which condoms were not used. Alcohol use, defined as number

of times used alcohol over the past month, was measured with a frequency scale [30].

Among participants who reported alcohol use over the past month, alcohol abuse was

assessed using the CAGE Scale [31]. HAART adherence over the past 1-month was

measured using a visual analog scale based on asking the question, "What percent of the

time did you take your medications exactly as your doctor prescribed them over the last

one month?"(11 response categories, 0, 10, 20, . . .100%) [32], which has been shown to

be an effective method in other resource-limited settings [21].

Medical chart review data: We also conducted a medical record review, through utilizing

the

YRGCARE Chennai HIV Natural History Study Observational Database [33, 34]. This

database, updated daily, collects information on patient demographics, including probable

route of HIV infection, date of HIV diagnosis, and ART history; clinical assessments,

including data related to the occurrence of opportunistic infections and adverse events

(AEs); and laboratory data. We confirmed ART history and obtained relevant clinical

data, including CD4 cell count at time of enrollment to care, at the time of initiating

HAART, and at the time of survey assessment (measurement within 6 months of date of

survey), and past STIs diagnosed by clinic physicians. The medical record was

considered the referent measure for inconsistencies between patient self-report and

medical record data documented by clinic physicians.

Definitions of variables used in analyses: The outcome of HAART adherence during the

past 1-month was calculated based on dividing percentages from the 30-day visual analog

scale [32]. Because this variable was highly skewed, we dichotomized adherence, coding participants achieving <95% adherence as "1" and those ≥95% adherence as "0". This cut-off point is consistent with prior research that has employed categorical classifications, and that suggests a high level of HAART adherence is necessary for adequate viral suppression [35].

We defined sexually active as having engaged in anal or vaginal intercourse either with a primary or non-primary partner in the last three months. Participants who had not engaged in anal or vaginal intercourse in the last three months were defined as not being sexually active. We defined unprotected sexual intercourse as having engaged in at least one act of anal of vaginal intercourse without a condom with a primary or non-primary partner in the last three months, which is in accordance with indicators used in other studies [36, 37]. In terms of primary relationship status, a concordant relationship was defined as the HIV-infected patient enrolled in care and his/her primary partner were both HIV-infected, and a discordant relationship was defined as the primary partner of the HIV-infected patient enrolled in care had tested HIV-negative up to the study date.

Statistical analysis: Descriptive statistics were calculated with mean and standard deviation for variables that were normally distributed; and the median and interquartile range (IQR) were calculated for variables influenced by extreme values. We first compared socio-demographic, clinical, and behavioral characteristics stratified by participant sex to see whether characteristics varied across men vs. women, and then examined odds ratios (OR) of these characteristics associated with HAART non-adherence. Multivariable logistic regression models were used to assess predictors of

HAART non-adherence. Significance was determined using the likelihood ratio test (LRT). Colinearity of included covariates was assessed.

We employed a stepwise model to identify independent socio-demographic, behavioral, and clinical predictors of HAART non-adherence in which variables initially associated with non-adherence that reached a threshold value (p<0.20) were examined, and those associated with HAART non-adherence (p<0.10) in a multivariable model were retained. After introducing the primary predictors based on the stepwise model, each covariate was introduced into the model to assess confounding, which was assessed based on a change of at least 0.10 or 10% of the non-log transformed beta coefficients of the independent predictors. The following socio-demographic variables were included in the final multivariable model: sex, age (>30 years vs. ≤30 years), and current employment status (employed vs. not employed); clinical variables: current CD4 cell count (<350 cells/ul, 350-500 cells/ul, vs. >500 cells/ul) and time on HAART (<12 months, 12-24 months, vs. >12 months); and behavioral variables, general health perceptions (low, intermediate, vs. high), distress (low, intermediate, vs. high), alcohol use in the past month, sexually active in the last three months, and reported unprotected sex in the last three months.

We also examined adjusted interaction effects (effect measure modification) through conducting stratified analyses to assess whether the alcohol-adherence association was moderated by patient characteristics [38]. The population attributable fraction (PAF) of HAART non-adherence associated with significant preventable risk factors in the final model was estimated from the adjusted OR (adj OR) [39]. The adjusted PAF and its confidence intervals (CI) were obtained using the *aflogit* command

in STATA [40]. All data analyses were conducted using STATA (STATACORP, version 10.0, College Station, TX) software. A 95% confidence interval (CI) and a 5% level of significance were used to interpret statistical significance. All statistical tests were two-tailed.

Results

About a third (31.5%) of the participants were female and most participants (85.9%) were 30 years of age or older. The primary mode of HIV transmission was via heterosexual intercourse (>95%). Over three-fourths of participants were married (83.3%) and had children (79.3%). Over half of the participants (58.1%) were in a HIV concordant primary relationship. Almost three-fifths (58.6%) of participants reported being sexually active, of whom 12.1% reported unprotected sexual intercourse. Only 2 participants reported having sexual intercourse with their non-primary sex partner in the last three months.

The median CD4 cell count at the time of enrolling to care was 248 cells/ul (IQR: 100-339), and the median CD4 cell count at the time of initiating HAART was 220 cells/ul (IQR: 150-285). At the time of the current study, the median CD4 cell count was 435 cells/ul (IQR: 273-585).

Characteristics of study population stratified by participant sex: Table 1 presents participant socio-demographic, behavioral, and clinical characteristics stratified by sex. Men were more likely to be older, not have children, to be currently employed, and have low general health perceptions. Almost all participants who used alcohol (96.7%) were

men. Women were more likely to be in a HIV concordant relationship and to be *herpes simplex* type 2 antibody positive. Both men and women had similar levels of education, residential status, cohabitation status, distress, sexual activity, reported unprotected sex, current CD4 cell count, time on HAART, and time in clinical care. No participants reported drug use.

Patterns of treatment adherence: Half of the participants (50.5%) reported 100% HAART adherence, 31.8% reported 90% HAART adherence, 10.8% reported 80% adherence, and the remainder (7.1%) reported 70% adherence or below. Almost a third of participants (28.8%) reported initiating HAART as soon as they were enrolled into HIV clinical care. Over a fourth of participants (28.3%) had been on HAART for 12 months or less, 21.7% between 12-24 months, and 50% greater than 24 months. The most common HAART regimens included: lamivudine + stavudine + nevirapine (31.0%), lamivudine + stavudine + efavirenz (19.9%), zidovudine + lamivudine + efarvirenz (17.3%), and nevirapine + zidovudine + lamivudine (11%). The proportion of participants who were non-adherent was similar across different HAART regimens.

Patterns of alcohol use: Table 2 presents patterns of alcohol use and dependence as well as participant characteristics associated with alcohol use. In the last month, 16.7% of participants reported alcohol use. Among these participants who used alcohol, over two-thirds (67.7%) reported using alcohol once a week or more and a tenth (9.1%) had a CAGE score of at least 3. Participants who used alcohol were more likely to be men, in a HIV concordant primary relationship, and be currently employed.

Association between HAART non-adherence and selected socio-demographic,

behavioral, and clinical risk factors: Almost half (49%) of the 198 participants had

below 95% adherence, and these participants are classified as non-adherent in the current

analysis. Participants who had been HAART-experienced for greater than 24 months

were more likely to be non-adherent than participants who had been on HAART for less

than 24 months (OR: 2.01 [95% CI: 1.03-3.92]; 0.040) (See Table 3). Participants who

reported low (OR: 4.94 [95% CI: 2.05-11.92]; p<0.0001) and intermediate (OR: 3.69

[95% CI: 1.68-8.09]; p=0.001) general health perceptions were more likely to be non-

adherent compared to participants who reported high general health perceptions.

Similarly, participants who reported high (OR: 3.29 [95% CI: 1.47-7.36]; p=0.004) and

intermediate (OR: 2.24; 95% CI: 1.10-4.54); p=0.025) levels of distress were more likely

to be non-adherent compared to participants who reported a low level of distress.

Participants who reported alcohol use were more likely to be non-adherent compared to

participants who had not used alcohol (OR: 3.93 [95% CI: 1.67-9.24]; p=0.002).

Participants who were sexually active were less likely to be non-adherent

compared to those who were not sexually active (OR: 0.49 [95% CI: 0.27-0.87];

p=0.016). Participants who were sexually active were less likely to have low general

health perceptions (OR: 0.23 [95% CI: 0.09-0.58]; p=0.002) and a high level of distress

(OR: 0.34 [95% CI: 0.15-0.78); p=0.011) compared to participants who were not sexually

active. Though not statistically significant, the few participants who reported unprotected

sex were more likely to be non-adherent than participants who reported only protected

sex (OR: 2.49 [95% CI: 0.62-9.91]; p=0.196). Among non-adherent participants, out of a

total of 84 reported anal/vaginal sex acts in the last 3 months, only 25 (29.8%) were

protected with condoms, but all sex acts were with a HIV concordant primary partner. Among adherent participants, out of a total of 17 reported anal/vaginal sex acts, none were protected with condoms, five of which were with a HIV discordant primary partner.

Multivariable analysis of risk factors of antiretroviral non-adherence: In the final multivariable model, participants with current CD4 cell counts > 500 cells/ul were over two times more likely to be non-adherent compared to participants with lower CD4 cell counts (adj OR: 2.22 [95% CI: 1.04-4.75]; p=0.038) (See Table 3). Participants who had been on HAART for > 24 months were over three times more likely to be non-adherent compared to participants who had been on HAART for a shorter period of time (adj OR: 3.07 [95% CI: 1.35-7.01]; p=0.007). Participants who reported alcohol use were over five times more likely to be non-adherent compared to participants who had not used alcohol (adj OR: 5.68 [95% CI: 2.10-15.32]; p=0.001). Participants who reported low (adj OR: 3.58 [95% CI: 1.20-10.66]; p=0.021) and intermediate (adj OR: 3.32 [95% CI: 1.28-8.63]; p=0.014) general health perceptions were over three times more likely to be non-adherent compared to participants who reported high general health perceptions. Similarly, participants who reported a high level of distress were more likely to be non-adherent compared to participants with lower levels of distress (adj OR: 3.32 [95% CI: 1.19-9.26]; p=0.022). Though not statistically significant, participants who were sexually active were less likely to be non-adherent compared to those who were not sexually active (adj OR: 0.58 [95% CI: 0.29-1.14]; p=0.113), and also participants who were currently unemployed compared to those who were employed (adj OR: 0.41 [95% CI: 0.15-1.11]; p=0.080). Participant gender, age, and reported unprotected sex were not significant predictors of HAART non-adherence.

The adjusted association between alcohol consumption and non-adherence was two times greater among sexually active participants (adj OR: 10.44 [95% CI: 2.61-41.63]; p=0.001) compared to those who were not sexually active (adj OR: 5.39 [95% CI: 0.66-43.49]; p=0.114).

The adjusted PAF for alcohol use was 11.4% (95% CI: 0.05-0.17), for low/intermediate general health perceptions was 37.3% (95% CI: 0.02-0.60), for high/intermediate distress was 24.0% (95% CI: -0.05-0.45), and for CD4 cell count > 500 cells/ul was 10.0% (95% CI: -0.01-0.20).

Discussion

The current study documents several modifiable risk factors for non-adherence, namely alcohol use and psychosocial status, in a population of HIV-infected Indians in clinical care with substantial experience to NNRTI-based HAART. Participants who had recently used alcohol as well as those with increasingly higher distress and lower general health perceptions were more likely to be non-adherent. It is of concern that participants with higher CD4 cell counts and a longer time period of HAART experience were less likely to be adherent, suggesting possible treatment exhaustion and the need for sustained efforts to emphasize continued adherence over time. In accordance with earlier studies in resource-limited studies [17], demographic characteristics, such as age, gender, occupation, and residential status, did not predict treatment adherence.

The current study found that only about half of the participants had greater than 95% adherence, which is lower than most studies conducted in resource-limited settings

and closer to adherence levels documented in North America [15]. A recent study from western India conducted at private health clinics found that among patients paying for treatment out-of-pocket, three-fourths of patients had 95% adherence or higher [24]. Earlier studies monitoring treatment adherence from resource-limited setting have generally been conducted soon after patients initiated HAART, when patients were experiencing dramatic increases in health status. However, in the current study, half the population had been HAART-experienced for over two years, suggesting the need for sustained efforts to maintain high levels of adherence well after the initial immune-restorative effects of treatment. In light of the continued fall in prices of generic HAART and the Indian government treatment roll-out at the time of the current study, we had anticipated a higher level of treatment adherence. Cost of treatment has frequently been cited as a major barrier to adequate adherence in resource-limited settings [15], including in our patient population [25, 26]. Further longitudinal studies are needed to elucidate how treatment adherence may vary over time based on changing patient clinical and behavioral characteristics, as well as policies over the provision of accessible treatment.

Participants who reported alcohol use were at a substantially increased likelihood of being non-adherent. Alcohol use can diminish qualify of life, decrease adherence to medical regimens, and is a prevalent concern among HIV-infected individuals [38, 41]. Data have suggested the deleterious consequences of alcohol use on markers of immunological functioning and viral suppression, which could be moderated by non-adherence [42, 43]. In the current study, we were interested in conditions under which alcohol use was more likely to influence adherence, and participants who were sexually active were more likely to use alcohol and be non-adherent. The prominence of the

alcohol-adherence association that was documented in men is concordant with a recent meta-analysis [38]. The findings of this study suggest that proactive screening and referral for counseling about alcohol use should be a component of HIV care in India.

Participants with lower levels of general health perceptions and higher levels of distress were more likely to be non-adherent. Earlier studies from varying regional settings have identified psychological distress as a barrier to optimal adherence [44, 45]. Further in-depth studies in this patient population are needed to understand the impact of psychological function on treatment adherence, and psychosocial interventions (eg cognitive behavioral therapy) should be examined [46]. Having sex is an important part of overall health and quality of life, including in patients infected with HIV [41]. In the current study, participants who were sexually active were less likely to be non-adherent. Participants who were sexually active generally had lower levels of distress and higher general health perceptions. However, though not significant, participants who were non-adherent were more likely to report unprotected sex. It is possible that a larger sample size than the current study would be required to detect a significant effect of unprotected sex on treatment non-adherence.

There are several limitations to note. We did not have plasma viral load measurements to correlate with the adherence data because these tests were not standard of care in this resource-limited setting. The current study was cross-sectional in design, and hence may not reflect the dynamic nature of adherence which can vary over time. We assessed adherence based on patient self-report using a validated instrument, while commonly utilized [21], it may not perfectly reflect actual adherence levels. Prior research among this patient population has suggested that self-report may be an

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acceptable method in a clinic-based assessment situation [47]. Despite a relatively small

sample size, we documented associations of sufficient magnitude. We also attempted to

make the results of the current sample generalizable to patients receiving outpatient care

in this HIV clinic population through matching the sample on relevant demographic and

clinical characteristics. The sample included a diverse population of HIV-infected

Indians from urban and rural locations as well as varying levels of socio-economic status.

Due to the limited availability of second-line treatment in addition to the lack of

adequate virological monitoring in India, both primarily driven by cost considerations,

maintaining optimal adherence on first-line HAART is critical to ensure long-term

treatment efficacy. We identified severable modifiable behavioral risk factors of ART

adherence in this patient population with substantial treatment experience, suggesting that

health care providers could play a central role in integrating adherence interventions into

follow-up HIV care to improve patient treatment outcomes. Continued monitoring of

treatment-experienced Indian patients and further targeted culturally-specific

interventions will need to be developed that address long-term barriers to optimal

adherence. As programs to expand the coverage of HAART continue in India,

optimizing patient adherence via understanding unique regional factors will be a crucial

part of a comprehensive treatment strategy.

Tables

Table 1. Characteristics of HAART-experienced HIV-infected South Indians stratified by sex (N=198)

Characteristic	Proportion by sex, %		Odds Ratio, OR (95% CI); p-value
Socio-demographic characteristics	Men (N=136)	Women (N=62)	(Men as outcome vs women)
Age			
≥30 years	94.1	67.7	**7.61 (3.12-18.57); <0.0001**
<30 years	5.9	32.3	1.00
Has children			
No	25.0	11.3	**2.61 (1.08-6.29); 0.031**
Yes	75.0	88.7	1.00
Education			
University or >	19.9	11.3	1.39 (0.89-2.17); 0.144
< Secondary	80.1	88.7	1.00
Currently employed			
No	5.1	54.2	**0.35 (0.26-0.48); <0.0001**
Yes	94.9	45.8	1.00
Residential status			
Urban	65.4	66.1	0.96 (0.51-1.82); 0.925
Rural	34.6	33.9	1.00
Truck driver/travels for work			
No	15.4	100.0	--
Yes	84.6	0.0	
Currently lives with spouse			
No	16.9	24.2	0.63 (0.30-1.32); 0.230
Yes	83.1	75.8	1.00
Alcohol use in the last month			
Yes	23.5	1.6	**18.76 (2.50-140.82); 0.004**
No	76.5	98.4	1.00
Partner HIV status			
Concordant	52.2	71.0	**0.44 (0.23-0.85); 0.014**
Discordant	47.8	29.0	1.00
General health perceptions			
Low	28.6	21.0	**2.40 (1.01-5.67); 0.046**
Intermediate	52.9	46.8	1.98 (0.95-4.11); 0.065
High	18.4	32.3	1.00
Distress			
High	22.8	33.9	0.59 (0.26-1.35); 0.218
Intermediate	50.0	41.9	1.06 (0.50-2.24); 0.879
Low	27.2	24.2	1.00
Sexually active			

Yes	60.3	54.8	1.25 (0.68-2.29); 0.470
No	39.7	45.2	1.00
Reported unprotected sex			
Yes	5.9	3.2	1.21 (0.36-3.98); 0.754
No	94.1	96.8	1.00
Clinical characteristics			
HSV-2 antibody positive			
Yes	15.4	29.0	**0.44 (0.21-0.91); 0.028**
No	84.5	70.0	1.00
Current CD4 cell count			
>500 cells/ul	58.1	72.6	0.36 (0.11-1.15); 0.087
350-500 cells/ul	27.9	21.0	0.61 (0.17-2.14); 0.446
≤350 cells/ul	14.0	6.5	1.00
Time on HAART			
>24 months	55.7	44.1	1.27 (0.59-2.72); 0.528
12-24 months	19.1	30.5	0.63 (0.26-1.49); 0.295
<12 months	25.2	25.4	1.00
Time in clinical care			
>24 months	69.1	72.6	0.92 (0.37-2.29); 0.872
12-24 months	17.6	14.5	1.18 (0.38-3.67); 0.769
<12 months	13.2	12.9	1.00

Table 2. Patterns of alcohol use and characteristics of participants who used alcohol (N=33)

Patterns of alcohol use	Proportion (%)
Frequency of alcohol consumption	
≤2 times a month	33.3
Once a week	57.6
> 2 times a week	9.0
CAGE score	
+1	45.5
+2	27.3
+3	9.1
Characteristics of those who used alcohol	**OR (95% CI); p-value**
Sex	
Men	18.77 (95% CI: 2.95-776.38); p=0.0001
Women	1.00
Partner HIV status	
Concordant	2.17 (95% CI: 0.90-5.62); p=0.06
Discordant	1.00
Employment status	
Employed	4.96 (95% CI: 1.16-44.38); p=0.0197
Unemployed	1.00

Table 3. Unadjusted and adjusted socio-demographic, behavioral, and clinical predictors of non-adherence to HAART among HIV-infected South Indians (N=198)

	Proportion Non-adherent		Unadjusted Analysis OR (95% CI); p-value	Adjusted Analysis OR (95% CI); p-value
	No (%) N=98	Yes (%) N=100	Unadjusted (bivariate) association	Adjusted (multivariable) association
Sex				
Female	28.6	34	0.78 (0.42-1.41); 0.411	1.25 (0.49-3.17); 0.635
Male	71.4	66	1.00	1.00
Age				
≥30 years	85.7	86	0.98 (0.44-2.17); 0.954	0.48 (0.16-1.41); 0.186
<30 years	14.3	14	1.00	1.00
Current employment				
No	16.3	26.0	0.55 (0.27-1.11); 0.098	0.41 (0.15-1.11); 0.080
Yes	83.7	74.0	1.00	1.00
Current CD4 cell count				
>500 cells/ul	45.9	35.0	1.51 (0.80-2.85); 0.202	**2.22 (1.04-4.75); 0.038**
350-500 cells/ul	19.4	25.0	0.89 (0.42-1.89); 0.770	1.57 (0.64-3.88); 0.322
≤350 cells/ul	34.7	40.0	1.00	1.00
Time on HAART				
>24 months	57.1	43.0	**2.01 (1.03-3.92); 0.040**	**3.07 (1.35-7.01); 0.007**
12-24 months	20.4	23.0	1.34 (0.60-3.00); 0.471	2.24 (0.84-5.94); 0.103
<12 months	22.4	34.0	1.00	1.00
General health perceptions				
Low	32.6	34.0	**4.94 (2.05-11.92); <0.0001**	**3.58 (1.20-10.66); 0.021**
Intermediate	56.1	46.0	**3.69 (1.68-8.09); 0.001**	**3.32 (1.28-8.63); 0.014**

High	11.2	34.0	1.00	1.00
Distress				
High	32.7	20	**3.29 (1.47-7.36); 0.004**	**3.32 (1.19-9.26); 0.022**
Intermediate	50.0	45	**2.24 (1.10-4.54); 0.025**	1.75 (0.73-4.19); 0.206
Low	17.3	35	1.00	1.00
Alcohol use				
Yes	25.6	8.0	**3.93 (1.67-9.24); 0.002**	**5.68 (2.10-15.32; 0.001**
No	74.5	92.0	1.00	1.00
Sexually active				
Yes	50.0	67.0	**0.49 (0.27-0.87); 0.016**	0.58 (0.29-1.14); 0.113
No	50.0	33.0	1.00	1.00
Unprotected sex				
Yes	7.1	3.0	2.49 (0.62-9.91); 0.196	1.63 (0.32-8.12); 0.550
No	92.9	97.0	1.00	1.00

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"Decreased sexual risk behavior in the era of HAART among HIV-infected urban and rural South Africans attending primary care clinics"

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Abstract

Background: In light of the increasing access to highly active antiretroviral treatment (HAART) in sub-Saharan Africa, we conducted a longitudinal study to assess the impact of HAART on sexual risk behavior among HIV-infected South Africans in urban and rural primary care clinics.

Methods: A Prospective observational cohort study. We conducted a cohort study at a rural and an urban primary care HIV clinic in South Africa consisting of 1544 men and 4719 women between 2002-2009, and including 19703 clinic visits. The primary outcomes were being sexually active, unprotected sex, and >1 sex partner and were evaluated at 6 monthly intervals. Generalized estimated equations were used to assess the impact of HAART on sexual risk behaviors.

Results: Among 6263 HIV-infected men and women, over a third (37.2%) initiated HAART during study follow-up. In comparison to pre-HAART follow-up, visits while receiving HAART were associated with a decrease in those reporting being sexually active (AOR: 0.86 [95% CI: 0.78-0.95]). Unprotected sex and having >1 sex partner were reduced at visits following HAART initiation compared to pre-HAART visits (AOR: 0.40 [95% CI: 0.34-0.46] and AOR: 0.20 [95% CI: 0.14-0.29], respectively).

Conclusions: Sexual risk behavior significantly decreased following HAART initiation among HIV-infected South African men and women in primary care programs. The further expansion of antiretroviral treatment programs could be an effective means of enhancing HIV prevention efforts in Africa.

Background

Increasing access to highly active antiretroviral therapy (HAART) has extended life and reduced morbidity and mortality among HIV-infected individuals [1, 2]. However, as HAART improves physical health, HIV-infected individuals may be more likely to engage in unsafe sex (i.e. risk compensation or behavioral disinhibition) [3-6]. On the other hand, increased access to clinical care via HIV prevention counseling and receiving HAART may encourage positive changes in sexual risk behavior. As HAART becomes more readily available in resource-limited settings, the relationship between treatment and sexual behavior also becomes more important [7, 8]. A key component of the recently proposed HIV prevention strategy of "Universal Test and Treat," in which everyone diagnosed with HIV infection is promptly initiated on HAART to decrease HIV transmission by reducing population viral load, partially depends on sexual risk behavior not increasing once individuals are on HAART [9, 10].

South Africa has an adult HIV prevalence of 18.1% and has the largest HIV epidemic in the world with 5.7 million HIV-infected individuals[11]. Since 2005, a growing number of HIV-infected South Africans have gained access to HAART so that by 2007, a third of South Africans in need of treatment were receiving HAART[12]. In South Africa, the high prevalence of HIV is likely fueled by a range of high risk sexual behaviors, including inconsistent condom use, early age at sexual debut, and multiple sex partners [13-17].

Secondary prevention efforts that aim to decrease the risk of HIV transmission from already infected individuals through behavioral and biomedical interventions have

yet to be widely implemented in southern Africa [7, 18]. There is some evidence that HAART may not be associated with an increase in sexual risk taking behavior in sub-Saharan Africa[19], although much of this data has included only limited patient follow-up or cross-sectional studies, or was conducted exclusively among high risk groups [19-24]. With increasing efforts to expand treatment access and secondary prevention in the region, quantifying and comparing potential shifts in sexual behaviors over time among populations of HAART initiators remains an urgent priority.

We examine the relationship between HAART status and being sexually active, having unprotected sex, and having >1 sex partner before and after HAART initiation, overall and stratified by gender, among an operational cohort of South African men and women enrolled in urban and rural primary care programs.

Methods

Setting and participants: Between June 2003 and January 2010, HIV-infected patients were recruited to participate in an operational cohort study at HIV primary care and support clinics in urban and rural South Africa. Eligible participants were >18 years, HIV-infected, and had given written informed consent. The urban clinic was at the Perinatal HIV Research Unit (PHRU) at Chris Hani Baragwanath Hospital in Soweto, and the rural at Tintswalo Hospital in Mpumalanga Province. Participants were either self-referred for HIV care, or were referred from mother-to-child transmission prevention programs, hospital wards, or HIV counseling and testing programs. Clinical care, delivered primarily by nurses with physician oversight, included the following HIV-

related clinical services: symptom screening for sexually transmitted infections (STIs) and tuberculosis (TB)[25], prophylactic treatment for opportunistic infections (OIs), treatment for STIs and HIV-related OIs, annual cervical smears[26], and female family planning methods. Since 2004 at PHRU and 2005 at Tintswalo, participants were also offered HAART when they were diagnosed with WHO stage 4 disease, or when their CD4 cell counts fell below 200 cells/ul per South African guidelines [27, 28]. Prior to HAART initiation, all patients were offered adherence counseling. All care was provided free of charge. The Ethics Committee at the University of the Witwatersrand approved this study.

Data collection: At baseline, participants were interviewed using a standardized questionnaire that collected demographic, socio-economic, behavioral, and health history information. Participants were interviewed using a similar instrument at data collection visits scheduled 4-7 months apart, but could visit the clinic at any time for care. Laboratory data included CD4 cell count at baseline and every 6 months. For the current study, we assessed socio-demographic variables: age, employment, urban or rural residential status, marital status, number of people living in household, and current contraception status (for women); and behavioral variables: sexual activity, alcohol use, needing assistance in completing daily activities, and disclosure of HIV status. At baseline and study follow-up, participants were asked about their sexual behaviors, including whether or not they had a regular partner, whether they had a casual sex partner, and the frequency of condom use with both regular and casual partners (if they had one). Recall for these questions was the past 6 months since the last clinic visit. Condom use for each partner type was collected using categorical variables, and

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consistent condom use was defined as self-report of always using a condom with a sex partner. These measures of sexual behavior have been employed in this setting [29].

Statistical analyses: We assessed three measures of sexual behavior as outcomes in the current study: 1) being sexually active; 2) having unprotected sex with a regular and/or casual partner; and 3) having >1 sex partner. Since not all participants reported a regular or casual sex partner, we first examined factors associated with being sexually active. The outcomes of having unprotected sex and having >1 sex partner were analyzed only among those who reported being sexually active. We restricted our analyses to CD4 cell counts taken within 90 days of a study visit. Data was analyzed according to an intent-to-treat analysis, where once participants were initiated on HAART, they were considered HAART-experienced at all subsequent clinic visits. To assess the effect of HAART initiation on potential changes in sexual risk behavior, we compared sexual behavior during pre-HAART visits to behavior reported after HAART initiation. After introducing HAART status—the primary predictor variable—into the models, each covariate was introduced into the three models to assess potential confounding based either on a change of at least 10% of the non-log transformed beta coefficient of independent risk factors, or *a priori* confounders based on a review of earlier studies. The three sexual behavior outcomes were assessed as time-varying outcomes. CD4 cell count and HAART status were adjusted for as time-varying covariates. The baseline status of all other socio-demographic and behavioral covariates were also adjusted for in the models. We controlled for time-dependent changes in risk behavior by adjusting for years since enrollment in care via calendar year category (2002-2004, 2004-2006, and 2006-2009) [24]. We employed generalized estimating equations (GEE) with a logit link and

exchangeable correlation structure to assess the impact of HAART on sexual risk behavior utilizing PROC GENMOD in SAS [30]. To further examine within-participant variation (i.e. treatment effect) while still controlling for stable participant characteristics, we also employed fixed effects regression methods utilizing PROC LOGISTIC in SAS [31]; however this analysis was broadly similar to the GEE analysis and is therefore not presented here. We examined three multivariable models of sexual behavior using GEE, namely being sexually active (Model I), unprotected sex (Model II), and having >1 sex partner (Model III). In a sensitivity analysis these three outcomes were re-examined by restricting analyses to those participants who initiated HAART during follow-up. We also assessed the impact of CD4 cell count on sexual behavior through examining clinic visits for which CD4 cell count data was available. All analyses used STATA (STATACORP, version 10.0, College Station, TX) and SAS (SAS Institute, version 9.2, Cary, NC) software.

Results

Characteristics of participants: Between 2003 to 2009, there were a total of 6263 participants, of whom 4719 (75.3%) were women, accounting for a total of 19703 clinic visits (4479 for men and 15224 for women). During the study period, 2332participants (37.2 %) initiated HAART, of whom 71.7% were women. Table 1 presents the characteristics of all 6263 participants, stratified by gender and treatment status. The median age at study enrollment was 33.8 years (IQR: 29.1-40.0) and the median CD4 cell count at study enrolment was 253 cells/ul (IQR: 110-440). The urban cohort was larger (65.3%), and most participants were unemployed (76.4%) and never married (53.8%). At

baseline, most (87.3%) had disclosed their HIV status, and 33.2% reported alcohol use. About a third enrolled into care between 2002-2004, 2005-2006, and 2006-2009, respectively. The mean number of study visits was 3.22 (SD 2.45) per person, with a mean number of 2.64 (SD 1.59) post-HAART visits and 2.59 (SD 2.15) pre-HAART visits per person. At study enrollment, compared to those who did not initiate HAART, participants who did start HAART during the study were less likely: to be women (71.7% vs. 77.5%; p<0.0001), to be urban residents (42.6% vs. 78.7%; p<0.0001), to be employed (18.3% vs. 26.8%, p<0.0001), and to be never married (48.6% vs. 56.9%; p<0.0001), and were more likely to be older (age>40 years: 32.6% vs. 20.5%; p<0.0001).

Sexual behavior and HAART: Table 2 presents the frequency of being sexually active (Model I), reporting unprotected sex (Model II), and having >1 sex partner (Model III) at visits before and after HAART initiation. Out of a total of 9568 pre-HAART and 3496 post-HAART visits, participants were more likely to be sexually active before HAART compared to after HAART initiation (70.7% vs. 56.6%; p<0.0001). By partner type, participants with: both a primary and casual partner, a primary partner only, and a casual partner only, reported a higher frequency of being sexually active before HAART initiation compared to after HAART initiation (p<0.0001). Participants reported a higher frequency of abstinence (i.e. no partner) at visits after HAART initiation (43.4% vs. 29.3%; p<0.0001). Both men and women were more likely to report being sexually active before HAART initiation (p<0.0001). In regards to unprotected sex, of 13064 visits at which sexual activity was reported, participants reported unprotected sex at 1968 pre-HAART (20.6%) visits compared to 346 post-HAART (9.9%) visits (p<0.0001). By partner type, participants with both a primary and casual partner and only a primary

partner reported a higher frequency of unprotected sex before HAART initiation than after HAART initiation (p<0.05). Both men and women reported unprotected sex at a higher frequency before HAART initiation (p<0.0001). Of 600 visits during which having >1 sex partner was reported, participants reported having >1 sex partner at 542 pre-HAART (5.7%) visits compared to 58 post-HAART (1.7%) visits (p<0.0001), a difference that held across genders. We also examined these three sexual behavior outcomes only among the subset of participants who initiated HAART who contributed a total of 9032 visits. Similar to the previous analyses, participants reported a higher frequency of being sexually active, engaging in unprotected sex, and having >1 sex partner at pre-HAART visits compared to post-HAART visits (p<0.0001).

Adjusted analyses of HAART and being sexually active (Model I) overall and stratified by gender: Overall, the likelihood of being sexually active decreased after HAART initiation (AOR: 0.86 [95% CI: 0.78-0.95]; p=0.0036), and this decrease was greater for women (AOR: 0.40 [95% CI: 0.35-0.46]; p<0.0001) than for men (AOR: 0.90 [95% CI: 0.74-1.08]; p=0.2745) (See Table 3). Other independent predictors of decreased sexual activity included female gender (AOR: 0.76 [95% CI: 0.66-0.87]; p=0.0001), older age (AOR >40 years: 0.31 [95% CI: 0.27-0.36]; p<0.0001), and needing assistance with daily activities (AOR: 0.59 [95% CI: 0.50-0.71]; p<0.0001); and of increased sexual activity included urban residence (AOR: 1.97 [95% CI: 1.71-2.26]; p<0.0001) and married/living together (AOR: 4.42 [95% CI: 3.85-5.08]; p<0.0001). Though not significant predictors overall, unemployment for men and alcohol use, injectable hormone- and pill-based contraception, and enrollment in care since 2006 for women were significantly associated with being sexually active.

Adjusted analyses of HAART and unprotected sex (Model II) overall and stratified by gender: Overall unprotected sex decreased after HAART initiation (AOR: 0.40 [95% CI: 0.34-0.46]; p<0.0001), and this decrease was greater for men (AOR: 0.33 [95% CI: 0.24-0.44]; p<0.0001) than for women (AOR: 0.71 [95% CI: 0.59-0.86]; p=0.0005) (See Table 4). Overall other independent predictors of increased unprotected sex were: female gender (AOR: 1.63 [95% CI: 1.37-1.95]; p<0.0001), marred/living together (AOR: 1.27 [95% CI: 1.10-1.46]; p=0.0010), STI symptoms (AOR: 1.35 [95% CI: 1.20-1.53]; p<0.0001), and older age (AOR for >40 years: 1.25 [95% CI: 1.03-1.53]; p=0.0229); and of decreased unprotected sex were: urban residence (AOR: 0.71 [95% CI: 0.58-0.85]; p=0.0004) and enrollment in care since 2006 (AOR: 0.71 [95% CI: 0.59-0.85]; p=0.0003). Though not significant predictors overall, needing assistance with daily activities for men and unemployment, hormone-based contraception, and disclosure of HIV status for women were significantly associated with unprotected sex.

Adjusted analyses of HAART and having >1 sex partner (Model III) overall and stratified by gender: Overall the likelihood of having >1 sex partner decreased after HAART initiation (AOR: 0.20 [95% CI: 0.14-0.29]; p<0.0001), and this decrease was greater for women (AOR: 0.09 [95% CI: 0.05-0.17]; p<0.0001) than for men (AOR: 0.35 [95% CI: 0.23-0.53]; p<0.0001) (See Table 5). Other independent predictors associated with a decreased odds of having >1 sex partner were female gender (0.45 [95% CI: 0.36-0.56]; p<0.0001), married/living together (AOR: 0.41-0.67]; p<0.0001), and enrollment in care since 2005 (AOR for 2005-2006: 0.20 [95% CI: 0.15-0.27]; p<0.0001 and AOR for 2006-2009: 0.19 [95% CI: 0.13-0.29]; p<0.001) . Though not significant predictors

overall, urban residential status and disclosure of HIV status for men and older age (AOR for >40 years) for women were significantly associated with having >1 sex partner.

Sensitivity analyses: Restricting analyses to the subset of 2307 participants who initiated HAART during follow-up time did not alter the overall association between HAART and being sexually active (AOR: 0.87 [95% CI: 0.77-0.98]; p=0.0238), unprotected sex (AOR: 0.43 [95% CI: 0.36-0.52]; p<0.0001), and having >1 sex partner (AOR: 0.17 [95% CI: 0.12-0.24]; p<0.0001). Additionally, to examine the impact of behavior change following HAART imitation that was independent of CD4 cell count, we examined the three behavioral outcomes adjusting for CD4 cell count in the 5704 visits with CD4 cell counts, (65.2% were pre-HAART and 34.8% were post-HAART); outcomes were consistent with the earlier analyses for the association between HAART and being sexually active (AOR: 0.78 [95% CI: 0.67-0.93]; p=0.0047), unprotected sex (AOR: 0.32 [95% CI: 0.23-0.44]; p<0.0001), and having >1 sex partner (AOR: 0.25 [95% CI: 0.13-0.50]; p<0.0001). We also assessed effect modification by strata of CD4 cell count based on cut-offs that have been considered for treatment initiation (<200 cells/ul, 200-350 cells/ul, vs. >500 cells/ul) and these stratum-specific AORs were not significantly different from each other, suggesting that sexual risk behavior did not differ by CD4 cell count strata.

Discussion

In this population of HIV-infected South African men and women enrolled in urban and rural primary care programs, we documented a strong and sustained reduction

in sexual risk behaviors following HAART initiation. Among both men and women in these two cohorts, we observed reductions in those reporting sexual activity, unprotected sex, and >1 sex partner, suggesting that HAART in this population is not associated with risk compensation. Furthermore, these findings were independent of CD4 cell count. To our knowledge, this is one of the first studies to report on sexual risk among a longitudinal HIV-infected cohort spanning nearly a decade of observation before and after HAART initiation in a resource-limited setting. These findings add to our understanding of how HAART could further assist in reducing the secondary transmission of HIV.

There has been a paucity of longitudinal data examining the relationship between initiating HAART and sexual risk among HIV-infected Africans. Our findings from a large clinic-based sample of men and women provide greater generalizability than earlier studies from the region. Recent data from HIV-infected female sex workers in Kenya found that unprotected sex but not the number of sex partners decreased following HAART initiation [24]. South African and Kenyan cohorts with 12 months of HAART follow-up have also documented a decrease in the frequency of unprotected sex [32, 33]. A clinic-based cohort from Uganda found that while sexual activity increased following HAART, condom use increased and the number of sex partners decreased [34]. An earlier Ugandan cohort with up to 6 months of HAART also documented reductions in risky sexual behavior [23]. Recent cross-sectional studies from African settings have also suggested that HAART was not associated with increased sexual risk behaviors [20-22, 35]. In contrast, a study from Cote d'Ivoire found that unprotected sex significantly increased during the first 6 months of treatment [36]. Differing results in these settings

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highlight the complexity of measuring the association between HAART and sexual behavior and variations in study populations and treatment program characteristics. As HAART continues to be rolled-out in resource-limited settings and an increasing number of individuals are on treatment for an extended period of time, further quantitative and qualitative research should examine whether initial decreases in sexual risk behavior are sustained and reasons for this. We unfortunately have no evidence for reasons for our findings however, apart from counseling prior to HAART initiation, other reasons may include treatment optimism and metabolic effects of HAART.

Sexual activity was reported at two-thirds of study visits overall, and decreased following HAART initiation. Data from Uganda and Cote d'Ivoire have also found that a substantial number of patients on HAART do not engage in sexual activity [21, 37]. In the current study, despite the finding that HAART was not associated with an increase in unprotected sex, many participants still engaged in unprotected intercourse and hence the potential risk for HIV transmission persists. Earlier data from South Africa has documented high levels of unprotected sex (i.e. 30-50%) among HIV-infected individuals [38]. It is important that HIV clinical care programs continue to emphasize consistent condom use even after initiating therapy.

Overall urban residents were less likely to report unprotected sex or multiple sex partners. It is possible that urban residents have greater access to prevention messages through the media. Participants who had disclosed their HIV status were less likely to engage in sexual risk behaviors. HIV disclosure was very high in this population (>80%) at clinic enrollment, and may suggest that many patients could negotiate condom use and discuss sensitive issues such as sex and relationships with their partners [33]. These

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findings are similar to an earlier cross-sectional analysis we undertook prior to the wider

roll-out of HAART [29]. Additionally, unprotected sex was more frequent among

couples who were married or living together, which is in accordance with earlier data

from Africa [23]. Data from Uganda among discordant couples showed that HAART

was associated with reduced HIV transmission risk and sexual risk behavior decreased

following enrollment [39]. Due to the fact that HIV discordance is common within

African couples, couples-based prevention in care settings remains important [37, 40,

41].

The current study included only patients enrolled in primary care programs in

which they received ongoing counseling and prevention messages, and hence patients

may have been less likely to report risky sexual behaviors. However, study staff received

training to ask questions in a non-judgmental manner to minimize social desirability.

Also, due to the comprehensive care and prevention package, it is not possible to

disentangle the relative effects of prevention activities, counseling, and condom provision

from the effects of providing HAART. It is possible that the documented reductions in

sexual risk behavior may have occurred due to the comprehensive nature of care as

opposed to HAART alone. Additional variables that are important determinants of

sexual risk behavior that we were unable to assess include: desire for children,

involvement in commercial sex, drug use, and primary partner HIV status. Though

patients who did not initiate HAART varied on socio-demographic characteristics, we

adjusted for these variables in our multivariable analysis and also conducted further

sensitivity analyses excluding patients who did not initiate HAART. To elucidate the

impact of HAART on within participant sexual behavior, we also conducted further

analyses using fixed effects modeling, and those findings were consistent with the analyses presented here.

Strengths of the current study include prospective data collection before and after HAART initiation. Participants received the same clinic-based HIV prevention and counseling services before and after HAART initiation, reducing potential information bias. A large sample size allowed us to examine a range of confounding variables in our models. We also assessed sexual behavior using a variety of relevant outcome measures, which demonstrated consistent changes toward lower levels of risk taking. Earlier studies in this region have often had short study follow-up or limited generalizability due to being conducted among high-risk sub-populations. The current study can be generalized to HIV-infected patients receiving primary care in both urban and rural settings in sub-Saharan Africa where HAART is increasingly available.

To develop effective secondary prevention interventions in African settings in the era of expanding access to treatment, a broad evidence base about patterns of sexual risk behaviors among HIV-infected individuals before and after initiating HAART is necessary. More interventions are needed to promptly initiate HIV-infected individuals on treatment in resource-limited settings, and to consider providing HAART to individuals who currently do not meet treatment guidelines as they may be at considerable risk for transmitting HIV. Integrating access to prompt treatment with appropriate counseling and prevention programs could reduce HIV transmission in the hyperendemic settings of southern Africa.

Tables

Table 1. Baseline socio-demographic, clinical, and behavioral characteristics of HIV-infected South African participants overall, stratified by gender and HAART status

	All, % (N=6263)	Men, % (N=1544)	Women, % (N=4719)	Initiated HAART, % (N=2332)
Gender				
Men	24.7	--	--	28.3
Women	75.3			71.7
Age, (years)				
<30	29.4	15.5	34.0	22.8
30-40	45.5	47.3	44.9	44.6
>40	25.0	37.1	21.1	32.6
Residential status				
Urban	65.3	57.7	67.7	57.4
Rural	34.7	42.3	32.3	42.6
Employment				
Employed	23.6	31.9	20.8	18.3
Unemployed, wants to work	52.8	38.3	57.6	47.1
Unemployed, does not want to work	23.7	29.8	21.7	34.7
Marital status				
Never married	53.8	38.6	58.7	48.6
Married or living together	29.4	44.6	24.4	27.6
Divorced/separated/widowed	16.8	16.8	16.9	23.8
Number of individuals in household				
2 or less	15.9	26.3	12.5	13.4
3-5	48.1	43.9	49.5	47.4
> 5	36.0	29.8	38.0	39.2
Needs assistance with daily activities				
No	89.9	92.4	89.1	84.8
Yes	10.1	7.6	10.9	15.2
Contraception status	--	--		--
None			92.2	
Injectable hormone			6.6	
Pill			1.2	
Alcohol use				
No	66.8	34.4	77.3	69.6
Yes	33.2	65.6	22.7	30.4

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Disclosed HIV status				
No	12.7	14.0	12.3	11.7
Yes	87.3	86.0	87.7	88.3
Current STI symptoms				
No	80.6	88.7	78.0	77.4
Yes	19.4	11.3	22.0	22.6
CD4 cell count at enrollment, (cells/ul)				
<200	41.7	36.0	43.6	45.4
200-350	22.7	24.6	22.1	22.6
>350	35.5	39.5	34.3	32.0
Year enrolled into care				
2002-2004	36.3	33.8	37.1	32.2
2005-2006	32.9	33.3	32.7	30.9
2006-2009	30.9	32.9	30.2	36.9

Table 2. Frequency of being sexually active (Model I), unprotected sex (Model II), and having >1 sex partner (Model III) at clinic visits stratified by HAART status

N (%) Reporting being sexually active at visit (Model I)				
Category	**Total # of visits**	**Pre-HAART 13,528 visits**	**Post-HAART 6175 visits**	**p-value****
Total	19703	9568/13528 (70.7)	3496/6175 (56.6)	<0.0001
By partner type				
Both primary and casual	19703	542/13528 (4.0)	58/6175 (0.9)	<0.0001
Primary only	19703	8914/13528 (65.9)	3422/6175 (55.4)	<0.0001
Casual only	19703	112/13528 (0.8)	16/6175 (0.3)	<0.0001
No partner	19703	3960/13528 (29.3)	2679/6175 (43.4)	<0.0001
By gender				
Men	4479	2140/2847 (75.2)	1086/1632 (66.5)	<0.0001
Women	15224	7428/10681 (69.5)	2410/4543 (53.0)	<0.0001
N (%) Reporting having unprotected sex at visit*-Model II				
Category	**Total # of visits**	**Pre-HAART 9568 visits**	**Post-HAART 3496 visits**	**p-value****
Total	13064	1968/9568 (20.6)	346/3496 (9.9)	<0.0001
By partner type				
Both primary and casual	600	213/542 (39.3)	15/58 (25.9)	0.045
Primary only	12336	1720/8914 (19.3)	328/3422 (9.6)	<0.0001
Casual only	128	35/112 (31.3)	3/16 (18.8)	0.306
By gender				
Men	3226	359/2140 (16.8)	68/1086 (6.3)	<0.0001
Women	9839	1609/7428 (21.7)	278/2410 (11.5)	<0.0001
N (%) Reporting >1 sex partner at visit*-Model III				

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Category	Total # of visits	Pre-HAART 9568 visits	Post-HAART 3496 visits	p-value**
Total	13064	542/9568 (5.7)	58/3496 (1.7)	<0.0001
By gender				
Men	3226	201/2140 (9.4)	43/1086 (4.0)	<0.0001
Women	9838	341/7428 (4.6)	15/2410 (0.6)	<0.0001
N (%) restricted to those participants who initiated HAART				
Being sexually active	9032	1832/2857 (64.1)	3496/6175 (56.6)	<0.0001
Unprotected sex*	5328	392/1832 (21.4)	346/3496 (9.9)	<0.0001
>1 sex partner*	5328	175/1832 (9.6)	58/3496 (1.7)	<0.0001
*Analyzed at 13064 of 19703 visits at which sexual activity was reported. **The chi-square p-value compare each row category before HAART initiation to after HAART initiation.				

Table 3. Predictors of being sexually active (Model I) overall and stratified by gender (N=19703 visits)

	All (N=19703 visits)	Men (N=4479 visits)	Women (N=15224 visits)
	AOR* (95% CI); p-value	AOR (95% CI); p-value	AOR (95% CI); p-value
HAART status			
No	1.00	1.00	1.00
Yes	0.86 (0.78-0.95); 0.0036	0.90 (0.74-1.08); 0.2745	0.40 (0.35-0.46); <0.0001
Gender			
Men	1.00	--	--
Women	0.76 (0.66-0.87); 0.0001		
Age, (years)			
<30	1.00	1.00	1.00
30-40	0.71 (0.63-0.80); <0.0001	0.83 (0.59-1.16); 0.2965	0.78 (0.68-0.90); 0.0006
>40	0.31 (0.27-0.36); <0.0001	0.51 (0.35-0.74); 0.0004	0.37 (0.31-0.45); <0.0001
Residential status			
Rural	1.00	1.00	1.00
Urban	1.97 (1.71-2.26); <0.0001	2.74 (2.03-3.71); <0.0001	0.72 (0.60-0.86); 0.0004
Employment			
Employed	1.00	1.00	1.00
Unemployed, wants to work	0.77 (0.68-0.87); <0.0001	0.56 (0.43-0.74); <0.0001	1.04 (0.88-1.21); 0.6261
Unemployed, does not want to work	0.57 (0.48-0.68); <0.0001	0.45 (0.32-0.62); <0.0001	0.96 (0.76-1.20); 0.7385
Marital status			
Never married	1.000	1.00	1.00
Married or living together	4.42 (3.85-5.08); <0.0001	5.78 (4.34-7.71); <0.0001	3.24 (2.69-3.90);. <0.0001
Divorced/separated/widowed	0.63 (0.54-0.73); <0.0001	0.70 (0.50-0.98); 0.0413	0.65 (0.55-0.77); <0.0001
Needs assistance with daily activities			
No	1.00	1.00	1.00

Yes	0.59 (0.50-0.71); <0.0001	0.61 (0.39-0.94); 0.0249	0.72 (0.59-0.89); 0.0031
Contraception status None Injectable hormone Pill	--	--	1.00 1.56 (1.27-1.92); <0.0001 2.66 (1.70-4.15); <0.0001
Alcohol use No Yes	1.00 1.25 (1.11-1.41); 0.0002	1.00 1.05 (0.84-1.32); 0.6301	1.00 1.36 (1.16-1.60); 0.0001
Year enrolled into care 2002-2004 2005-2006 2006-2009	1.00 1.12 (0.99-1.26); 0.0550 0.97 (0.86-1.11); 0.7436	1.00 0.90 (0.69-1.17); 0.4575 0.81 (0.61-1.07); 0.1451	1.00 0.98 (0.84-0.87); 0.8434 0.84 (0.71-0.98); 0.0296
*AOR, adjusted odds ratio			

Table 4. Predictors of unprotected sex (Model II) overall and stratified by gender (N=13064 visits)*

	All (N=13064 visits)	Men (N=3226 visits)	Women (N=9838 visits)
	AOR** (95% CI); p-value	AOR (95% CI); p-value	AOR (95% CI); p-value
HAART status			
No	1.00	1.00	1.00
Yes	0.40 (0.34-0.46); <0.0001	0.33 (0.24-0.44); p<0.0001	0.71 (0.59-0.86); 0.0005
Gender			
Men	1.00	--	--
Women	1.63 (1.37-1.95); <0.0001		
Age, (years)			
<30	1.00	1.00	1.00
30-40	0.88 (0.76-0.98); 0.0898	0.61 (0.40-0.92); 0.0191	0.83 (0.71-0.98); 0.0335
>40	1.25 (1.03-1.53); 0.0229	0.93 (0.60-1.45); 0.7692	1.06 (0.83-1.34); 0.6135
Residential status			
Rural	1.00	1.00	1.00
Urban	0.71 (0.58-0.85); 0.0004	0.59 (0.40-0.89); 0.0118	1.71 (1.34-2.17); <0.0001
Employment			
Employed	1.00	1.00	1.00
Unemployed, wants to work	1.22 (1.04-1.43); 0.0106	1.01 (0.72-1.42); 0.9356	1.27 (1.05-1.54); 0.0135
Unemployed, does not want to work	1.66 (1.32-2.08); <0.0001	1.33 (0.85-2.07); 0.2026	1.58 (1.19-2.10); 0.0014
Marital status			
Never married	1.00	1.00	1.00
Married or living together	1.27 (1.10-1.46); 0.0010	1.47 (1.04-2.08); 0.0276	1.25 (1.06-1.48); 0.0079
Divorced/separated/widowed	1.20 (0.95-1.50); 0.1138	1.58 (0.93-2.65); 0.0842	1.08 (0.82-1.42); 0.5562
Needs assistance with daily activities			
No	1.00	1.00	1.00

Yes	1.38 (1.06-1.81); 0.0166	1.74 (0.95-3.19); 0.0692	1.12 (0.82-1.53); 0.4537
Contraception status			
None	--	--	1.00
Injectable hormone			0.47 (0.35-0.62); <0.0001
Pill			0.67 (0.38-1.19); 0.1813
Alcohol use			
No	1.00	1.00	1.00
Yes	1.12 (0.97-1.30); 0.1045	1.05 (0.18-1.76); 0.3336	1.08 (0.91-1.29); 0.3409
Disclosed HIV status			
No	1.00	1.00	1.00
Yes	0.69 (0.57-0.84); 0.0002	0.74 (0.48-1.12); 0.1602	0.73 (0.58-0.92); 0.0089
STI symptoms			
No	1.00	1.00	1.00
Yes	1.35 (1.20-1.53); <0.0001	1.55 (1.10-2.17); 0.0111	1.34 (1.15-1.56); 0.0002
Year enrolled into care			
2002-2004	1.00	1.00	1.00
2005-2006	1.05 (0.91-1.21); 0.4340	0.96 (0.69-1.33); 0.8251	1.59 (1.33-1.89); <0.0001
2006-2009	0.71 (0.59-0.85); 0.0003	0.58 (0.38-0.88); 0.0109	1.14 (0.92-1.41); 0.02024
*Analyzed at 13064 of 19703 visits at which sexual activity was reported.			
**AOR, adjusted odds ratio			

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Table 5. Predictors of >1 sex partner (Model III) overall and stratified by gender (N=13064 visits)

	All (N=13064 visits)	Men (N=3226 visits)	Women (N=9838 visits)
	AOR** (95% CI); p-value	AOR (95% CI); p-value	AOR (95% CI); p-value
HAART status			
No	1.00	1.00	1.00
Yes	0.20 (0.14-0.29); <0.0001	0.35 (0.23-0.53); <0.0001	0.09 (0.05-0.17); <0.0001
Gender			
Men	1.00	--	--
Women	0.45 (0.36-0.56); <0.0001		
Age, (years)			
<30	1.00	1.00	1.00
30-40	0.96 (0.76-1.21); 0.7355	0.77 (0.50-1.18); 0.2393	1.00 (0.76-1,32); 0.9539
>40	1.58 (1.17-2.13); 0.0023	0.88 (0.54-1.43); 0.6201	2.29 (1.61-3.25); <0.0001
Residential status			
Rural	1.00	1.00	1.00
Urban	0.73 (0.56-0.96); 0.0277	0.64 (0.42-0.97); 0.0366	0.80 (0.56-1.13); 0.2177
Marital status			
Never married	1.00	1.00	1.00
Married or living together	0.53 (0.41-0.67); <0.0001	0.47 (0.32-0.67); <0.0001	0.56 (0.41-0.77); 0.0004
Divorced/separated/widowed	0.88 (0.63-1.22); 0.4639	0.57 (0.32-1.00); 0.0505	1.12 (0.76-1.65); 0.5482
Disclosed HIV status			
No	1.00	1.00	1.00
Yes	0.82 (0.62-1.08); 0.1733	0.62 (0.41-0.96); 0.0338	0.86 (0.60-1.23); 0.4361
STI symptoms			
No	1.00	1.00	1.00
Yes	1.16 (0.94-1.44); 0.1510	1.40 (0.92-2.13); 0.1152	1.09 (0.84-1.41); 0.5028
Year enrolled into care			
2002-2004	1.00	1.00	1.00

2005-2006	0.20 (0.15-0.27); <0.0001	0.49 (0.32-0.73); 0.0006	0.10 (0.07-0.16); <0.0001
2006-2009	0.19 (0.13-0.29); <0.0001	0.51 (0.32-0.82); 0.0056	0.06 (0.03-0.14); <0.0001
*Analyzed at 13064 of 19703 visits at which sexual activity was reported.			
** AOR, adjusted odds ratio			

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CHAPTER 4: HIV AND MATERNAL AND CHILD HEALTH

"Morbidity and mortality among infants born to HIV-infected women in South Africa: implications for child health in resource-limited settings"

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Abstract

Background: We examined correlates of infant morbidity and mortality within the first 3 months of life among HIV-exposed infants receiving post-exposure antiretroviral prophylaxis in South Africa.

Methods: We conducted a prospective cohort study of 848 mother-child dyads. Multivariable Cox proportional hazards models were used.

Results: The main causes of infant morbidity were gastrointestinal and respiratory infections. Morbidity was higher with infant HIV infection (HR: 2.61, 95%CI: 1.40-4.85;p=0.002) and maternal plasma viral load>100,000 copies/ml (HR: 1.87; 95%CI: 1.01-3.48;p=0.048), and lower with maternal age<20 years (HR: 0.25, 95%CI: 0.07-0.88;p=0.031). Mortality was higher with infant HIV infection (HR: 4.10, 95%CI: 1.18-14.31;p=0.027) and maternal plasma viral load>100,000 copies/ml (HR: 6.93, 95%CI: 1.64-29.26;p=0.008). Infant feeding status did not influence the risk of morbidity nor mortality.

Conclusions: Future interventions that minimize pediatric HIV infection and reduce maternal viremia, which are the main predictors of child health soon after birth, will impact positively on infant health outcomes.

Background

In South Africa, it is estimated that almost 3% of children are HIV-infected, and most of these children have acquired HIV-infection through mother-to-child transmission (MTCT)[1]. Breast milk transmission of HIV in sub-Saharan Africa is estimated to be responsible for 40% of perinatally acquired HIV infections [2], and over a third of women of childbearing age are HIV-infected [3, 4]. HIV-infected mothers face a dilemma regarding how to feed their newborn infants due to the competing risk of HIV transmission associated with breastfeeding and the risk of increased morbidity and mortality associated with formula-feeding [1, 5-7]. Postnatal transmission through breastfeeding remains an important source of possible infection [2, 8]. Several African studies have suggested that exclusive breastfeeding could decrease the cumulative risk of HIV transmission while maintaining the benefits of breastfeeding[9-11], but the risk of HIV infection does not exist if breast exposure is completely avoided[12]. However, non-breastfed infants can be at increased risk of hospitalization and dying from infectious diseases [13, 14].

Antiretroviral (ARV) prophylaxis during pregnancy and delivery has been shown to be an effective means of reducing the risk of MTCT [15, 16]; however, less than 50% of South African women attending MTCT sites have been tested for HIV [17]. Despite expanding access to highly active antiretroviral therapy (HAART) in resource-limited settings, it is estimated that less than half of those in need are currently receiving treatment [18]. Major gaps remain in adequate coverage of MTCT services as well as HAART access in sub-Saharan Africa for women and their infants [19], highlighting the need for continued studies to examine the impact of HIV infection on infant health

outcomes. Although evidence on the effect of HIV on childhood morbidity and mortality in sub-Saharan Africa is increasing[20, 21], to date use of large cohorts of mother-infant dyads with detailed measurement of clinical outcomes remains very limited.

The current study examines maternal and infant correlates of infant morbidity and mortality within the first 3 months of life in a cohort of HIV-exposed infants receiving ARV post-exposure prophylaxis in South Africa.

Methods

Setting: This study was conducted at three hospitals in South Africa: Chris Hani Baragwanath Hospital (Soweto), Coronation Hospital (Johannesburg), and Mombray Hospital (Cape Town) between October 2000 and September 2002. The primary study was a randomized, open-label, multi-center clinical trial to compare the use of single dose nevirapine to 6 weeks of zidovudine commenced within 24 hours of delivery in infants of ART-naïve HIV-infected mothers [22]. The study was undertaken before HAART was readily available. Clean public drinking water was available in the urban South African settings of the study [23]. This study was approved by the Gauteng Department of Health Provincial Review Committee, the University of the Witwatersrand Committee for Research on Human Subjects, and the Mowbray Maternity Hospital Research Committee.

Participants: Women delivering without prior knowledge of their HIV status were offered postpartum voluntary counseling and rapid onsite testing within 24 hours of delivery. Eligible women testing HIV-positive were offered enrollment. Infants were excluded if they were preterm and weighing <1200 grams, required ventilation, were

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unable to take oral medication, or had congenital abnormalities. Women with CD4 cell counts <200 cells/ul were started on co-trimoxazole prophylaxis. Infants found to be HIV-infected received co-trimoxazole prophylaxis from 6 weeks of age. As was current practice in South Africa, enrolled women were counseled on infant feeding practices per current national guidelines and subsidized formula was provided to women who chose not to breastfeed [24]. Women who decided to breastfeed were encouraged to breastfeed exclusively for 3-6 months.

Among the enrolled 1051 mother-child dyads, 234 patients completed the first visit, but then did not attend any follow-up visits, and 4 patients were missing infant HIV status. The current analyses have been conducted only on the remaining 813 mother-child dyads that provided follow-up time, defined as a minimum of 2 clinical evaluations within the first 3 months of life. The final cohort of patients (N=813) and excluded patients (N=238) were of similar maternal age, maternal plasma viral load (PVL), maternal CD4 cell count, infant gender, infant weight, and infant ARV prophylaxis status.

Clinical assessments: Baseline socio-demographic, medical, and pregnancy history were collected from all enrolled mothers. Obstetric and neonatal data was collected after delivery. Follow-up visits at 10 days, 6 weeks, and 3 months included a clinical examination and a blood sample for HIV-1 diagnosis. At each visit, infant feeding method was ascertained via interviewer-administered structured standardized questionnaires. Mortality outcomes and hospitalization diagnoses were captured from patient records. Staff training, site visits, and ongoing external monitoring were conducted to ensure uniformity of the study across all sites.

Laboratory procedures: Maternal blood samples were tested with Determine HIV-1/2

tests (Abbot Laboratories, Abbot Park, IL, USA), and, if reactive, a second confirmatory

test using the Uni-Gold HIV test (Trinity Biotech, Wicklow, Ireland) was performed.

Women who tested negative with the initial Determine test were considered uninfected.

At study enrollment, maternal blood was sent for HIV-1 RNA quantitative HIV testing

(viral load) and CD4 cell counts. Blood samples were collected from infants for HIV-1

DNA polymerase chain reaction (PCR) using the Roche Amplicor Monitor version 1.5

qualitative PCR assay (Roche Diagnostics, Basel, Switzerland).

Clinical definitions: Confirmed infant HIV-1 infection was defined as two consecutive

blood samples testing positive for HIV-1 DNA by PCR. Infants who had a single

documented positive result and were then lost to follow-up were considered infected. A

child was considered to be uninfected when a week 6 or later result was negative in the

absence of breastfeeding. In breastfed infants, retesting occurred 1 month after

breastfeeding cessation. These infants were then considered uninfected if this sample

was negative. For the Kaplan-Meier survival analysis, feeding status was assessed for

infants who were hospitalized or died at the time of event, and for infants who did not

experience either outcome, the feeding status of longest duration. For the multivariable

analysis, feeding status was assessed as a time-dependent covariate as feeding status

could change between clinic visits.

World Health Organization (WHO) International Classification of Disease (ICD-

10) criteria were used to classify causes of hospitalization and mortality [25].

Hospitalizations and deaths were classified into the following criteria: Birth related: birth

asphyxia, neonatal jaundice, congenital pneumonia, acute respiratory distress syndrome;

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Respiratory: pulmonary tuberculosis, *Pneumocystis jiroveci* pneumonia (PCP),

pneumococcal pneumonia, other chest infection; Gastrointestinal: acute infection, chronic

infection; Neurological: meningitis, encephalitis; Other infections: infection unspecified,

HIV, viral infection, septicemia, urinary tract infection; Malnutrition: kwashiorkor,

marasmus; and Other: immunization/adverse event, anemia requiring transfusion,

unknown.

Outcomes that occurred within the first 24 hours of life as well as birth-related

diagnoses were excluded as these events were neither associated with HIV status nor

feeding status. Of 107 total hospitalizations, 48 (44.9%) birth-related and 2 (1.9%)

within the first 24 hours of birth were excluded from the analysis. Of 16 total deaths, 4

(25%) birth-related deaths were excluded from the analysis. Deaths and hospitalizations

with unknown dates were included in the 12-week analysis, and time to hospitalization

was estimated as midpoint between baseline visit and last visit.

Statistical analysis: In the univariate analysis, mother-infant dyads were stratified by

method of infant feeding and infant HIV status. Categorical variables were compared

using chi-square tests and continuous variables were compared using student t-tests.

Descriptive analyses of the incidence of hospital admissions and deaths were conducted

using Kaplan-Meier survival analysis, and survival curves were compared using log-rank

tests[26]. Univariate and multivariable Cox proportional hazards models were used to

assess maternal and infant correlates associated with infant death and hospitalization. To

check the proportional hazards assumption, a test based on estimation was used to verify

that the squared linear predictor was insignificant. Confounding variables were included

in the multivariable model based on *a priori* confounders identified from the literature

and variables that were significant at a 0.1 level in the univariate analysis. Interaction

effects between infant feeding status and infant HIV status were examined, however

these findings were not statistically significant and are not presented here. Risk factors

that were included in both regression models for mortality and hospitalization included

ARV prophylaxis status, time-varying infant feeding exposure, infant HIV status, infant

birth weight, mode of delivery, maternal PVL, maternal CD4 cell count, and maternal

age. Maternal death was only included in the hospitalization model as no deaths were

documented among the mothers of infants who died. All data analyses were conducted

using STATA (STATACORP, version 10.0, College Station, TX) software. A 95%

confidence interval (CI) and a 5% level of significance were used to assess statistical

significance. All statistical tests were two-tailed.

Results

Baseline characteristics of mothers and infants: Table 1 describes the demographic and

clinical characteristics of the 813 mother-infant dyads stratified by infant feeding method

and HIV status. By the end of the study, among 179 breast-fed infants (22%), 18.4% of

infants became HIV-infected, and among 634 exclusively formula-fed infants (78%),

13.2% of infants became HIV-infected (p=0.081). Maternal PVL was higher among

HIV-infected infants compared to HIV-uninfected infants among both breast-fed infants

(89250 copies/ml vs. 12395 copies/ml; p<0.0001) and exclusively formula-fed infants

(72200 copies/ml vs. 16200 copies/ml; p=<0.0001). Maternal CD4 cell count was lower

among HIV-infected infants compared to HIV-uninfected infants among both breast-fed

infants (401 cells/ul vs. 489 cells/ul; p=0.0447) and exclusively formula-fed infants (357

cells/ul vs. 491 cells/ul; p=0.0013). Among exclusively formula-fed infants, maternal

death during study follow-up was more common among HIV-infected infants compared

to HIV-uninfected infants (6.0% vs. 1.6%; p=0.044). Women above 25 years of age were

more likely to have a PVL >100,000 copies/ml compared to women under 25 years

(11.7% vs. 9.4%; p=0.03). Also, women above 25 years of age were less likely to have a

CD4 cell count >350 cells/ul compared to women under 25 years (63.5% vs. 73.3%;

p=0.004).

Infant morbidity: Table 2 presents the frequencies and causes of infant hospitalization

stratified by infant HIV status and feeding method separately. Among the 57 infants

(7.0%) who were hospitalized, the most frequent clinical diagnoses requiring

hospitalization were respiratory (40.4%) and gastrointestinal infections (42.1%). The

overall incidence rate of hospitalization was 0.87 (95%CI: 0.67-1.13) per 1000 child-

days. Although the incidence rate of hospitalization among formula-fed infants (0.95 per

1000 child-days) was higher than among breast-fed infants (0.56 per 1000 child-days)

(p=0.4712), this was not statistically significant. The incidence rate of hospitalization

among HIV-infected infants (2.33 per 1000 child-days) was over three times higher than

among HIV-uninfected infants (0.64 per 1000 child-days) (p<0.0001). The median

number of days from birth to hospitalization was similar for all clinical diagnoses (range:

42-63 days). The median duration of hospitalization was 6 days (IQR: 2-8), and was

broadly the same across all clinical diagnoses. Seven infants were hospitalized a second

time within the first 3 months of life, 5 of which were due to gastrointestinal infections,

and 4 infants were hospitalized three times within the first 3 months of life. As shown in

Figure 1, among breast-fed infants, 84% of the HIV-infected infants and 96% of HIV-

uninfected infants remained free of hospitalization (p=0.1730), and among formula-fed

infants, 65% of HIV-infected infants and 92% of HIV-uninfected infants remained free of

hospitalization (p<0.0001). The difference in overall probability of remaining free of

hospitalization between HIV-infected and HIV-uninfected infants was also significant

(p<0.0001).

Infant mortality: Among the 12 infants who died, 4 deaths occurred during the neonatal

period. The main causes of death were gastrointestinal infections (25%), pneumonia

(20%), and other infections (25%). The overall mortality rate was 0.18 per 1000 child-

days. The mortality rate among formula-fed infants (0.19 per 1000 child-days) was

higher than among breast-fed infants (0.14 per 1000 child-days) (p=0.1958), but this was

not statistically significant. The mortality rate among HIV-infected infants (0.72 per

1000 child-days) was eight times higher than among HIV-uninfected infants (0.09 per

1000 child-days) (p<0.0001). As shown in Figure 2, among breast-fed infants, 100% of

HIV-infected infants and 92% of HIV-uninfected infants remained alive (p=0.0047), and

among formula-fed infants, 94% of HIV-infected infants and 99% of HIV-uninfected

infants remained alive (p=0.0005). The difference in overall probability of remaining

alive between HIV-infected and HIV-uninfected infants was also significant (p<0.0001).

Multivariable analysis of infant morbidity and mortality: Tables 3 and 4 present the Cox

proportional hazards regression models for predictors of infant death and hospitalization.

The occurrence of hospitalization was significantly higher with infant HIV infection (HR:

2.61, 95% CI: 1.40-4.85; p=0.002) and maternal plasma viral load > 100,000 copies/ml

(HR: 1.87; 95% CI: 1.01-3.48; p=0.048), and lower with maternal age < 20 years (HR:

0.25, 95% CI: 0.07-0.88; p=0.031), but not with infant feeding method, infant birth

weight, infant ARV prophylaxis, maternal death, and maternal CD4 cell count. The

occurrence of death was significantly higher with infant HIV infection (HR: 4.10, 95%

CI: 1.18-14.31; p=0.027) and maternal plasma viral load > 100,000 copies/ml (HR: 6.93,

95% CI: 1.64-29.26; p=0.008), but not with infant feeding status, infant birth weight,

infant ARV prophylaxis, maternal CD4 cell count, and maternal age.

Discussion

The current study among infants born to HIV-infected South African women

provides further evidence of the potent detrimental effect of HIV infection on outcomes

in early infancy, contributes to the ongoing debate about the most beneficial approach to

infant feeding, and emphasizes the importance of increasing timely access to HAART

among pregnant women [17, 19]. Our findings indicate that infant HIV status is the

primary predictor of morbidity and mortality soon after birth. HIV-infected infants were

at over twice the risk of hospitalization and at over four times the risk of death compared

to HIV-uninfected infants. Early detection of infant HIV infection should be a priority in

order to intervene as soon as possible. Elevated maternal PVL also predicted infant

morbidity and mortality, highlighting the importance of early diagnosis of maternal HIV

as well as the need to promptly initiate HIV-infected mothers on HAART.

Infant feeding method did not influence the risk of infant morbidity and mortality

in this urban setting where women had ready access to clean water and infant formula

[23, 24]. The findings of the current study are concordant with a multi-site African study

that found that mortality among infants born to HIV-infected mothers was associated

with maternal clinical factors as well as infant HIV status, but was not associated with infant feeding practice [27]. A recent two-year observational study from Cote d'Ivoire also found that two-year adverse health outcomes and mortality were similar among breast-fed and formula-fed infants [20]. Similar findings have been documented in Kenya and South Africa [28, 29]. However, other recent studies from African settings have suggested that breast-feeding is strongly protective against infant mortality among HIV-infected infants [30, 31]. Comparing risk of hospitalization and mortality attributable to feeding method between studies is not straightforward and can be misleading due to differing outcome definitions, varying periods of follow-up and study entry after birth, differing regional settings with variable access to safe formula and water, and varying ART strategies.

In the current study, infants of HIV-infected mothers with PVL >100,000 copies/ml were at almost 2 -fold greater risk of hospitalization and at over 6-fold greater risk of mortality, which were independent of the effect of infant HIV infection status. This finding of the impact of maternal immunodeficiency on childhood morbidity and mortality is in accordance with earlier studies from multiple African settings[21, 32, 33]. Maternal PVL is not only a major predictor of the risk of perinatal HIV transmission[34], but may also closely predict viral levels in maternal breastmilk[35] and the health of both HIV-infected and uninfected infants [33, 36]. Women with higher PVL may also be at higher risk of co-infection with other pathogens that could be transmitted to their offspring[37]. HIV-infected mothers with unsuppressed viremia may be less likely to be able to provide appropriate child care that could harm their infants compared to healthy mothers. Infants of younger women were at significantly lower hazard of hospitalization,

which was independent of maternal plasma viral load and CD4 cell count. This finding suggests that rather than maternal HIV disease, other social and cultural factors associated with younger maternal age may be protective against infant morbidity. Our results highlight the importance of prompt initiation of HAART among HIV-infected pregnant women, but not necessarily all women of childbearing age. Decreasing breast milk viral load through HAART throughout lactation is likely to reduce the risk of infection[38, 39], and also provide the infant with the beneficial aspects of breastfeeding if the mother chooses to breastfeed.

In the current study, the incidence of hospitalization for diarrhea and pneumonia, which constituted over two-thirds of all hospitalizations, was similar among formula-fed compared to breastfed infants, but the risk of hospitalization due to diarrhea and pneumonia was close to 4 times greater among HIV-infected infants than HIV-uninfected infants. Among non-HIV infected mothers, sustained breastfeeding has been shown to be associated with a lower risk of gastrointestinal and respiratory illness in infants from multiple regional settings[40, 41]. The most common cause of infant pneumonia requiring hospitalization in our study population has been shown to be *Pneumocystis jiroveci* pneumonia[42]. Many infectious complications can be prevented through primary prophylaxis with co-trimoxazole in this infant population with a substantial risk of HIV-infection[12], and further efforts are needed to assure timely prophylaxis initiation.

We are unable to make conclusive comments on an association between infant feeding method and morbidity and mortality among infants born to HIV-infected mothers [43]. It is possible that the benefits accrued through breast-milk exposure require a

longer duration of lactation, but the protective effects of breast-feeding likely decrease over time [13]. Despite possible gains in avoiding HIV transmission through avoiding breastfeeding, healthcare workers, policy makers, and mothers must also consider the extra morbidity, primarily from diarrhea and acute respiratory infections soon after birth, that could be associated with not breast-feeding[13, 44]. In the absence of timely access to HAART in settings where there is available clean water and a safe supply of breast-feeding substitutes, alternatives to breast-feeding with appropriate nutritional counseling and care could be considered as a safe intervention [45]. Our results may not be generalizable to all resource-limited settings where the provision of safe drinking water is not available and where the supply of non-breast milk substitutes may be intermittent. It is advisable that feeding decisions be context-specific [46].

Due to the exclusion criteria of the original clinical trial, these findings may be generalizable only to full-term infants. Data on maternal co-infections was not available in the current study, however all women with CD4 cell counts <200 cells/ul were started on co-trimoxazole prophylaxis per study protocol. At the time of the study, antiretroviral therapy was not freely available in the public sector. The current study utilized hospital admission data to assess infant morbidity and mortality and it is possible that these outcomes could have been under ascertained or misclassified. However, we reviewed infant clinical records over time to confirm hospital admissions and participants who did not follow-up for visits were contacted by study staff. Additionally, we were able to examine clinical outcomes only during the first 3 months of life, and hence we were unable to assess feeding method in the post-weaning (>6 months) period.

Despite the data being from 2000-2002, these findings are still relevant in light of high HIV-associated infant morbidity and mortality as well as due to a lack of adequate HAART coverage of mothers and their infants in this region. These findings, showing the excessive morbidity and mortality in HIV-infected infants, highlight the need for rapid infant HIV diagnosis, prompt initiation of HAART in HIV-infected infants and their mothers, and interventions that will enhance child health. Unlike earlier studies from African settings, the current study included a sizeable number of women who did not breast-feed, but a larger sample of women may be necessary to assess the impact of feeding method on infant morbidity and mortality. Our detailed collection of feeding methods over time allowed us to assess feeding as a time-dependent measure, while many earlier studies have assessed feeding at a single time point. A strength of the current study was detailed outcome data obtained on a large cohort of infants through physician diagnosis and patient records, which allowed for exclusion of outcomes that were unrelated to feeding method and infant HIV status.

The findings of the current study can assist in the development of further HIV diagnostic, monitoring, and care interventions that can be integrated into current HAART treatment programs for HIV-infected women and their infants[47]. New evidence supports the concept that ART given to the infant during breastfeeding can reduce postnatal transmission[38], and that ART can substantially reduce early infant mortality and HIV progression by over 75% among South African infants[48]. Despite increasing access to HAART along with PMTCT in South Africa, major gaps in coverage remain. Optimizing the health of HIV-infected women and their infants involves a careful consideration of competing clinical risks as well as local circumstances. Given the

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overwhelming impact HIV infection has on infant health outcome, the increased

provision of HAART could have the impact of not only decreasing MTCT, but

substantially improving both maternal and child health in hyperendemic HIV settings.

Tables

Table 1. Baseline demographic and clinical characteristics of HIV-infected mothers and infants (N=813)

	Breast milk (N=179)			Exclusive Formula fed (N=634)		
	HIV-infected infants (N=33)	HIV-uninfected infants (N=146)	*p*-value	HIV-infected infants (N=84)	HIV-uninfected infants (N=550)	*p*-value
Mothers						
Median age (IQR), years	24 (22-26)	24 (21-28)	0.5539	27 (22-30)	25 (22-29)	0.2585
Median plasma viral load (IQR), copies/ml	89250 (38550-198500)	12395 (3520-39900)	<0.0001	72200 (18800-219000)	16200 (3270-67300)	<0.0001
Median CD4 cell count (IQR), cells/ul	401 (303-527)	489 (355-696)	0.0447	357 (198-559)	491 (312-687)	0.0013
Mode of delivery, % Normal vaginal delivery	89.0	97.0	0.443	88.1	89.1	0.943
Mother died, %	0.0	0.7	0.727	6.0	1.6	0.044
Infants						
Gender, % Male Female	42.4 57.6	37.7 62.3	0.612	66.7 33.3	48.9 51.1	0.002
Gestational age (IQR), weeks	40 (37-40)	39 (37-40)	0.4508	39 (37-40)	39 (36-40)	0.8159
Median weight (IQR),	2850	3000 (2700-	0.0232	2875 (2500-	2900 (2600-	0.4667

grams	(2500-3020)	3200)		3150)	3200)	
Premature birth, %	21.2	19.9	0.703	22.6	26.0	0.224
Prophylaxis status, %						
Nevirapine	48.5	50.0	0.875	44.0	49.1	0.389
Zidovudine	51.5	50.0		56.0	50.9	

Table 2. Pattern of infant hospitalizations within the first 100 days of life*

	Median time to event (IQR), days	Breast milk N=179 (%)	Formula fed N=634 (%)	Hazard ratio (HR) (95%CI)	HIV-infected N=117 (%)	HIV-unifected N=696 (%)	Hazard ratio (HR) (95%CI)
Incidence rate (95%CI) per 1000 child-days**	--	0.56 (0.28-1.12)	0.95 (0.72-1.26)		2.33 (1.52-3.57)	0.64 (0.46-0.88)	
Total	52 (42-80)	8 (4.5)	49 (7.7)		21 (17.9)	36 (5.2)	
Respiratory (n=23)	62 (42-91)	4 (2.2)	19 (3.0)	1.37 (0.47-4.03)	9 (7.7)	14 (2.0)	4.02 (1.74-9.29)
Gastrointestinal (n=24)	50 (41-71)	3 (1.7)	21 (3.3)	1.99 (0.59-6.68)	9 (7.7)	15 (2.2)	3.79 (1.66-8.66)
Neurological (n=3)	46 (29-81)	0	3 (0.5)	--	1 (0.9)	2 (2.9)	3.21 (0.29-35.49)
Infections (n=4)	45 (36-61)	0	4 (0.6)	--	1 (1.9)	3 (0.4)	2.11 (0.22-20.33)
Malnutrition (n=1)	63 (-)	0	1 (0.2)	--	0	1 (0.1)	--
Other/unknown (n=2)	42 (-)	1 (0.6)	1 (0.2)	0.28 (0.02-4.41)	1 (0.9)	1 (0.1)	5.98 (0.37-95.62)

***1) Birth related: birth asphyxia, neonatal jaundice, congenital pneumonia, acute respiratory distress syndrome; 2) Respiratory: pulmonary tuberculosis, *Pneumocystis jiroveci* pneumonia (PCP), pneumococcal pneumonia, other chest infection; 3) Gastrointestinal: acute infection, chronic infection; 4) Neurological: meningitis, encephalitis; 5) Other infections: infection unspecified, HIV, viral infection, septicemia, urinary tract infection; 6) Malnutrition: kwashiorkor, marasmus; and 7) Other: immunization/adverse event, anemia requiring transfusion, unknown.

**Overall incidence rate excludes birth-related and HIV-related hospitalizations

Table 3. Predictors of hospitalization among infants born to HIV-infected mothers within the first 100 days of life (N=813)

Category	Univariate analysis		Multivariable analysis	
	Hazard ratio (HR) (95% CI)	p-value	Hazard ratio (HR) (95% CI)	p-value
Maternal correlates				
Maternal age				
≤20	0.34 (0.13-0.92)	0.034	0.25 (0.07-0.88)	0.031
20-25	0.47 (0.26-0.95)	0.034	0.51 (0.24-1.07)	0.075
25-30	0.79 (0.41-1.51)	0.473	0.79 (0.40-1.57)	0.502
>30	1.00	--	1.00	--
Maternal CD4 cell count				
≤350 cells/ul	1.82 (1.06-3.15)	0.031	1.27 (0.70-2.28)	0.427
>350 cells/ul	1.00	--	1.00	--
Maternal plasma viral load				
>100000 copies/ml	2.39 (1.38-4.13)	0.002	1.87 (1.01-3.48)	0.048
≤100000 copies/ml	1.00	--	1.00	--
Maternal death				
Yes	1.63 (0.40-6.69)	0.50	0.40 (0.05-3.07)	0.380
No	1.00	--	1.00	--
Infant correlates				
Infant prophylaxis status				
Zidovudine	1.15 (0.68-1.93)	0.604	0.92 (0.53-1.62)	0.782
Nevirapine	1.00	--	1.00	--
Infant HIV status				
HIV infected	3.43 (2.00-5.88)	<0.0001	2.61 (1.40-4.85)	0.002
HIV uninfected	1.00	--	1.00	--
Infant birth weight				
≤2,500 grams	1.24 (0.67-2.30)	0.496	1.05 (0.55-2.02)	0.879
> 2,500 grams	1.00	--	1.00	--
Infant feeding method*				
Formula feeding	1.02 (0.98-1.06)	0.33	1.03 (0.99-1.07)	0.102
Breast milk	1.00	--	1.00	--

*Infant feeding method was analyzed as a time-dependent covariate in the multivariate analysis

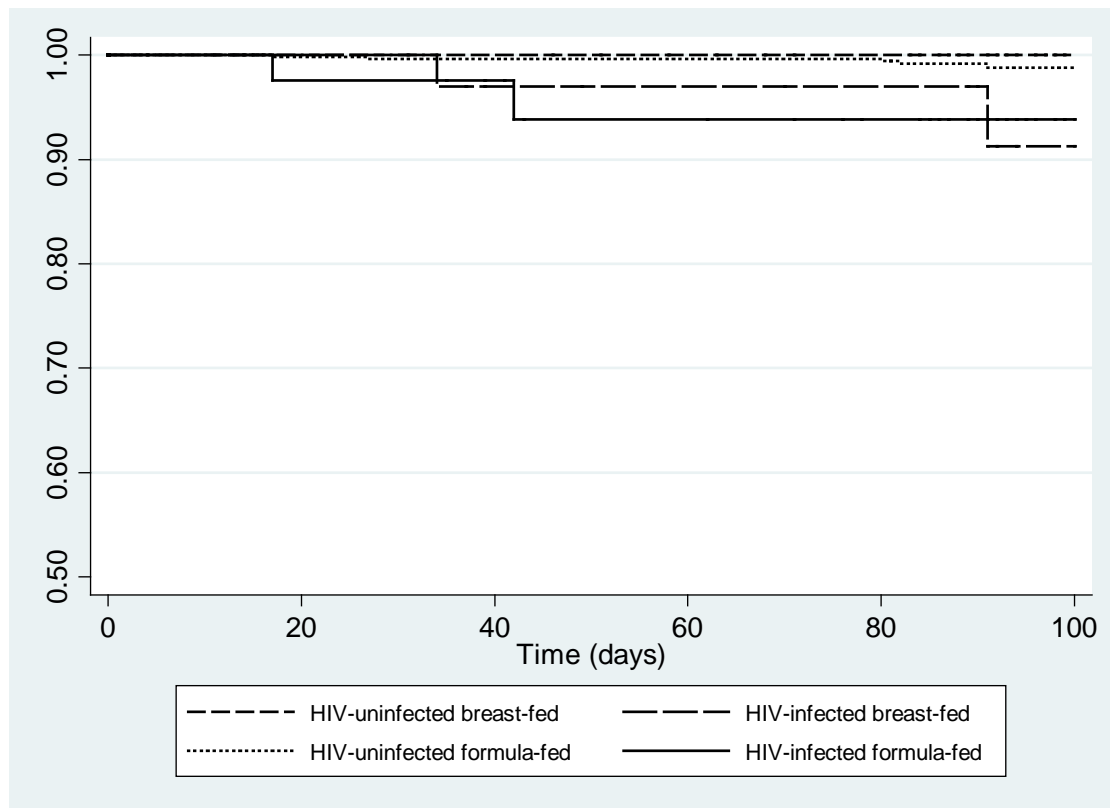**Table 4. Predictors of mortality among infants born to HIV-infected mothers within the first 100 days of life (N=813)**

	Univariate analysis		Multivariable analysis	
Category	**Hazard ratio (HR) (95% CI)**	**p-value**	**Hazard ratio (HR) (95% CI)**	**p-value**
Maternal correlates				
Maternal age				
≤20	1.66 (0.28-9.99)	0.579	1.78 (0.23-13.57)	0.577
20-25	1.02 (0.19-5.59)	0.981	1.24 (0.22-6.92)	0.809
25-30	1.00 (0.17-5.97)	0.998	1.23 (0.20-7.46)	0.824
>30	1.00	--	1.00	--
Maternal CD4 cell count				
≤350 cells/ul	3.80 (1.11-12.98)	0.033	1.02 (0.52-2.02)	0.945
>350 cells/ul	1.00	--	1.00	--
Maternal plasma viral load				
>100000 copies/ml	10.26 (2.72-38.71)	0.001	6.93 (1.64-29.26)	0.008
≤100000 copies/ml	1.00	--	1.00	--
Infant correlates				
Infant prophylaxis status				
Zidovudine	0.97 (0.31-3.02)	0.964	1.25 (0.36-4.31)	0.725
Nevirapine	1.00	--	1.00	--
Infant HIV status				
HIV infected	7.99 (2.53-25.17)	<0.0001	4.10 (1.18-14.31)	0.027
HIV uninfected	1.00	--	1.00	--
Infant birth weight				
≤ 2,500 grams	2.99 (0.95-9.42)	0.062	1.48 (0.42-5.25)	0.547
>2,500 grams	1.00	--	1.00	--
Infant feeding method*				
Formula feeding	1.08 (0.91-1.29)	0.369	1.04 (0.95-1.14)	0.361
Breast milk	1.00	--	1.00	--

*Infant feeding method was analyzed as a time-dependent covariate in the multivariate analysis

Figures

Figure 1. Kaplan-Meier: Probability (95% CI) of remaining free from hospitalization within the first 100 days of life according to infant HIV status and mode of infant feeding

	Frequency	**30 days**	**60 days**	**100 days**
Breastfed children		0.99 (0.95-1.00)	0.96 (0.91-0.98)	0.94 (0.87-0.97)
HIV-infected	3/57 (5.3)	1.00	0.93 (0.76-0.98)	0.84 (0.53-0.95)
HIV-uninfected	5/57 (3.4)	0.99 (0.94-1.00)	0.96 (0.91-0.98)	0.96 (0.91-0.93)
Formula fed children		0.99 (0.98-1.00)	0.95 (0.93-0.97)	0.88 (0.83-0.91)
HIV-infected	18/57 (21.4)	0.99 (0.91-1.00)	0.86 (0.76-0.92)	0.65 (0.46-0.78)
HIV-uninfected	31/57 (5.6)	0.99 (0.98-1.00)	0.96 (0.94-0.98)	0.92 (0.87-0.94)

*The overall log-rank p-value was p<0.001. The overall log-rank p-value between breast-fed and formula-fed infants was p=0.1406. The overall log-rank p-value between HIV-infected and HIV-uninfected infants was p<0.0001. Among breast-fed infants, the log-rank p-value between HIV-infected and HIV-uninfected infants was p=0.1730. Among formula-fed infants, the log-rank p-value between HIV-infected and HIV-uninfected infants was p<0.0001.

Figure 2. Kaplan-Meier: Probability (95% CI) of remaining alive within the first 100 days of live according to infant HIV status and mode of infant feeding

	Frequency	30 days	60 days	100 days
Breastfed children		1.00	0.99 (0.96-1.00)	0.98 (0.93-1.00)
HIV-infected	0/12 (0.0)	1.00	0.97 (0.80-1.00)	0.92 (0.68-0.98)
HIV-uninfected	2/12 (16.7)	1.00	1.00	1.00
Formula fed children		0.99 (0.98-1.00)	0.99 (0.98-0.99)	0.98 (0.96-0.99)
HIV-infected	5/12 (41.7)	0.98 (0.91-0.99)	0.94 (0.86-0.97)	0.94 (0.86-0.97)
HIV-uninfected	5/12 (41.7)	1.00 (0.98-1.00)	1.00 (0.98-1.00)	0.99 (0.97-1.00)

*The overall log-rank p-value was p=0.0003. The overall log-rank p-value between breast-fed and formula-fed infants was p=0.6689. The overall log-rank p-value between HIV-infected and HIV-uninfected infants was p<0.0001. Among breast-fed infants, the log-rank p-value between HIV-infected and HIV-uninfected infants was p=0.0047. Among formula-fed infants, the log-rank p-value between HIV-infected and HIV-uninfected infants was p=0.0005.

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"Growth in infants born to HIV-infected women in South Africa according to maternal and infant characteristics"

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Abstract

Background: The current study prospectively evaluates growth parameters assessed by weight and length in HIV-infected and -uninfected infants born to HIV-infected mothers in South Africa from birth to six months of age.

Methods: We calculated z-scores for weight-for age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) prospectively after birth among a cohort of 840 mother-infant dyads. Multivariable Cox proportional hazards models with time-varying covariates were used to estimate the risk of falling <-2.00 z-scores for WAZ, LAZ, and WLZ as a function of infant and maternal characteristics.

Results: By 6 months following birth, a fifth of infants had <-2.00 WAZ, 19% had a <-2.00 LAZ, and 29% had a <-2.00 WLZ. WLZ and WAZ were significantly lower in HIV-infected infants compared to uninfected infants by 3 months of age, and LAZ by 6 months of age (p<0.001). The risk of falling <-2.00 for WAZ was associated with increasingly lower maternal CD4 cell count (adj. HR for CD4 cell count<200 cells/ul: 1.64; 95%CI: 1.10-2.43; p=0.01) and premature birth (adj. HR: 2.82; 95%CI: 2.06-3.86; p=0.01). The risk of falling <-2.00 for LAZ was associated with increasingly lower maternal age (adj. HR for<20 years: 0.54; 95%CI: 0.31-0.96; p=0.04), maternal CD4 cell count (adj. HR for CD4 cell count <200 cells/ul: 1.72;95% CI: 1.14-2.59; p=0.01), breast feeding (adj. HR: 0.99; 95%CI: 0.98-1.00; p=0.03), and premature birth (adj. HR: 2.37; 95%CI: 1.70-3.30); p=0.01). The risk of falling <-2.00 for WLZ was significantly associated with only infant HIV infection (adj. HR: 1.64; 95%CI: 1.16-2.32; p=0.01).

The risk of falling <-2.00 for WAZ and LAZ was over two times greater for HIV-infected infants than uninfected infants with gastrointestinal infections.

Conclusions: HIV-infected infants were more likely to be stunted and wasted compared to uninfected infants, which occurred soon after birth. Infants born to mothers with advanced HIV disease as well as HIV-infected infants with gastrointestinal infections were at greater risk for growth disturbances. Further interventions are needed to promptly initiate both HIV-infected mothers and infants on appropriate antiretroviral therapy and nutritional supplementation.

Background

HIV infection affects an estimated 2.3 million children worldwide, and the majority (>90%) live in sub-Saharan Africa [1]. Pediatric HIV infection is associated with growth retardation and is likely a significant contributor to infant malnutrition and morbidity [2]. Additionally, poor growth can be one of the first clinically recognized manifestations of HIV infection in children and has a significant impact on short-term survival [3, 4]. Disturbances in growth are likely to occur well before the onset of opportunistic infections or other HIV-related disease manifestations [5]. It has been suggested that over half of all HIV-infected children experience abnormal growth patterns [3, 6]. HIV-infected children have been shown to demonstrate stunting and wasting compared to HIV-uninfected children, which can occur within the first few months after birth [7, 8].

Despite expanding access to highly active antiretroviral therapy (HAART) in resource-limited settings, it is estimated that less than half of those in need are currently receiving treatment [9]. Major gaps remain in adequate coverage of mother-to-child transmission (MTCT) services as well as HAART access in sub-Saharan Africa for women and their infants [10], highlighting the need for continued studies to examine the impact of HIV infection on infant health outcomes.

The degree to which maternal characteristics, vertically acquired HIV infection, or an adverse environment place children at increased risk for growth retardation remains to be fully elucidated in resource-limited settings [11-13]. Growth may be one of the most sensitive indicators of disease progression in HIV-infected infants [14]. Studies

conducted among infants born to HIV-infected mothers can provide insight into the nutritional implications of pediatric HIV infection. The current prospective cohort study examines growth patterns during the first six-months of life among both HIV-infected and -uninfected South African infants born to HIV-infected mothers. We estimate the risk of child growth retardation according to both child and maternal characteristics.

Methods

Setting: The study was conducted at three hospitals in South Africa: Chris Hani Baragwanath Hospital (Soweto), Coronation Hospital (Johannesburg), and Mombray Hospital (Cape Town) between October 2000 and September 2002. The primary study was a randomized, open-label, multi-center clinical trial in South Africa to compare the use of single dose nevirapine (NVP) to 6 weeks of zidovudine (AZT) commenced within 24 hours of delivery in infants whose HIV-infected mothers had no prior exposure to antiretrovirals (ARVs). More details on the methods of the original randomized controlled trial can be found elsewhere [15]. Clean public drinking water was available in the urban South African settings of the study [16]. The study was undertaken before HAART was readily available in South Africa. This study was approved by the Gauteng Department of Health Provincial Review Committee, the University of the Witwatersrand Committee for Research on Human Subjects, and the Mowbray Maternity Hospital Research Committee in Cape Town.

Participants: Women delivering without prior knowledge of their HIV status were offered postpartum voluntary counseling and rapid onsite testing within 24 hours of

delivery. Eligible women testing HIV positive were offered enrollment. Infants were excluded if they were preterm weighing <1200 grams, required ventilation, were unable to take oral medication, or had congenital abnormalities. Infants found to be HIV-infected received co-trimoxazole prophylaxis from 6 weeks of age. Enrolled women were counseled on infant feeding practices per current South African infant feeding guidelines. Subsidized formula was provided to women who chose not to breastfeed. Women who decided to breastfeed were encouraged to breastfeed exclusively for 3-6 months [17]. Mother-infant pairs were followed for 6 months or until one month after cessation of breastfeeding.

Among the 1051 mother-child dyads originally enrolled in this study, 205 patients completed the first visit, but then did not attend any follow-up visits, and an additional 6 patients were missing length and weight data. These patients were excluded due to lack of adequate longitudinal growth data. The current analyses have been conducted on the remaining 840 mother-child dyads. The final cohort of patients (N=840) and those patients excluded from the final cohort (N=211) had similar median maternal age (both groups 25 years), median maternal plasma viral load (18200 vs. 23,000 copies/ml, p=0.60), median maternal CD4 cell count (439 vs. 415 cells/ul, p=0.12), infant gender (Male: 48% vs. 47%, p=0.71), median infant birth weight (both groups 2900 grams), and infant ARV prophylaxis status (NVP: 49% vs 50%; p=0.71).

Clinical assessments: Standardized procedures for enrollment and data collection were used at all study sites [12]. Baseline socio-demographic, medical, and pregnancy history were collected from all enrolled mothers. Follow-up pediatric visits at 10 days, 45 days, 3 months, and 6 months after birth included a clinical examination, blood sample for

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HIV-1 diagnosis, and measurement of child weight in kilograms and length in centimeters. Since this was a secondary analysis of a randomized-controlled trial (RCT) to decrease MTCT, the timing of the four growth assessments was based on the primary therapeutic aim of the RCT. This report addresses an *a priori* secondary aim of the RCT designed to estimate predicted changes in infant growth and its determinants. At each visit, feeding of the infant and breastfeeding practices were ascertained via interviewer-administered structured standardized questionnaires. Child hospitalization diagnoses were abstracted from patient records by two authors (KKV and GEG).

Laboratory procedures: Maternal blood samples were tested with Determine HIV-1/2 tests (Abbot Laboratories, Abbot Park, IL, USA), and, if reactive, a second confirmatory test using the Uni-Gold HIV test (Trinity Biotech, Wicklow, Ireland) was performed. Women who tested negative with the initial Determine test were considered uninfected. Maternal blood was sent for HIV-1 RNA quantitative HIV testing (viral load) and CD4 cell counts. Blood samples were collected for HIV-1 DNA polymerase chain reaction (PCR) using the Roche Amplicor Monitor version 1.5 qualitative PCR assay (Roche Diagnostics, Basel, Switzerland).

Clinical definitions: Confirmed infant HIV-1 infection was defined as two consecutive blood samples testing positive for HIV-1 DNA by PCR. Infants who had a single documented positive result and were then lost to follow-up were considered infected. An infant was considered to be HIV-uninfected when PCR at 45 days or later was negative in the absence of breastfeeding. In breastfed infants, retesting occurred 1 month after breastfeeding cessation. These infants were then considered HIV-uninfected if this sample was negative. Premature births were defined as infants born before 36 weeks of

gestation. World Health Organization (WHO) International Classification of Disease

(ICD-10) criteria were used to classify gastrointestinal and respiratory hospitalizations

[18].

Statistical methods: In the univariate analysis, mother-infant dyads were stratified by

infant HIV status (infected or uninfected). Standard normal deviates (z-scores) for

length-for-age (LAZ), weight-for-age (WAZ), and weight-for-length (WLZ) were

calculated using National Center for Health Statistics (NCHS) reference using EPIINFO

(Centers for Disease Control and Prevention, Atlanta, GA). A -2.00 z-score was used as

the cutoff for low values of these anthropometric indices. Since infant feeding status

could change between study visits, infant feeding method was assessed as a time-varying

covariate. Confounding variables were included in the multivariable model based on *a*

priori confounders identified from the literature and variables that were significant at a

0.10 level in the univariate analysis. Cox proportional hazards models were used to

estimate the risk of reaching <-2.00 for WAZ, LAZ, and WLZ, which have been used in

earlier studies [11]. In order to assess the effects of infant- and maternal-specific

independent variables on growth retardation, separate multivariable models were run

containing only infant and maternal characteristics (Models I and II , respectively) and a

final multivariable model was then run that included both infant and maternal

characteristics (Model III). To assess whether the influence of covariates on growth

outcomes varied by infant HIV status and maternal disease [19], we also examined effect

modification through stratified multivariable analyses by infant HIV status (infected vs

uninfected) and maternal plasma viral load, PVL (PVL<100,000 vs. PVL >100,000). All

data analyses were conducted using STATA (STATACORP, version 10.0, College

Station, TX) software. A 95% confidence interval (CI) and a 5% level of significance were used to assess statistical significance.

Results

Baseline maternal and infant characteristics: Table 1 describes the baseline demographic and clinical characteristics of the 840 mother-infant dyads stratified by infant HIV status. Maternal median plasma viral load was significantly higher among HIV-infected infants compared to HIV-uninfected infants (68650 copies/ul vs. 13150 copies/ul; p<0.0001), and maternal median CD4 cell count was significantly lower (357 cells/ul vs. 459 cells/ul; p=0.0003). Mothers of HIV-infected infants were more likely to have died during study follow-up than mothers of HIV-uninfected infants (4.3% vs. 1.6%; p=0.0485). The proportion of male infants was higher in the HIV-infected group than in the HIV-uninfected group (59.3% vs. 46.5%; p=0.01). Infants, regardless of HIV status, had similar distributions of maternal age, modes of delivery, gestational age, weight at birth, premature birth, and ARV prophylaxis status.

Patterns of infant growth: Table 2 presents the growth parameters of median weight, median length, WAZ, LAZ, and WLZ at 10 days, 45 days, 3 months, and 6 months after birth stratified by infant HIV status. By the end of the study, 20% of infants had <-2.00 WAZ, 19% had a <-2.00 LAZ, and 29% had a <-2.00 WLZ. Twenty-three infants (2.7%) had values <-2.00 for WAZ, LAZ, and WLZ, 9.4% of infants had <-2.00 for both WAZ and LAZ, 7.1% had <-2.00 for both WAZ and WLZ, and 3.5% had <-2.00 for both LAZ and WLZ. A LAZ or WAZ <-2.00 occurred at the same time soon after birth (WAZ:

median of 14 days, IQR of 10-43 days; and LAZ: median of 15 days, IQR of 10-76 days). However, <-2.00 for WLZ occurred at a later age (median of 42 days, IQR of 13-91 days). By 3 months, HIV-infected infants had significantly lower mean WAZ (-0.11 vs. 0.89; p<0.0001) and mean WLZ (-0.91 vs. -0.04; p<0.0001) compared to HIV-uninfected infants. By 6 months, HIV-infected infants had significantly lower mean LAZ than HIV-uninfected infants (0.54 vs. 1.33; p=0.0003). HIV-infected infants had significantly lower weights than HIV-uninfected infants by 3 months (4800 gm vs. 5440 gm; p<0.0001).

Multivariable analysis of mean WAZ: Tables 3 presents the Cox proportional hazards regression models for predictors of infants falling <-2.00 for WAZ by 6 months of age. Three multivariable regression models are presented: model I with only maternal correlates, model II with only infant correlates, and a combined model III with both maternal and infant correlates. In the maternal model, the risk of falling <-2.00 for WAZ was significantly associated with maternal CD4 cell count <200 cells/ul (HR: 1.78; 95% CI: 1.20-2.62; p=0.01), maternal CD4 cell count between 200-350 cells/ul (HR: 1.67; 95% CI: 1.12-2.47; p=0.01, and maternal PVL> 100,000 copies/ml (HR: 1.57; 95% CI: 1.10-2.24); p=0.01). In the infant model, the risk of falling <-2.00 for WAZ was significantly associated with infant gastrointestinal infection (HR: 1.99; 95% CI: 1.08-3.70; p=0.03) and premature birth (HR: 2.89; 95% CI: 2.13-3.92; p=0.01). In the combined maternal and infant model, the risk of falling <-2.00 for WAZ was significantly associated with maternal CD4 cell count <200 cells/ul (HR: 1.64; 95% CI: 1.10-2.43; p=0.01), maternal CD4 cell count between 200-350 cells/ul (HR: 1.62; 95% CI: 1.09-2.41; p=0.02), and premature birth (HR: 2.82; 95% CI: 2.06-3.86; p=0.01).

Multivariable analysis of mean LAZ scores: Tables 4 presents the Cox proportional hazards regression models for predictors of infants falling <-2.00 for LAZ by 6 months of age. Three multivariable regression models are presented: model I with only maternal correlates, model II with only infant correlates, and a combined model III with both maternal and infant correlates. In the maternal model, the risk of falling <-2.00 for LAZ was significantly associated with maternal age <20 years (HR: 0.54; 95% CI: 0.30-0.95; p=0.03) and maternal CD4 cell count <200 cells/ul (HR: 1.93; 95% CI: 1.29-2.88; p=0.01). In the infant model, the risk of falling <-2.00 for LAZ was significantly associated with infant HIV infection (HR: 1.62L 95% CI: 1.07-2.49; p=0.02), breast feeding (HR: 0.99; 95% CI: 0.97-1.00; p=0.03), and premature birth (HR: 2.47; 95% CI: 1.79-3.41; p=0.01). In the combined maternal and infant model, the risk of falling <-2.00 for LAZ was significantly associated maternal age < 20 years (HR: 0.54; 95% CI: 0.31-0.96; p=0.04), maternal age 20-25 years (HR: 0.65; 95% CI: 0.43-0.98; p=0.04), maternal age 25-30 years (HR: 0.61; 95% CI: 0.39-0.96; p=0.03), maternal CD4 cell count <200 cells/ul (HR: 1.72; 95% CI: 1.14-2.59; p=0.01), breast feeding (0.99; 95% CI: 0.98-1.00; p=0.03), and premature birth (HR: 2.37; 95% CI: 1.70-3.30); p=0.01).

Multivariable analysis of mean WLZ scores: In regards to WLZ scores, the risk of falling <-2.00 was not significantly associated with any of the maternal correlates. In the infant model, the risk of falling <-2.00 was significantly associated with only infant HIV infection (HR: 1.75; 95% CI: 1.25-2.46; p=0.01). In the combined maternal and infant model, the risk of falling <-2.00 for WLZ was significantly associated with only infant HIV infection (HR: 1.64; 95% CI: 1.16-2.32; p=0.01).

Multivariable analyses of mean WAZ and LAZ scores stratified by infant HIV

infection status and maternal PVL: Table 5 presents two stratified Cox proportional

hazards models by infant HIV status (infected vs uninfected) and maternal PVL (PVL

>100,000 copies/ml vs <100,000 copies/ml) for the risk of falling <-2.00 for WAZ and

LAZ, adjusting for all other covariates in the combined maternal and infant multivariable

model. The risk of <-2.00 for WAZ was almost three times greater for HIV-infected

infants than uninfected infants with gastrointestinal infections. Similarly, the risk of <-

2.00 for LAZ was four times greater for HIV-infected infants than uninfected infants with

gastrointestinal infections. A similar pattern was observed for WAZ with mothers having

PVL>100,000 copies/ml compared to mothers with PVL<100,000 copies/ml.

Discussion

We found that HIV infection is an independent predictor of infant stunting

(length-for-age) and wasting (weight-for-length), but not being underweight (weight-for-

age). HIV-infected infants experienced significantly greater growth retardation soon

after birth compared to HIV-uninfected infants. LAZ z-scores were lower in HIV-

infected infants compared to uninfected infants by 0.79 at 6 months after birth. Similarly,

WLZ z-scores were lower in HIV-infected infants compared to uninfected infants by 0.87

at 3 months and 0.76 at 6 months, and WAZ z-scores were lower by 0.31 at 45 days, 1.00

at 3 months, and 1.33 at 6 months. At birth, infants had similar weight regardless of HIV

status. Similar to earlier studies from both the developed world as well as resource-

limited settings, these findings suggest that the difference in growth between HIV-

infected and uninfected infants occurs soon after birth and increases with age [7, 11, 12].

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A cohort study of infants from Durban, South Africa found that HIV-infected infants had early (i.e. by 3 months) and sustained low mean z-scores for LAZ and WAZ but not for WLZ compared to the HIV-uninfected infants [20]. An earlier infant cohort in Rwanda also found that stunting but not wasting was more common among HIV-infected infants[21].

In the current study, infant HIV infection was associated with stunting and wasting. It has recently been suggested that height velocity measured as LAZ is more strongly associated with HIV clinical progression, immune reconstitution, and decline in viral replication among ART-experienced US children than weight velocity measured as WAZ [22]. The current study supports earlier findings that wasting is characteristic of HIV-infected children and that HIV-infection is likely a causative factor in initiating and maintaining the process of wasting [11]. It is possible that HIV-infected infants may experience proportional declines in both height and weight such that normal height-for-weight is maintained [20, 21], or wasting may become apparent only later following the development of more advanced immunodeficiency [11]. The current study is notable for identifying wasting in HIV-infected infants within 3 months of birth. In the current study, lower WAZ and LAZ scores among HIV-infected infants were detected at the same time and before lower WLZ scores (in the case of WAZ), which is in accordance with earlier studies [19, 23] [24]. While in protein-energy malnutrition it would be anticipated for weight to decrease before height, the pattern of concurrent decreases in height and weight may indicate that other mechanisms may underlie HIV-related growth failure, such as secondary infections associated with HIV. Further longitudinal studies

are needed to examine the sequence of occurrence of different indices of anthropometric undernutrition.

Maternal CD4 cell count was an independent predictor of being underweight and stunted. A recent Tanzanian cohort also documented maternal CD4 cell count as predicting growth faltering [12], but an earlier study from the Congo did not find an association with maternal disease stage [11]. Infant disease progression by 6 months of age has been shown to be associated with maternal immune suppression [25, 26], and poor maternal health during pregnancy may adversely impact the infant immune system [27, 28]. Additionally, women with advanced immunodeficiency may be too weak to provide adequate care and nurturing to their children after delivery. In the current study, maternal plasma viral load at birth did not predict impaired infant growth. The risk of rapid progression in infants during the first six months of life may be more a product of a relatively ineffective immune response rather than of viral replication.

In the current study, though gastrointestinal infections did not independently predict growth failure, when infants were stratified by HIV status and maternal plasma viral load, HIV infected infants and infants with mothers with PVL >100,000 copies/ml who also had a gastrointestinal infection were at greater risk of experiencing <-2.00 WAZ and LAZ. A recent study among Tanzanian HIV-infected women and their infants found that episodes of diarrhea or respiratory infections were related to significantly lower WLZ but not LAZ scores, but interactions between HIV status and diarrhea or respiratory illness were not significant [12]. Diarrhea has been shown to be strongly associated with decreased growth and increased mortality [29]. In HIV-infected infants, initiation of antiretroviral therapy leads to a decrease in the incidence of opportunistic infections [30].

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Further interventions aimed at prevention, early detection, and management of gastrointestinal infections among HIV-infected infants is warranted.

Preterm infants were at significantly increased risk of being underweight and stunted, which is in accordance with earlier data [12]. HIV-infected women may be at higher risk for preterm labor and intrauterine growth retardation (IUGR) [31, 32]. Also, IUGR may depend on the degree of maternal immunodeficiency [33]. Preterm delivery is hypothesized to be a result of maternal viral load rather than fetal HIV infection [32]; [3]. It is also possible that increased losses to follow-up attributable to mortality could have reduced the contributions of later anthropometric measurements among pre-term infants. In the current study, breastfeeding was protective against lower LAZ, but was not associated with diminished WAZ or WLZ. However, though statistically significant for LAZ, the hazard ratio was close to the null. This finding is in contrast to an earlier study conducted among uninfected children born to HIV-infected mothers in Zambia [34]. Among non-HIV infected mothers, sustained breastfeeding has been shown to be associated with a lower risk of gastrointestinal and respiratory illness in infants from multiple regional settings [35-37]. Due to the association of growth faltering associated with gastrointestinal infections among HIV-infected infants, breastfeeding should be encouraged [13].

To our knowledge, the current study is one of the largest cohorts to report growth outcomes among infants born to HIV-infected mothers. It is difficult to compare our results with other studies examining growth outcomes among HIV-infected infants due to differences in populations studied, varying prenatal growth patterns, the availability of ART, food supplementation or socioeconomic conditions, viral subtypes, prevalence of

maternal sexually transmitted infections, varying sample size and statistical power, and other intercurrent nutritional deficiencies. A strength of the current study was that we controlled for important maternal characteristics, which many earlier studies did not [19]. A limitation of the current study is the lack of a control group of infants born to HIV-uninfected women [38]. We were only able to follow infant growth for six months and hence these findings may not apply to long-term infant growth, however the measurement of infant growth at close intervals during this six month period allowed for ascertaining changes in anthropometry between HIV-infected and -uninfected infants during a time of rapid growth. Due to the exclusion criteria of the original clinical trial, these findings may be generalizable only to full-term infants.

Due to the close association between infant growth with immune function and HIV disease progression, understanding growth patterns of HIV-infected infants is important for developing appropriate treatment and clinical programs. HIV-infected children should be promptly initiated on HAART as treatment has a positive sustained influence on growth as well as decreased plasma viral load and increased CD4 cell count [39, 40]. Children with greater viral loads have been shown to be significantly shorter and lighter than children with lower viral loads [41, 42]. Promptly identifying HIV-infected infants and assessing growth in these children is important to determine disease stage and prognosis as well as the effectiveness and toxicities of antiretroviral therapy in the era of HAART. Early nutritional management among HIV-exposed infants is warranted and should be a priority of comprehensive MTCT clinical programs.

Tables

Table 1. Baseline demographic and clinical characteristics of HIV-infected mothers and infants stratified by infant HIV-status (N=840)

	HIV-infected infant (N=118)	**HIV-uninfected infant (N=722)**	**p-value**
Mother characteristics			
Median age (IQR), years	26 (22-30)	25 (22-29)	0.6734
Median plasma viral load (IQR), copies/ml	68650 (18800-189000)	13150 (2500-59400)	<0.0001
Median CD4 cell count (IQR), cells/ul	357 (177-534)	459 (282-670)	0.0003
Mode of delivery, % Normal vaginal delivery	90.1	97.5	0.677
Mother died, %	4.3	1.6	0.0485
Infant characteristics			
Gender, % Male Female	59.3 40.7	46.5 53.5	0.010
Gestational age (IQR), weeks	40 (37-40)	39 (37-40)	0.6318
Median weight (IQR), grams	2850 (2500-3120)	2905 (2600-3200)	0.1498
Premature birth, %	22.0	24.9	0.498
ARV prophylaxis, % Nevirapine Zidovudine	45.8 54.2	49.3 50.7	0.475

Table 2. Longitudinal patterns of infant growth at 10 days, 45 days, 3 months, and 6 months after birth stratified by infant HIV status (N=840)

	HIV-infected infants (N=118)	HIV-uninfected infants (N=722)	p-value
Median growth weight (IQR)			
10 days	3070 (2720-3500)	3080 (2740-3400)	0.5483
45 days	3940 (3540-4500)	4140 (3660-4600)	0.0500
90 days	4800 (4280-5430)	5440 (4900-6080)	<0.0001
180 days	6020 (5100-6960)	6945 (6320-7760)	<0.0001
Median growth length (IQR)			
10 days	51 (48-53)	50 (48-53)	0.9073
45 days	54 (52-58)	54 (52-58)	0.3128
90 days	58 (55-61)	59 (56-62)	0.3586
180 days	62 (59-66)	64 (62-67)	0.0987
Mean WAZ (SD)			
10 days	-1.27 (1.03)	-1.30 (0.88)	0.7321
45 days	-0.77 (1.16)	-0.46 (1.18)	0.0171
90 days	-0.11 (1.49)	0.89 (1.48)	<0.0001
180 days	0.25 (1.70)	1.58 (1.50)	<0.0001
Mean LAZ (SD)			
10 days	-0.69 (1.26)	-0.84 (1.26)	0.3309
45 days	-0.53 (1.35)	-0.34 (1.34)	0.2490
90 days	0.34 (1.56)	0.63 (1.50)	0.1118
180 days	0.54 (1.56)	1.33 (1.47)	0.0003
Mean WLZ (SD)			
10 days	-0.81 (1.46)	-0.74 (1.51)	0.7351
45 days	-0.62 (1.97)	-0.38 (1.64)	0.2536
90 days	-0.91 (1.80)	-0.04 (1.59)	<0.0001
180 days	-0.54 (1.82)	0.22 (1.45)	0.0005

Table 3. Correlates associated with -2.00 WAZ z-score by 6 months of age among South African infants born to HIV-infected mothers (N=840)

Category	Univariate analysis	Multivariable analysis	
		Model I Maternal characteristics	Model III Maternal and Infant Characteristics
	Hazard ratio (HR) (95% CI); p-value	Hazard ratio (HR) (95% CI); p-value	Hazard ratio (HR) (95% CI); p-value
Maternal correlates			
Maternal age <20 20-25 25-30 >30	1.06 (0.65-1.72); 0.82 0.85 (0.56-1.29); 0.45 0.93 (0.60-1.45); 0.76 1.00	1.21 (0.74-1.99); 0.44 0.89 (0.58-1.36); 0.58 0.96 (0.62-1.50); 0.87 1.00	1.34 (0.81-2.19); 0.25 0.87 (0.57-1.34); 0.53 0.86 (0.55-1.35); 0.51 1.00
Maternal CD4 cell count <200 200-350 >350	**2.19 (1.53-3.12); 0.01** **1.76 (1.20-2.60); 0.01** 1.00	**1.78 (1.20-2.62); 0.01** **1.67 (1.12-2.47); 0.01** 1.00	**1.64 (1.10-2.43); 0.01** **1.62 (1.09-2.41); 0.02** 1.00
Maternal plasma viral load >100000 copies/ml <100000 copies/ml	**1.90 (1.37-2.64); 0.01** 1.00	**1.57 (1.10-2.24); 0.01** 1.00	1.38 (0.95-1.98); 0.08 1.00
Maternal death Yes No	**2.21 (1.04-4.74); 0.04** 1.00	1.27 (0.56-2.88); 0.56 1.00	1.64 (0.73-3.70); 0.23 1.00
Infant correlates		Model II infant characteristics	
Infant ARV prophylaxis Zidovudine	1.09 (0.81-1.48); 0.56	1.08 (0.80-1.47); 0.60	1.09 (0.80-1.48); 0.60

Nevirapine	1.00	1.00	1.00
Infant HIV status			
HIV infected	1.23 (0.82-1.86); 0.32	1.21 (0.79-1.84); 0.39	1.04 (0.67-1.60); 0.86
HIV uninfected	1.00	1.00	1.00
Infant feeding method*			
Breast milk	0.99 (0.98-1.00); 0.14	0.99 (0.98-1.00); 0.12	0.99 (0.98-1.00); 0.15
Formula feeding	1.00	1.00	1.00
Gastrointestinal infection			
Yes	**1.94 (1.05-3.58); 0.03**	**1.99 (1.08-3.70); 0.03**	1.87 (0.99-3.53); 0.06
No	1.00	1.00	1.00
Respiratory infection			
Yes	1.13 (0.62-2.10); 0.68	1.09 (0.58-2.05); 0.80	1.04 (0.55-1.99); 0.88
No	1.00	1.00	1.00
Infant gender			
Male	1.29 (0.95-1.76); 0.09	1.23 (0.90-1.67); 0.20	1.20 (0.88-1.65); 0.25
Female	1.00	1.00	1.00
Premature birth			
Yes	**2.93 (2.16-3.96); 0.01**	**2.89 (2.13-3.92); 0.01**	**2.82 (2.06-3.86); 0.01**
No	1.00	1.00	1.00

Table 4. Correlates associated with -2.00 LAZ z-score by 6 months of age among South African infants born to HIV-infected mothers (N=840)

Category	Univariate analysis	Multivariable analysis	
		Model I Maternal Characteristics	Model III Maternal and Infant Characteristics
	Hazard ratio (HR) (95% CI); p-value	Hazard ratio (HR) (95% CI); p-value	Hazard ratio (HR) (95% CI); p-value
Maternal correlates			
Maternal age			
<20	**0.50 (0.29-0.87); 0.02**	**0.54 (0.30-0.95); 0.03**	**0.54 (0.31-0.96); 0.04**
20-25	0.68 (0.45-1.02); 0.07	0.67 (0.45-1.02); 0.06	**0.65 (0.43-0.98); 0.04**
25-30	0.70 (0.45-1.08); 0.11	0.69 (0.45-1.08); 0.10	**0.61 (0.39-0.96); 0.03**
>30	1.00	1.00	1.00
Maternal CD4 cell count			
<200	**2.17 (1.50-3.14); 0.02**	**1.93 (1.29-2.88); 0.01**	**1.72 (1.14-2.59); 0.01**
200-350	**1.64 (1.08-2.48); 0.02**	1.50 (0.98-2.29); 0.06	1.49 (0.97-2.28); 0.07
>350	1.00	1.00	1.00
Maternal plasma viral load			
>100000 copies/ml	**1.73 (1.22-2.45); 0.01**	1.40 (0.96-2.05); 0.08	1.20 (0.81-1.77); 0.37
<100000 copies/ml	1.00	1.00	1.00
Maternal death			
Yes	1.67 (0.68-4.09); 0.26	0.95 (0.37-2.44); 0.91	1.11 (0.43-2.87); 0.83
No	1.00	1.00	1.00
Infant correlates		Model II Infant characteristics	
Infant ARV prophylaxis			
Zidovudine	0.86 (0.63-1.18); 0.34	0.85 (0.62-1.17); 0.31	0.81 (0.58-1.12); 0.20
Nevirapine	1.00	1.00	1.00
Infant HIV status			
HIV infected	**1.57 (1.04-2.36); 0.03**	**1.62 (1.07-2.49); 0.02**	1.47 (0.95-2.28); 0.08
HIV uninfected	1.00	1.00	1.00
Infant feeding method*			
Breast milk	0.99 (0.98-1.01); 0.67	**0.99 (0.97-1.00); 0.03**	**0.99 (0.98-1.00); 0.03**

Formula feeding	1.00	1.00	1.00
Gastrointestinal infection Yes No	 1.25 (0.69-2.26); 0.45 1.00	 1.73 (0.88-3.41); 0.12 1.00	 1.61 (0.80-3.23); 0.18 1.00
Respiratory infection Yes No	 1.13 (0.50-2.57); 0.76 1.00	 1.02 (0.74-1.40); 0.91 1.00	 0.95 (0.50-1,81); 0.89 1.00
Infant gender Male Female	 1.08 (0.79-1.48); 0.63 1.00	 1.02 (0.74-1.40);0.91 1.00	 0.97 (0.70-1.35); 0.86 1.00
Premature birth Yes No	 **2.40 (1.75-3.31); 0.01** 1.00	 **2.47 (1.79-3.41); 0.01** 1.00	 **2.37 (1.70-3.30); 0.01** 1.00

Table 5.	Correlates associated with -2.00 WAZ and LAZ z-scores by 6 months of age stratified by infant HIV infection status and maternal plasma viral load*			
	Infant HIV infection status (N=840)		Maternal plasma viral load (PVL) (N=840)	
Category	HIV-infected (N=118)	HIV-uninfected (N=722)	Maternal PVL >100,000 (N=171)	Maternal PVL <100,000 (N=669)
	Hazard ratio (HR) (95% CI); p-value	Hazard ratio (HR) (95% CI); p-value	Hazard ratio (HR) (95% CI); p-value	Hazard ratio (HR) (95% CI); p-value
	WAZ		WAZ	
Maternal CD4 cell count <200 200-350 >350	1.71(0.66-4.44);0.27 0.96(0.29-3.18);0.95 1.00	1.56(1.00-2.43);0.05 1.69(1.10-2.60);0.02 1.00	1.44(0.71-2.92);0.31 1.56(0.72-3.39);0.26 1.00	1.85(1.13-3.00);0.01 1.76(1.10-2.81);0.02 1.00
Maternal plasma viral load >100000 copies/ml <100000 copies/ml	2.23(0.95-5.22);0.07 1.00	1.32(0.87-2.00);0.20 1.00	--	--
Gastrointestinal infection Yes No	4.93(1.24-19.58);0.02 1.00	1.71(0.77-3.81);0.19 1.00	3.17(1.31-7.64);0.01 1.00	1.04(0.37-2.89);0.94 1.00
Respiratory infection Yes No	1.07(0.34-3.34);0.91 1.00	1.09(0.47-2.53);0.85 1.00	0.59(0.17-2.00);0.39 1.00	1.59(0.75-3.38);0.23 1.00
	LAZ		LAZ	
Maternal CD4 cell count <200 200-350 >350	1.08 (0.41-2.86);0.88 1.38 (0.47-4.08);0.56 1.00	1.94 (1.24-3.08);0.01 1.47 (0.91-2.38);0.12 1.00	1.52(0.71-3.24);0.28 1.41(0.59-3.39);0.44 1.00	1.82 (1.10-3.01);0.02 1.72 (1.04-2.82);0.03 1.00
Maternal plasma viral load				

>100000 copies/ml <100000 copies/ml	1.62 (0.71-3.69);0.25 1.00	1.04 (0.65-1.67);0.85 1.00	--	--
Gastrointestinal infection Yes No	 4.09(1.14-14.68);0.03 1.00	 0.90 (0.32-2.49);0.83 1.00	 1.63 (0.55-4.91);0.38 1.00	 1.39 (0.55-3.52);0.48 1.00
Respiratory infection Yes No	 1.72 (0.60-4.91);0.31 1.00	 0.81(0.32-2.05);0.65 1.00	 0.56 (0.16-1.96);0.36 1.00	 1.27 (0.59-2.74);0.55 1.00

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CHAPTER 5: CONCLUSIONS

Methodological conclusions

This dissertation includes the three major observational study designs utilized in modern epidemiology, namely case-control, cohort, and cross-sectional studies. Though randomized controlled trials were not included per se, two of the observational studies were secondary analyses of randomized controlled trials. In the case of these two trials, analytical steps were taken to ensure appropriate analysis, such as including treatment arm assignment as a covariate in the model because randomization was not maintained for secondary analyses.

Chapter 2 involved a nested case-control study utilizing risk-set sampling. Unlike the current study, case-control studies examining HIV incidence have generally employed survival/cumulative incidence sampling and have also been unable to clearly assess the temporality between HIV incidence and STI exposures. The methods used in the current study would have presumably been more likely to produce attenuated associations towards the null value compared to survival sampling and studies that include STI exposures that occurred at the time of the outcome. Interestingly, the measures of association for STI and behavioral covariates in the current study are very similar to previous studies that have used less conservative analytical methods. For instance, the documented association of an adjusted odds ratio of 2.00 for prevalent HSV-2 and 4.00 for incident HSV-2 is in accordance with earlier data. Additionally the robust

number of HIV incident infections (N=309) coupled with a high frequency of STI exposures and other behavioral covariates provided statistical power to examine the impact of relatively rare exposures.

Chapter 3 first included a cross-sectional analysis of sexual risk behaviors on a relatively small sample (N=247). Although the methods were not necessarily novel, quantitative data about sexual risk behavior after initiating ART remains very limited from India. Despite low levels of reported unprotected sex (<10%), most cases of unprotected sex were occurring among couples who wanted to have children as well as among HIV seroconcordant couples (i.e. serosorting). The final part of chapter 2 from a large cohort of HIV-infected South Africans with substantial participant follow-up examined sexual risk behaviors longitudinally before and after ART initiation. Though we initially employed generalized estimating equations with a logit link, we also conducted further analyses using fixed effects models to examine the effects of within-participant change attributable to treatment effect. This study demonstrated consistent significant decreases in sexual behaviors across a variety of measures, namely being sexually active, reporting unprotected sex, and having multiple sex partners.

Chapter 4 addressed infant morbidity and mortality and then growth outcomes among HIV-exposed South African infants. This is one of the largest cohorts of HIV-exposed infants from southern Africa, which allowed us to examine a range of maternal and infant characteristics associated with infant health outcomes. Importantly, we assessed infant feeding status based on multiple criteria, both as a time-dependent and independent covariate. Ultimately, infant feeding status did not predict health outcomes, which in this setting may be linked to ready access to clean drinking water and infant

formula. It is also possible that an even larger sample than 840 mother-infant dyads

would be needed to assess the impact of feeding method. This study including validated

clinical outcomes per WHO ICD-9 criteria, which permitted exclusion of birth-related

outcomes as well as events soon after birth which were unrelated to HIV status and

feeding method. Earlier studies have often relied on datasets where the cause of

morbidity and mortality was unknown, leading to outcome misclassification. Both

analyses for this chapter utilized a Cox proportional hazards model. In the case of the

infant growth analysis, even though infants could fall below -2.00 z-score for the growth

outcomes on multiple occasions, because follow-up was only for 6-months and a time-to-

event based approach had been used in earlier studies, we employed survival analyses;

however, it appears that more recent studies are using newer longitudinal methods based

on growth trajectories.

Thematic conclusions

Increasing evidence suggests that ART that has transformed the natural history of

HIV into a chronic disease and dramatically improved patient quality of life, could also

have an impact on HIV transmission. Beyond individual clinical benefits, by rendering

an individual less infectious, expanding treatment access could also have the larger public

health impact of curbing new HIV infections. It is conceivable that in the future

antiretrovirals will be a component of a toolbox of various biomedical and behavioral

HIV prevention interventions. Other interventions, including STI control, promotion of

MTCT, and condom distribution, will also be important parts of a combination HIV

prevention agenda. This dissertation has public health implications for the development and execution of these diverse HIV prevention programs in resource-limited settings.

In light of the continued high incidence of HIV in young women in sub-Saharan Africa, further data is needed to understand biomedical and behavioral potentiators of the epidemic. Future HIV primary prevention interventions in this region will need adequate descriptive data to understand current risk factors for HIV acquisition. Chapter 2 documenting HIV acquisition highlights the continued burden of viral and bacterial STIs among women at high risk for HIV infection in southern Africa. While both STIs and HIV are caused by the same risk taking behaviors, increasing evidence also suggests that STIs can promote HIV acquisition and transmission. Due to the high burden of viral STIs, namely HSV-2, for which curative treatment is not available and a vaccine is still years away, further attention should be focused on the potential for treating bacterial STIs, namely *N gonorrhea*. This study also identified multiple behavioral and socio-demographic risk factors for HIV acquisition, suggesting the need for prevention programs that target the male partners of women and younger women at the time of sexual debut.

With the increasing number of HIV-infected individuals receiving ART in resource-limited settings, an emerging question has been whether sexual risk behaviors could potentially increase following the immunorestorative effects of treatment, potentially diminishing the secondary prevention gains of ART. Preliminary cross-sectional data as well as a few studies with limited longitudinal follow-up and conducted among high risk groups have suggested that high risk behavior does not increase following treatment initiation in resource-limited settings. However, due to the variance

of access to care, drug regimens, gender norms, patterns of sexual behavior, and socio-

cultural contexts, further longitudinal data from ART-experienced HIV-infected patients

in care is warranted. The first part of chapter 3 examined sexual behavior cross-

sectionally among HIV-infected South Indian men and women enrolled in clinical care.

Despite relatively low levels of reported unprotected sex, participants with fewer children

as well as those who desired children did report unprotected sex. Also, most unprotected

sex occurred within the context of HIV concordant primary relationships; however based

on the date of seroconversion among currently HIV seroconcordant couples, most were

HIV serodiscordant at the time of enrollment to care. This study emphasized the need for

a greater integration of reproductive health and family planning programs within the

context of HIV care and treatment in pronatal societies, such as India. An ancillary study

also examined the association between treatment adherence and sexual risk taking

behavior. While patients who were non-adherent to therapy were not more likely to

report unprotected sex, patients who reported alcohol use, low psychosocial status, and

being on treatment for an extended period with high CD4 cell counts were more likely to

be non-adherent. While most studies examining treatment adherence in resource-limited

settings have focused on the first few months after initiating treatment, this study

conducted among patients with substantial ART experience suggested possible treatment

exhaustion following the immunerestorative effects of treatment, and the need for

interventions that focus on substance use and psychological well-being. The final part of

chapter 3 included a longitudinal observational cohort of South African HIV-infected

men and women attending rural and urban HIV primary care clinics spanning close to a

decade. This is one of the largest cohorts to date with substantial patient follow-up

conducted among the general population from a resource-limited setting to examine the association between ART and sexual risk behaviors. This study found substantial decreases in sexual behaviors measured across a range of outcomes following treatment initiation. The findings of this study add to our understanding of how expanded access to ART can be an effective component of HIV prevention.

Despite the proven efficacy of ARVs in minimizing the risk of HIV transmission from HIV-infected mother to infant and expanding access to antenatal prevention programs for pregnant women, the coverage gap remains especially acute in resource-limited settings. In sub-Saharan Africa, the increasingly feminized HIV epidemic, particularly among young women of reproductive age, is cause for great concern. Most infants infected with HIV reside in this region and are often detected late in the course of HIV disease. Chapter 4 examined the impact of maternal and infant HIV infection on infant health and growth outcomes. This study reinforces the need for prompt detection and treatment of HIV-infected pregnant women, which can not only improve maternal health but also greatly minimize the risk of onward HIV transmission to their infants. HIV-infected women often face a dilemma in resource-limited settings as formula feeding can minimize the risk of HIV transmission to their infants, but can also increase the risk of infant morbidity and mortality due to the lack of access to safe water and infant formula. In the current study conducted in urban South Africa with available drinking water and subsidized formula, negative infant health outcomes were not associated with formula feeding, suggesting that for women who cannot access ART, formula could be a feeding option. It is best that decisions about feeding method be context specific.

This dissertation emphasizes the utility of ART in HIV prevention as well as other biomedical and behavioral HIV prevention methods within the regional context of the two nations with the highest populations of HIV-infected individuals, South Africa and India. This dissertation also focuses on the implications of HIV infection particularly among women, which is relevant in light of the high prevalence of HIV among women in these settings. The future of HIV prevention will increasingly include ART as a means of decreasing sexual transmission from HIV-infected individuals to their sex partners, as well as ARV-based pre- and post- exposure prophylaxis for uninfected individuals at risk for HIV infection. While the lines between treatment and prevention will continue to blur as studies increasingly demonstrate the prevention benefits of utilizing ARVs, other biomedical and behavioral interventions will also remain important methods of HIV prevention. Together antiretrovirals with other proven methods will be a part of a multifaceted armamentarium of HIV prevention that can be selectively utilized for different regional epidemics.

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