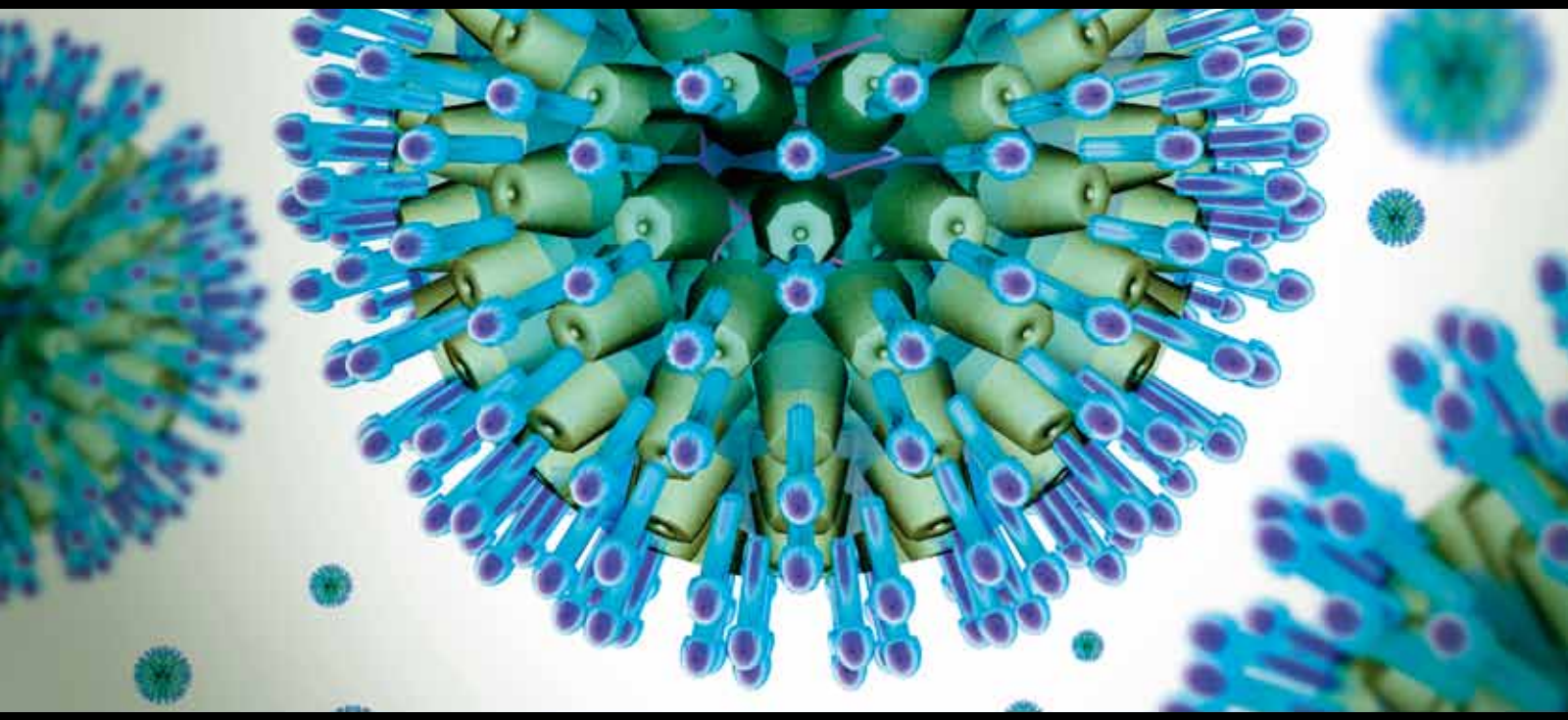
Infectious Diseases in Obstetrics and Gynecology

HIV and Reproduction: Fertility, Contraception, and Preconception Issues and Interventions

Guest Editors: Jean R. Anderson, Deborah Cohan, and Susan Cu-Uvin



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Editorial

HIV and Reproduction: Fertility, Contraception, and Preconception Issues and Interventions

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The cumulative advances in HIV care and treatment and in prevention of perinatal transmission over the past decade and a half have led not only to significant reductions in mortality and morbidity for women living with HIV and dramatic reductions in new infections in infants, but also to a sea change in the lens through which HIV-infected women view their lives and possibilities. In this context the 150% increase in live births to HIV-infected women in the era of effective combination antiretroviral therapy [1] can be seen as a sign of success. Somewhat belatedly HIV and women's health providers have recognized the critical need to address issues related to the fertility of women with HIV proactively and without judgment.

Although a substantial number of HIV-infected individuals express the intention to have children, unintended pregnancy rates remain high, and there continue to be questions regarding the safety of contraceptive methods, particularly hormonal contraceptives, in the setting of HIV. The more recent developments in biomedical prevention, including preexposure prophylaxis (PrEP) and antiretroviral therapy (ART) as prevention, offer new opportunities for safe conception with HIV serodiscordant couples.

This special issue contains 13 papers, which address a range of reproductive issues relevant to fertility in the setting of HIV in both resource-rich and resource-limited settings. Although not exhaustive, they demonstrate both the diversity of issues that need to be considered and the accumulation of knowledge in this area, now over 30 years into the HIV/AIDS pandemic. We thank the authors for their excellent contributions and our reviewers for their thoughtful reading and suggestions that have strengthened this offering.

In the paper "*Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel* (plan B), *and Efavirenz*" M. L. Carten et al. examine the area under the curve concentration of single-dose levonorgestrel (LNG) alone and after 14 days of efavirenz (EFV) exposure in 21 women. They report that EFV significantly reduced LNG exposure, with implications for the efficacy of LNG as a widely used emergency contraception method and the potential need for higher doses in the setting of EFV-based ART.

S. Mark et al. in "*HIV mother-to-child transmission, mode of delivery, and duration of rupture of membranes: experience in the current era*" report a retrospective series of 210 HIV-infected pregnant women on effective combination ART with viral suppression <1000 copies/mL (<50 copies/mL in 80%) to examine the effect of duration of membrane rupture on perinatal transmission in the setting of viral suppression. Although almost half of women were delivered by cesarean delivery, 28% had membrane rupture for four hours or longer and 16% rate had preterm birth; there were no cases of perinatal transmission, giving further support for the effectiveness of ART and viral suppression in the setting of membrane rupture for more prolonged periods of time.

"*Reproductive healthcare needs and desires in a cohort of HIV-positive women*" by M. L. Badell et al. reports survey results examining contraceptive use, desires, and knowledge along with future fertility desires and sterilization regret in 127 HIV-infected women receiving care at an urban

infectious disease clinic. Approximately one-third desired future fertility, including 18% of women who had undergone sterilization. Less than 1% of women used a long acting reversible method of contraception, and only one-half of those sexually active had discussed contraception with their providers in the previous year, identifying important gaps in reproductive health care for these women.

Because of concerns about increased teratogenic risk with efavirenz exposure in early pregnancy, EFV use has historically been discouraged in women planning pregnancy or not using effective contraception; however, EFV-based regimens are widely used for treatment because of their potency and relative simplicity and are a primary treatment regimen recommended by WHO in limited resource setting. S. Schwartz et al. in "*Efavirenz conceptions and regimen management in a prospective cohort of women on antiretroviral therapy*" report on a prospective cohort of over 800 HIV-infected South African women on ART, finding high rates of pregnancy on EFV and inconsistencies in management of women trying to conceive while on EFV, highlighting the need for clearer guidelines around the issue of fertility in women on EFV-based regimens.

J. Firth et al. in "*the changing face of HIV in pregnancy in Rhode Island 2004–2009*" call attention to the changing demographics of HIV in pregnancy being seen in many US locations, with an increasing proportion of foreign-born HIV-infected pregnant women, as well as an increase in repeat pregnancies after learning of an HIV diagnosis. These and other changes are important to track, as they will affect the specific and evolving needs of HIV-infected women in pregnancy.

In "*Incidence of pregnancy after initiation of antiretroviral therapy in South Africa: a retrospective clinical cohort analysis*" D. Westreich and colleagues evaluated 5,996 women who experienced 727 pregnancies for an overall pregnancy rate of 5.2 per 100 person-years; after 6 years, the cumulative incidence of pregnancy was 52.2% among women ages 18–25 at ART initiation. Lower CD4 cell counts and poor adherence to ART were associated with lower pregnancy rates. This paper reinforces other studies that suggest that ART may restore or improve fertility, with significant implications for contraceptive counseling and access.

E. Aaron et al. address the relationship between small-for-gestational-age (SGA) infants and HIV in "*Small for gestational age births in pregnant women with HIV, due to severity of HIV disease, not antiretroviral therapy.*" In their urban cohort of 183 HIV-infected women, rate of SGA was high and most notably associated with smoking. Importantly, ART, whether NNRTI or PI based, was not associated with increased risk of SGA, but more advanced HIV, as reflected by CD4 count <200 cells/mm^3, was.

The intrauterine contraceptive device (IUCD) is an effective long-acting and reversible method of contraception, and both the Cu-IUCD and levonorgestrel-containing IUCD can be safely initiated or continued in women with HIV/AIDS who are clinically doing well on ART [2]. However, C. S. Todd et al. found that just over one-third of HIV-infected women attending a primary health care clinic in South Africa were aware of the IUCD in "*Aawareness and interest in intrauterine contraceptive device use among HIV-positive women in Cape Town, South Africa*." However, after learning about this method, 86% of women expressed interest in the IUCD, pointing to the need not only for access to this method but also access to information.

A qualitative analysis of 30 HIV-infected Kenyan women accessing HIV treatment, "*Fertility intentions and interest in integrated family planning services among women living with HIV in Nyanza Province, Kenya: a qualitative study*" by E. K. Harrington et al. found a significant expressed need for contraception; however, only one-third were using a modern method of contraception other than condoms. Women expressed a strong preference for integrated HIV and family planning services.

O. Mmeje et al. in "*Evaluating safer conception options for HIV-serodiscordant couples* (*HIV-infected female/HIV-uninfected male*): *a closer look at vaginal insemination*" review safer conception strategies for serodiscordant couples in which the woman is HIV-infected. They focus on vaginal insemination of partner's semen during the fertile period of the woman's cycle, coupled with 100% condom use during sexual contact, as a safe and effective method to achieve conception.

J. A. Robinson et al. present a detailed and extensive review of a topic that is of significant interest and importance with implications for both safety and effectiveness of concomitant use of ART and hormonal contraception in "*Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy*."

Serodiscordant couples were also the focus of L. T. Matthews et al.'s paper "*Reproductive counseling by clinic healthcare workers in Durban, South Africa: perspectives from HIV-infected men and women reporting serodiscordant partners*." In in-depth interviews with 30 HIV-infected women and 20 HIV-infected men, all in serodiscordant relationships, there was interest in safe conception advice and willingness to discuss this with providers, but these conversations seldom took place, highlighting the need for providers to be more proactive in assessing and addressing this need.

Finally, in "*Preconception and contraceptive care for women living with HIV*," M. J. Hoyt et al. review the rationale and the content of preconception counseling and care for HIV-infected women, advocating this as an essential component of primary health care services for all women living with HIV and with the capacity for childbearing.

In totality, these 13 papers illustrate the astounding diversity of issues that are of interest and importance in the area of fertility, pregnancy, and reproductive health for women living with HIV. Three decades into the HIV/AIDS pandemic, we welcome this focus on women and issues of critical importance to them both for care and for quality of life.

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References

[1] A. Sharma, J. G. Feldman, E. T. Golub et al., "Live birth patterns among human immunodeficiency virus-infected women before and after the availability of highly active antiretroviral therapy," *American Journal of Obstetrics and Gynecology*, vol. 196, no. 6, pp. e541–e546, 2007.

[2] CDC. U. S., "Medical eligibility criteria for contraceptive use," *MMWR. Recommendations and Reports*, vol. 59, no. RR-4, pp. 1–86, 2010.

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Review Article

Preconception and Contraceptive Care for Women Living with HIV

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Women living with HIV have fertility desires and intentions that are similar to those of uninfected women, and with advances in treatment most women can realistically plan to have and raise children to adulthood. Although HIV may have adverse effects on fertility, recent studies suggest that antiretroviral therapy may increase or restore fertility. Data indicate the increasing numbers of women living with HIV who are becoming pregnant, and that many pregnancies are unintended and contraception is underutilized, reflecting an unmet need for preconception care (PCC). In addition to the PCC appropriate for all women of reproductive age, women living with HIV require comprehensive, specialized care that addresses their unique needs. The goals of PCC for women living with HIV are to prevent unintended pregnancy, optimize maternal health prior to pregnancy, improve maternal and fetal outcomes in pregnancy, prevent perinatal HIV transmission, and prevent HIV transmission to an HIV-uninfected sexual partner when trying to conceive. This paper discusses the rationale for preconception counseling and care in the setting of HIV and reviews current literature relevant to the content and considerations in providing PCC for women living with HIV, with a primary focus on well-resourced settings.

1. Introduction

Access to preconception care (PCC) aimed at promoting pregnancy planning, reducing unintended pregnancies, optimizing maternal health prior to pregnancy, and using safer conception strategies is needed to optimize health outcomes for HIV-infected women and their infants, reduce adverse pregnancy outcomes, and strengthen prevention efforts for at-risk partners and children. Benefits of PCC in identifying and modifying risks to maternal health and pregnancy outcomes and in preventing unwanted pregnancies are well documented [1–3]. The American College of Obstetricians and Gynecologists (ACOG) and the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission in the United States and other national organizations recommend offering all HIV-infected women of childbearing age comprehensive family planning and the opportunity to receive preconception counseling and care as a component of routine primary medical care [2, 4]. This paper will discuss the rationale for preconception counseling and care in the setting of HIV and review current literature relevant to the content and considerations in providing PCC for women living with HIV, with a primary focus on well-resourced settings and on elements of PCC that are specific to women living with HIV.

2. Rationale for Preconception Care

2.1. Advances in HIV Care and Prevention of Perinatal HIV Transmission. HIV has become a chronic disease in developed countries. A recent report from the national observational HIV cohort in the Netherlands suggested that the life expectancy of recently diagnosed, asymptomatic HIV-positive patients approaches that of uninfected individuals,

Table 1: Factors associated with fertility desires and intentions in women living with HIV.

Positive influences	Negative influences
Younger age	Already having one or more children
No children	Personal health concerns
Antiretroviral therapy	Concerns about infecting partner
Interventions for PMTCT	Concerns about infecting child
Partner's/family members' wish for children	Negative or judgmental attitudes of healthcare workers, family, and community
HIV-related stigma	HIV-related stigma

particularly if they do not engage in high risk behaviors (e.g., injection drug use) and initiate effective antiretroviral (ARV) therapy before there is significant immune suppression [5]. With appropriate treatment, women with HIV can live normal or near normal life spans, have improved quality of life, and can realistically plan to have and raise children to adulthood. Current interventions for the prevention of mother-to-child transmission of HIV (PMTCT) have decreased perinatal transmission rates to 1-2% or less [4, 6], and it is estimated that fewer than 200 infants are infected annually in the US [7]. The majority of HIV-infected children now live to become adults [7, 8] and many are having children themselves [9, 10].

There is evidence that these or other factors are indeed resulting in an increase in births to women living with HIV. A Women's Interagency HIV Study (WIHS) cohort analysis found a 150% increase in live birth rates in the era of highly effective ARV therapy (HAART) (2001-2002) among HIV-infected women when compared to the pre-HAART era (1994-1995); during the latter time period, there was only a 5% increase in live birth rates among HIV-uninfected women in WIHS [11]. Increases were seen in all age and CD4 categories, with the greatest increase (306%) among women older than 35 years. Another WIHS analysis suggested that abortion was significantly less likely in the HAART era [12].

2.2. Fertility Desires and Intentions. Studies of fertility desires and intentions have shown that many women living with HIV want to have children [13–16]. In a recent survey of 450 HIV-infected women in the United Kingdom, 75% reported that they wanted more children, 11% stated that the HIV diagnosis made them want children sooner, and 41% of women who initially reported no desire to have children changed their minds following advances in HIV care [14]. As shown in Table 1, factors that have been associated with fertility desires and intentions [17–19] reflect issues related to personal health, ARV therapy, HIV transmission, and social factors [13–16, 18]. Findings from the recent Women Living Positive survey illustrate the perceived dichotomy between personal and societal perspectives on childbearing among women with HIV [19]. Although a majority (61%) of the 700 respondents believed that with appropriate medical care they could safely have children, 59% believed that society strongly urges them not to have children. An exploratory survey/interview with 74 HIV-positive women found that those with higher levels of personalized stigma and negative self-image reported increased desire for children as a way of concealing their HIV-positive status and improving feelings of self-worth [17]. However, some women who had disclosed their HIV status reported they were less likely to become pregnant in order to avoid negative judgments about the risk of transmitting HIV to their child [17, 19]. A recent comparison of childbearing desires and motivations between HIV-infected and HIV-uninfected urban, largely African-American youth (15–24 years old) found that HIV infection had no effect on desire for pregnancy [20].

2.3. High Rates of Unintended Pregnancy. The most recent US data indicates that nearly half (49%) of pregnancies are unintended, with unintended pregnancy rates among women who were 18–24 years old, poor or cohabitating were two to three times the national rate [21]. Studies among women living with HIV suggest that unintended pregnancies among HIV-infected women are equally high or higher and may be influenced by similar cultural and societal factors [12, 17, 19]. Unintended pregnancy rates of 54% were reported in Canadian women after HIV diagnosis [16] and 62% among HIV-infected women after ART initiation in both South Africa and Rwanda [22]. Unintended pregnancy is even more prevalent among adolescents with HIV, 83% in a cohort of US adolescents [23] and 81% in adolescents in the UK and Ireland growing up with HIV [24].

In the WIHS cohort analysis of pregnancies between 1994 and 2002, 77% of pregnancies occurred despite use of contraception [12], implying that the pregnancies were unintended and highlighting the importance of adequate and accurate counseling about use of effective birth control. Across almost 27,000 visits by 2784 HIV-infected and high-risk HIV-uninfected women in the WIHS cohort from 1994 to 2005, barrier methods were used in <40% of visits, hormonal methods in fewer than 10%, and no contraception in over 30% of visits [25]. HIV status was not correlated with barrier use but hormonal contraception was less likely among women with HIV (OR 0.73, 95% CI 0.60–0.89, $P = 0.002$). These data provide evidence of the underuse of hormonal contraception and barrier methods that leaves women with HIV at risk for unintended pregnancy, HIV transmission and acquisition of other sexually transmitted infections (STIs).

2.4. Unmet Need for Discussions about Pregnancy. Women living with HIV express the desire to talk about reproductive plans with their healthcare providers; however, data suggest that such counseling does not often occur until after conception [19, 26, 27]. In a recent study of 181 women, 67% reported having a general discussion about pregnancy with their HIV health provider, but only 31% of women reported a discussion that was personalized and specific to their future childbearing plans. Of those who had a personalized discussion, most were initiated by the patient rather than the provider [26]. The Women Living Positive survey found that only 42% of women who were currently or previously

Table 2: Components of preconception counseling for women living with HIV.

Current and future desires and plans to have children by woman, her partner and family and desired timing of pregnancy
Contraceptive options (for women who do not wish to become pregnant or who wish to delay pregnancy for better birth spacing or while health or nonhealth-related issues are managed)
Effect of HIV and ARVs on pregnancy course and outcomes
Effect of non-HIV-related factors on pregnancy and pregnancy outcome: for example, age, drug use, other medical conditions
Optimization of maternal health status and timing of pregnancy
Counseling on safer sexual practices and other counseling on healthy living (smoking cessation, eliminating alcohol, treatment for illicit drug use)
Options for conception that decrease risk of HIV transmission to an HIV-uninfected partner
Perinatal HIV transmission and PMTCT: the role of ARVs for mother and baby, mode of delivery, avoidance of breastfeeding, infant ARV prophylaxis
Long-term care plans, including advance directives and care of children if one or both parents were to become ill or die

pregnant had discussed pregnancy and appropriate HIV-related care before becoming pregnant [19]. Findings also indicated that many women had little or no awareness of the available treatment options for pregnant women with HIV.

2.5. HIV Serodiscordance in Couples. Although recent data are not available, a study of a population-based sample of HIV-infected persons in care in 1996 found that 58% of men and 70% of women had a primary partner or spouse; approximately 50% of couples were in serodiscordant relationships and almost 20% were in relationships with partners whose HIV status was unknown [13]. Extrapolating from this information and incorporating 2006 data about number and demographics of heterosexual adults living with HIV in the U.S., it has been estimated there are approximately 140,000 HIV-heterosexual serodiscordant couples in the US, about half of whom want more children [28]. This has significant implications about the need to provide accurate information about achieving safe conception in the presence of HIV discordance.

2.6. Potential Improvement in Fertility with ARV Therapy. A number of studies have suggested that HIV has an adverse effect on fertility in both symptomatic and asymptomatic women [29–33]. This includes both a decrease in pregnancy rates and an increased risk of pregnancy loss. The reason for this association is not entirely clear; it may be multifactorial and both directly and indirectly related to HIV. Although women with HIV have similar prevalence of gonorrhea and chlamydia infections as compared to high-risk HIV-uninfected women [34, 35], the majority of HIV-infected women are exposed to HIV sexually and history of other sexually transmitted infections is common, including infections that have an adverse effect on fertility. Sexually transmitted organisms, including *N. gonorrhea* and *C. trachomatis*, are implicated in most cases of pelvic inflammatory disease (PID), a major cause of infertility due to tubal damage. Furthermore, the clinical presentation among HIV-infected women with PID may be more severe than in uninfected women [36, 37]. A cross-sectional study from Spain of 130 HIV-infected women undergoing fertility assessment found that almost one-third had evidence of tubal occlusion [38]. Another potential contributing factor to subfertility in HIV-infected women is a possible increase in amenorrhea, oligomenorrhea, and irregular periods, particularly with lower CD4 counts [39–42]. Higher viral loads have also been independently associated with decreased fertility [33].

Recent data suggest that effective ARV therapy may restore or improve fertility [43, 44]. In an analysis from Rakai, Uganda, the pregnancy incidence almost doubled in women on ART as compared to women in pre-ART care; pregnancy rates were highest among women with good immunologic response to ART [43]. In a retrospective cohort study from Malawi, women on ART for at least 6 months had similar total fertility rates to women in the general; in multivariable analysis, longer time on ART was associated with increased probability of becoming pregnant [45]. Therefore, as women receive effective treatment, they may become at increased risk for unintended pregnancy.

3. Counseling and Assessment on Childbearing and Contraception

The components of preconception counseling for women living with HIV are summarized in Table 2. Because the decision to have a child is complex and may change over time, childbearing desires and intentions should be assessed during the initial evaluation and at intervals throughout the course of care. Formal preconception counseling, including contraceptive discussions, should take place when (1). The woman expresses a desire for future pregnancy or (2). She is uncertain about her plans or (3). She is not trying to conceive but is not using effective and consistent contraception.

Women's reproductive decisions are shaped by numerous personal, interpersonal, health-related, and socioeconomic factors which may make them reluctant to initiate discussions with healthcare providers [18]. Therefore, clinicians should be proactive in initiating discussions about childbearing, contraception, and reproductive health. Potential barriers to preconception counseling and care, described in Table 3, must be recognized and addressed in order to appropriately meet the reproductive health needs of HIV-infected

Table 3: Potential barriers to preconception counseling and care for women living with HIV.

Limited visit time
Competing priorities and more immediate concerns related to care of HIV and comorbidities
Reluctance of clinicians and HIV-infected women to discuss reproduction/fertility
Assumptions that HIV-positive women donnot want to become pregnant
Effects of the stigma associated with HIV
Challenges associated with lack of empowerment or control in sexual matters among HIV-infected women
Lack of knowledge about contraceptive counseling and PCC among HIV care providers
Lack of knowledge about HIV-specific elements of PCC and counseling among obstetricians and gynecologists (OB/GYNs)
Lack of clearly defined roles for multiple clinicians, for example, HIV provider, OB/GYN, primary care provider

Table 4: Components of the preconception evaluation for women living with HIV.

(1) History
(a) Comprehensive HIV history: when diagnosed; history of OIs or other HIV-related illnesses; ARV history (including use in prior pregnancies); reason for change in ARV regimens (adverse effects, resistance, tolerability); adherence history/challenges; results of resistance tests; nadir and current CD4 count; current HIV-RNA level
(b) Obstetric/Gynecological (OB/GYN) history
(i) Pregnancy history: number of previous pregnancies and their outcomes: miscarriages, abortions, ectopic pregnancy, preterm births; number of living children and ages; number of HIV-infected children; pregnancy complications (preterm labor, preeclampsia, birth defects, and so forth); mode of deliveries
(ii) GYN history: prior and current contraception use and satisfaction with method, adverse effects; current condom use; history of sexually transmitted/genital tract infections; difficulty getting pregnant in past; abnormal pap smears and treatment; other GYN problems and treatment (e.g., fibroids, endometriosis, etc.)
(c) General medical/surgical history: other medical conditions (e.g., diabetes, hypertension, renal or cardiac disease, depression or other psychiatric illness, etc.); all prior surgeries; blood type and history of transfusions; allergies
(d) Immunization history: HBV, HAV, influenza, pneumococcus, HPV, tetanus
(e) Medications: complete list, including over-the-counter or complementary medications
(f) Nutrition assessment: vegetarian or other special diet, use of nutritional supplements/vitamins, history of anemia or nutritional deficiencies
(g) Social history: relationship status; use of illicit drugs/tobacco/alcohol; employment status; social support and disclosure to partner/others; economic support; history of domestic violence and nature of violence (physical, sexual, psychological)
(h) Family history of heritable diseases: birth defects, chromosomal abnormalities, muscular dystrophy, sickle cell disease, mental retardation, etc.
(i) Relevant male partner history: HIV status and knowledge of partner's status; if HIV-infected: disclosure history; history of OIs, other HIV-related conditions; ART history and history of adverse effects, resistance, adherence problems; nadir/current CD4 count; current HIV-RNA level; medical/reproductive history; medications; use of illicit drugs, tobacco, alcohol; employment
(2) Examination: comprehensive, with focus on genital tract
(3) Laboratory: emphasis on labs that will affect counseling and/or result in changes in care prior to pregnancy
(a) STI screening (gonorrhea/chlamydia; syphilis; HSV culture or HSV-2 antibody (if indicated by exam or history in patient or partner)
(b) CBC
(c) Current CD4/HIV-RNA, resistance testing (if indicated)
(d) Rubella
(e) Hepatitis: HBV: HBsAb (if no history of HBV vaccination), HBsAg; HCV antibody, HCV-RNA, if indicated
(f) Pap
(g) Other as indicated by medical history, medications

women [26, 46–48]. A newly released clinician toolkit about PCC for women living with HIV, developed with input from a stakeholder group of clinical experts and clients, offers a resource aimed at reducing some of these barriers http://www.fxbcenter.org/resources_clinical.html#clinician.

Conducting a comprehensive evaluation, as outlined in Table 4, provides information to tailor preconception interventions to meet each woman's needs. Whenever possible both partners should be involved in preconception discussions [49].

4. Interventions for Women Wishing to Conceive

4.1. Support for Disclosure of Diagnosis. Supporting women's abilities to disclose their HIV diagnosis to sexual partners is an integral part of PCC and has important implications for women's health, HIV prevention and safer conception. Although few studies have focused on disclosure among women in well-resourced settings, disclosure of HIV-positive status by women to their sexual partners has been reported at 70–75% [50, 51]. Lack of disclosure has been associated with nonadherence to ARV therapy [52] and with nonoptimal PMTCT interventions including late initiation of ARV therapy, detectable HIV-RNA level at delivery, and lack of neonatal prophylaxis [53]. Referrals to psychosocial care providers and HIV focused community-based agencies can be helpful in supporting women through the disclosure process [54]. The primary provider's relationship with the patient can also support disclosure; however, it is also critical that reasons for nondisclosure be considered and addressed, such as fears of abandonment or violence [54–56].

4.2. Optimization of General Medical Conditions. Overall health should be optimized and health care coordinated with other providers to ensure attention to standard primary care and management of chronic diseases. A number of chronic medical illnesses (e.g., hypertension, diabetes, depression, seizure disorders) occur not infrequently in individuals with HIV and certain conditions may be associated with HIV or its treatment. Many of these illnesses are associated with adverse maternal and/or fetal outcomes, and medications used to treat them may also be associated with potential harm. Furthermore, ARV agents are associated with increased risk of certain chronic problems, such as glucose metabolic abnormalities [57, 58].

All current medications, including prescription, over-the-counter and complementary medications, should be reviewed and potential adverse effects associated with the drugs assessed. FDA drug classification can give some guidance about what is known or not known about potential teratogenic risk with use during pregnancy, based on animal data and human experience. A drug classified as FDA category D indicates positive evidence of human fetal risk, but potential benefits to mother may make risk acceptable; FDA category X indicates evidence of human fetal risk, which clearly outweighs any possible benefit. If a woman is taking an FDA category D or X drug, then the feasibility of safely stopping or substituting a drug that may be safer in pregnancy should be determined. For many drugs, in particular newer medications, experience in human pregnancy may be extremely limited and decisions should be made on a case by case basis, based on individual medical needs and the availability of alternative medications with equal efficacy and better safety profile. In general, teratogenic risk is limited to the first trimester of pregnancy when major fetal structures form, but often before pregnancy is realized. It is also important to remember that there can be other potential adverse effects of medications on the mother, fetus or pregnancy course which should be considered as well when a woman is planning to conceive.

Women should be evaluated for the need for appropriate prophylaxis or treatment for opportunistic infections (OIs) before attempting to conceive. Medications for OI treatment or prophylaxis should be carefully chosen based on safety, tolerability, and potential toxicity considerations when used in pregnancy [4]. Assessment prior to conception also allows the provider to implement appropriate management of anemia or other nutritional deficiencies.

4.3. Initiation or Modification of ARV Regimen. An assessment of the need to initiate or modify an ARV regimen should be made for all women living with HIV prior to conception. ARV therapy should be initiated in women who meet the criteria for HIV treatment according to the Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [52] and should be strongly considered when the male partner is not HIV-infected prior to attempting to conceive, with the primary treatment goal of achieving a stable, maximally suppressed maternal viral load prior to conception [4]. The choice of ART regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy and the risk of teratogenicity or other adverse effects. Even in women with high CD4 cell counts and in seroconcordant relationships, initiation of ARV therapy prior to conception may still be considered; early and sustained control of HIV viral replication potentially reduces the risk of perinatal transmission [59, 60]. However, the potential adverse effects of ARV therapy on certain pregnancy outcomes, readiness for life-long therapy, and risks versus benefits of stopping ARV therapy postpartum should be part of the deliberations [61, 62]. If a current ARV regimen is not effective (i.e., suboptimal suppression of viral load), not well tolerated, or associated with significant adverse effects, then it should be modified prior to attempts at conception. Efavirenz (EFV) is the only ARV drug with evidence of teratogenic risk, based on preclinical primate data and retrospective case reports after first trimester human exposure; however, recent data suggest that the risk is likely to be quite low [63]. Nevertheless, in women who are initiating ART prior to attempts to conceive, EFV should be avoided, if possible. For women planning to conceive and already on an effective ART regimen including EFV, regimen modification should be considered if there are available, acceptable, and effective alternatives.

4.4. Screening for Genital Tract Infections. Both partners should be screened for genital tract infections and treated if present. Genital tract inflammation is associated with genital tract shedding of HIV, even in the setting of fully suppressed HIV viral load, and may additionally increase plasma viremia [64, 65]. If untreated, genital tract infections may increase the risk of adverse pregnancy outcomes and potential perinatal transmission. Syphilis, HSV, and vaginal infections (bacterial vaginosis, yeast, trichomoniasis) have all been associated with increased risk of perinatal transmission

[66–68]. Couples should be counseled on safer sexual practices that prevent secondary HIV transmission to sexual partners, protect women from acquiring STIs, and reduce the potential to acquire more virulent or resistant strains of HIV [4].

4.5. Treatment of Drug and Alcohol Abuse and Assistance with Smoking Cessation. It is important to address modifiable factors that contribute to the risks of adverse pregnancy outcomes for all women and pose additional risks for women with HIV. About 40% of persons with HIV are current smokers [69] in contrast to 19% of adults in the US [70]. Among persons with HIV who are in care, data indicate that about half drink alcohol [71, 72], and while statistics vary, studies indicate that alcohol abuse or dependence is a common problem [73]. Alcohol consumption has been linked to increased HIV disease progression and reduced adherence to antiretroviral therapy [73, 74]. Although the majority of women become HIV-infected through sexual contact, 12% of Black African/American and Latino women and 25% of white women acquire HIV through injection drug use [75]. Studies have shown that alcohol and drug use are associated with risky sexual behaviors [76–78] that can contribute to acquisition of STIs or transmission of HIV. A study using the Enhanced Perinatal Surveillance system in 15 US jurisdictions for birth years 2005 through 2008 found that women with HIV who abused substances (smoking, alcohol, or drugs) were twice as likely to have an infected infant compared to women who did not [79].

Tobacco, alcohol, and drug abuse are all associated with poor maternal health but are also associated with adverse pregnancy and fetal outcomes. As much as 13% of subfertility and delay in time to conception in the general population has been attributed to smoking [80] and smoking has also been associated with pregnancy complications, including low birth weight (LBW) and pregnancy loss [81, 82]. In an analysis of hospital discharge records linked to birth records from the state of Florida for 1998–2007, Aliyu et al. [83] found that cigarette use and maternal HIV status were independent predictors of LBW, preterm birth, and small for gestational age (SGA), with the greatest risks, approximately a two-fold increase, among mothers who were HIV positive and smoked during pregnancy.

Opiate-dependent pregnant women have a significant increase in obstetrical and neonatal complications, including preeclampsia, low birth weight, neonatal withdrawal, neurobehavioral deficits, and increased perinatal mortality [84]. Cocaine use in pregnancy significantly increases risk of preterm birth, low birth weight, miscarriage, and placental abruption [85]. Alcohol appears to have negative effects throughout pregnancy and is associated with stillbirth and fetal alcohol syndrome, as well as more subtle difficulties with learning [86]. Identifying and addressing both legal and illicit substances of abuse is critical to deal with prior to conception whenever possible.

4.6. General Management Considerations. As with all women planning pregnancy, immunizations should be given, as indicated, and folic acid supplementation should be started. Many of the same behaviors that put women at risk of acquiring HIV also put them at risk for HBV infection and HIV infection is associated with increased risk of developing chronic HBV infection [87], more rapid progression of HBV-related liver disease, hepatocellular carcinoma (HCC), and fatal hepatic failure [88, 89]. Therefore, HBV vaccine is recommended for all susceptible HIV-infected individuals. Folic acid supplementation has been associated with reduced risk of neural tube defects, although it is unknown whether this benefit applies to women who conceive on EFV.

Women living with HIV who are unable to conceive should receive fertility evaluation and management. The American Society for Reproductive Medicine (ASRM) asserts that although HIV-infected patients may be referred to providers with more expertise in providing infertility services if their provider lacks that expertise, HIV-infected patients should not be denied access to health services solely based on their HIV status and that HIV antidiscrimination laws apply both to public or private settings [90].

5. Safer Conception with Serodiscordant Couples

There are an estimated 140,000 HIV-heterosexual serodiscordant couples in the US, about half of whom want more children [28]. The evidence suggests that many HIV-discordant couples have unprotected sex in their efforts to conceive [91]. Couples should be counseled regarding specific interventions to reduce the risk of transmission to an uninfected partner and approaches tailored to address specific needs, which may vary from couple to couple. It is important to confirm that the partner's HIV status is known and that the HIV status of the infected partner has been disclosed. Sensitive counseling and psychological support for disclosure and HIV testing of a partner of unknown HIV status should be coordinated with the HIV primary care team.

5.1. ARV Therapy as Prevention. Observational studies and a meta-analysis have demonstrated a decreased rate of HIV transmission among heterosexual serodiscordant couples on ARV therapy, particularly with fully suppressed HIV viral load [92]. Recent data from HPTN 052, a randomized clinical trial designed to evaluate the effectiveness of ARV therapy for prevention of sexual transmission among serodiscordant couples, found that earlier initiation of ARV therapy (at CD4+ cell counts of 350–550/mm^3) reduced HIV transmission to the uninfected partner by 96% [93]. The recommendation, therefore, is to initiate ARV therapy in an infected partner with a CD4+ cell count <550/mm^3 to protect the uninfected partner while the couple is trying to conceive, and to consider initiation of ART if the infected partner has higher CD4+ cell counts [4]. Recently, updated guidelines for nonpregnant adults and adolescents recommend that ART be offered to all patients who are at risk for transmitting HIV to a sexual partner [52]. Maximal viral suppression is recommended before attempts at conception.

Treatment of an infected partner does not fully protect against HIV transmission, even in the setting of maximal plasma viral load suppression. Although effective ARV therapy decreases virus in genital secretions, discordance between plasma and genital viral loads has been reported. HIV-infected males may have isolated semen HIV shedding even when plasma viral load is undetectable [94, 95] and independent of semen drug levels and ARV regimen [96]. Additionally, ARV genital tract penetration varies among ARV agents [97].

5.2. Female HIV Infected/Male HIV Uninfected. The uninfected partner of an HIV-infected woman should be encouraged to use condoms with each act of intercourse. Intravaginal insemination for conception using the partner's semen is effective with normal fertility and can be performed at home or by the care provider. Timed insemination during the most fertile period may be considered to maximize the chance of conception.

5.3. Male HIV Infected/Female HIV Uninfected. Male fertility screening and interventions to reduce the risk of HIV transmission during conception should be considered in this context.

5.3.1. Semen Analysis. Semen abnormalities are more common in the setting of HIV. Abnormalities are correlated with lower CD4+ cell counts and may include lower sperm volume, concentration, and motility along with higher rate of abnormal forms [98, 99]. Some data suggest that ARV therapy may have an adverse effect on semen quality: a longitudinal study of 34 men with serial semen analyses prior to ARV therapy and up to 48 weeks post-ARV initiation found that the proportion of progressively motile spermatozoa was low at all time points, but decreased significantly over the course of followup [100]. Therefore, when there is little or no likelihood of natural conception, an uninfected female partner may be at increased risk for infection through repetitive exposure over time.

5.3.2. Preexposure Prophylaxis (PrEP). Providing ARVs intravaginally or orally to an uninfected female partner may offer additional risk reduction to minimize HIV transmission when trying to conceive. Results of PrEP clinical trials to date have been mixed. One percent intravaginal tenofovir (TDF) gel used before and after sex reduced HIV acquisition by 39% in the CAPRISA 004 study [101]. However, in the VOICE study, in women at high risk of acquiring HIV, 1% TDF gel arm used daily was no better than placebo. A study of daily oral TDF+ emtricitabine (FTC) in uninfected male couples reported a 44% reduction overall in HIV acquisition as compared to placebo; effectiveness was significantly affected by adherence [102, 103]. In the Partners PrEP study conducted in Kenya and Uganda among more than 1,400 HIV serodiscordant couples, the use of daily TDF or daily TDF/FTC by the uninfected partner was found to have an efficacy of 66% and 73%, respectively, compared to placebo, in reducing HIV transmission. In another trial in Botswana, TDF/FTC given to 1,200 HIV-uninfected heterosexual men and women reduced transmission by 66% compared to placebo [104]. However, the FEM-PrEP clinical trial and the VOICE study, which were both conducted in high risk uninfected African women, found no efficacy with daily oral TDF/FTC and TDF, respectively [104]. Currently, data are insufficient to recommend PrEP as part of a strategy to reduce risk of HIV transmission when trying to conceive. If clinicians elect to use PrEP for HIV-uninfected women in serodiscordant couples, the couple should be fully educated about the potential risks and benefits and all available alternatives for safer conception.

5.4. Assisted Reproductive Technology. Assisted reproductive technology can be considered to minimize the risk of HIV transmission for serodiscordant couples. Ethics guidelines from the American College of Obstetricians and Gynecologists state that "Seropositivity for HIV per se should not be used as a reason to refuse to provide assisted reproductive technology to a family." [105].

The method with the lowest reported risk of transmission is semen washing, with negative PCR testing after preparation, coupled with intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI). A retrospective multicenter study at a network of eight European centers and involving 1036 serodiscordant couples used sperm washing to obtain motile spermatozoa for 3390 assisted reproduction cycles [106]. An HIV test was performed in female partners at least six months after assisted reproduction attempt. Outcome measures were the number of assisted reproduction cycles, pregnancy outcome and HIV test on women after treatment. The result of female HIV testing after assisted reproduction was known in 967 of 1036 women (7.1% lost to followup); all tests recorded were negative. A total of 580 pregnancies were documented from 3315 cycles, resulting in 410 deliveries and 463 live births; pregnancy outcome was unknown in 47 cases. These data are suggestive but not conclusive of a safety benefit of sperm washing and assisted reproduction over natural conception. There are no data examining comparative or additional safety of these techniques in serodiscordant couples where the infected partner is on effective ART.

Some states continue to have laws that ban assisted conception with semen from HIV-infected men [107] and some clinics may limit or deny services to HIV-infected couples [90]. In addition, most insurance plans (including Medicare/Medicaid) do not cover these services and the cost is usually prohibitive. The National Perinatal HIV Hotline (1-888-448-8765) can provide a list of institutions offering reproductive services for HIV serodiscordant couples.

5.5. Timed Unprotected Intercourse. For serodiscordant couples who cannot afford assisted reproduction and who, after comprehensive counseling, still wish to try to conceive, timed unprotected intercourse with strong recommendation to use condoms at all other times is the best approach. Unprotected intercourse should be considered only in the context of viral suppression and should be targeted to those times when

women are most likely to conceive. The most fertile time in a woman's menstrual cycle can be determined with use of ovulation predictors (available over the counter at pharmacies), basal body temperature measurement, or ovulation calculators (e.g., the March of Dimes ovulation calendar is available at http://www.marchofdimes.com/ovulation_calendar.html).

6. Interventions for Women Wishing to Prevent or Delay Pregnancy: Contraception Management and Safety

6.1. Contraception: General Considerations. General considerations for contraceptive counseling include those applicable to all women: efficacy, safety and side effects, convenience and ease of use, cost, potential noncontraceptive benefits, and protection against transmission of HIV or acquisition of other STIs. In addition, there are considerations specifically relevant to women with HIV, such as potential drug interactions and possible effects on HIV transmission or progression.

Women living with HIV can potentially use all available contraceptive methods [108, 109]. Current guidance from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) state that with use of methods involving spermicides (alone or with diaphragm) risk generally outweighs advantages of the method, because of potential disruption of cervical mucosa, which may increase viral shedding and HIV transmission to uninfected partners. Both the copper intrauterine device (Cu-IUD) and levonorgestrel-containing IUD can be initiated or continued in women living with HIV, including those with AIDS, who are clinically doing well on ARV therapy [110, 111].

6.2. Drug Interactions. There are concerns that pharmacokinetic interactions between hormonal contraceptives (HCs) and ARV drugs may modify steroid levels and potentially decrease contraceptive effectiveness [112] or increase risk of adverse effects. HCs are primarily metabolized by conjugation pathways (glucuronidation and sulfonation) as well as cytochrome P450 enzymes. Specific ARV drugs, such as protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), can affect these metabolic pathways through induction or inhibition resulting in altered concentrations of steroid hormones. These interactions are pharmacokinetic; the true clinical effect is not clear. Therefore, additional or alternative methods of contraception are recommended in some cases. Only with fosamprenavir (FPV), which is metabolized to amprenavir (APV), does the drug-drug interaction also reduce the concentration of the ARV; it is recommended that FPV be administered with hormonal contraceptives only when combined with low dose ritonavir (RTV) as a boosting agent. The nucleoside reverse transcriptase inhibitor (NRTI), CCR5 antagonist, and integrase inhibitor classes of ARV agents do not have significant interactions with oral contraceptives. Drug interactions between ARV agents and HCs are described in Table 5. There are no data on safety or efficacy in altering hormonal dosages in an effort to circumvent these interactions, but a preparation containing a minimum of 30 μg ethinyl estradiol (EE) is suggested [108]. Further study of the true clinical effect of pharmacokinetic drug interactions and the safety and efficacy of altering hormonal dosages in an effort to circumvent these interactions is warranted.

There is minimal information about drug interactions with use of alternative delivery methods for estrogen-progestin contraceptives (i.e., transdermal patch, intravaginal ring). However, a recent study suggests that these delivery methods may also be vulnerable to drug interactions and that different progestins (e.g., norethindrone versus norelgestr min) may be affected differently in interaction with specific ARV agents [113]. Further study is required to better understand potential drug interactions and to determine their clinical significance.

There is no evidence showing a decrease in the contraceptive efficacy in depot medroxyprogesterone acetate (DMPA) when used with ARV therapy [114].

6.3. Hormonal Contraception and HIV Progression. Most studies suggest no association between the use of hormonal contraception and HIV disease progression [115–119]. In a longitudinal US cohort and a prospective cohort in Kenya, hormonal contraception was not associated with a change in viral load over time as compared to women who were not using hormonal contraception [120, 121]. One randomized controlled trial found an increased risk of declining CD4+ count or death among women using hormonal contraceptives as compared with women using a copper IUD; however, this study had significant loss to followup and method-switching among groups, weakening the strength of the analysis [119]. WHO convened an advisory group in February, 2012, to examine recent evidence related to hormonal contraception and HIV acquisition, progression, and transmission [115]. The group agreed that use of hormonal contraceptives should remain unrestricted if a strong clarification was added to the medical eligibility criteria for contraceptive use [109] that emphasized the need for a strong message about condom use and the need for couples to have access to a wide range of contraceptive methods. A clear recommendation was also made on the need for further research on this issue and a need to continue to closely review emerging evidence.

6.4. Hormonal Contraception and HIV Transmission or Acquisition. There are also conflicting data on the role of HC in HIV susceptibility or infectiousness. Two large prospective studies have shown a modestly increased risk of HIV acquisition associated with use of combined oral estrogen/progestin and/or DMPA [122–124]. A recent secondary analysis of data from a large prevention trial found an increased risk of HIV seroconversion (both transmission and acquisition) associated with hormonal contraception (primarily DMPA) among over 3700 serodiscordant African couples. Furthermore, women with HIV who transmitted to an HIV-uninfected male sex partner also had higher genital viral load, a potential mechanism for increased transmission [125]. However, there are also significant methodological

Table 5: Drug interactions between antiretroviral agents and hormonal contraceptives.

Antiretroviral (ARV) drug	Effect on drug levels	Dosing recommendation/clinical comment
Nonnucleoside reverse transcriptase inhibitor (NNRTI)		
Efavirenz (EFV)	Oral ethinyl estradiol/norgestimate No effect on ethinyl estradiol concentrations: ↓ active metabolites of norgestimate (levonorgestrel AUC ↓83%; norelgestromin AUC ↓64%)	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. EFV had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on EFV plasma concentrations was observed.
	Implant: ↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and EFV has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in EFV-exposed patients.
	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished
Etravirine (ETR)	Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect	No dosage adjustment necessary
Nevirapine (NVP)	Ethinyl estradiol AUC ↓ 20% Norethindrone AUC ↓ 19%	Use alternative or additional methods
	DMPA: no significant change	No dosage adjustment needed
Ritonavir-(RTV-) boosted protease inhibitor (PI)		
Atazanavir/ritonavir (ATV/r)	↓ Ethinyl estradiol ↑ Norgestimate	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied
Darunavir/ritonavir (DRV/r)	Ethinyl estradiol AUC ↓ 44% Norethindrone AUC ↓ 14%	Use alternative or additional method
Fosamprenavir/ritonavir (FPV/r)	Ethinyl estradiol AUC ↓ 37% Norethindrone AUC ↓ 34%	Use alternative or additional method
Lopinavir/ritonavir (LPV/r)	Ethinyl estradiol AUC ↓ 42% Norethindrone AUC ↓ 17%	Use alternative or additional method
Saquinavir/ritonavir (SQV/r)	↓ Ethinyl estradiol	Use alternative or additional method
Tipranavir/ritonavir (TPV/r)	Ethinyl estradiol AUC ↓ 48% Norethindrone: No significant change	Use alternative or additional method
PI without RTV		
Atazanavir (ATV)	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol or use alternative method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied
Fosamprenavir (FPV)	With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20%	Use alternative method
Indinavir (IDV)	Ethinyl estradiol AUC ↑ 25% Norethindrone AUC ↑ 26%	No dose adjustment
Nelfinavir (NFV)	Ethinyl estradiol AUC ↓ 47% Norethindrone AUC ↓ 18%	Use alternative or additional method
CCR5 antagonist		
Maraviroc (MVC)	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination

Key to Abbreviations: AUC: area under the curve. DMPA: depot medroxyprogesterone acetate
Source: see [4].

issues with most studies, including potential selection bias confounding variables such as changes in HC use over time; presence of STIs—including herpes simplex virus 2 (HSV-2); and dependence on self-report regarding use of HC, sexual behaviors, and condom use [126].

A WHO expert group reviewed all the available evidence and concluded that the data were not sufficient to warrant a change in the current guidance on the use of hormonal contraception for women at risk of HIV infection [115]. The WHO technical statement recommends no restrictions

on the use of existing hormonal contraceptive methods for women at risk of HIV infection and that all women should have access to and use condoms and other measures to prevent and reduce the risk of HIV and other infections, particularly women on progestogen-only injectable contraception. The advisory group strongly recommended expansion of the current contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection.

7. Conclusion

PCC, which includes contraceptive care, is an important component of primary health care services for all women living with HIV with the potential for childbearing. The goal of PCC is to ensure that every pregnancy is planned and well timed that pregnancy occurs in the context of optimal maternal health and that the risk of HIV transmission to an uninfected partner and to the infant is reduced to the fullest extent possible. To achieve this goal, health care providers can be proactive in addressing the reproductive intentions and contraceptive practices and needs of every HIV-infected woman. This is an ongoing process that begins when healthcare providers initiate nonjudgmental conversations with women living with HIV at every visit about pregnancy intentions, contraception needs, and sexual health.

References

[1] American College of Obstetricians and Gynecologists (ACOG), "ACOG Committee Opinion number 313, September 2005. The importance of preconception care in the continuum of women's health care," *Obstetrics and Gynecology*, vol. 106, no. 3, pp. 665–666.

[2] American College of Obstetricians Gynecologists (ACOG), "Gynecological care for women with human immunodeficiency virus," Practice Bulletin, 2010, http://www.acog.org/~/media/Practice%20Bulletins/Committee%20on%20Practice%20Bulletins%20–%20Gynecology/Public/.pdf?dmc=1&ts=20120216T2109570331.

[3] K. Johnson, S. F. Posner, J. Biermann et al., "Recommendations to improve preconception health and health care—United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care," *Morbidity and Mortality Weekly Reports. Recommendations and Reports*, vol. 55, no. 6, pp. 1–23, 2006.

[4] Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, "Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States," 2012, http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/.

[5] A. Van Sighem, L. Gras, P. Reiss, K. Brinkman, and F. De Wolf, "Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals," *AIDS*, vol. 24, no. 10, pp. 1527–1535, 2010.

[6] G. S. Birkhead, W. P. Pulver, B. L. Warren et al., "Progress in prevention of mother-to-child transmission of HIV in New York state: 1988–2008," *Journal of Public Health Management and Practice*, vol. 16, no. 6, pp. 481–491, 2010.

[7] Centers for Disease Control and Prevention (CDC), "HIV Surveillance Report," 2009, http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/.

[8] R. Hazra, G. K. Siberry, and L. M. Mofenson, "Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection," *Annual Review of Medicine*, vol. 61, pp. 169–185, 2010.

[9] A. Elgalib, A. Hegazi, A. Samarawickrama et al., "Pregnancy in HIV-infected teenagers in London," *HIV Medicine*, vol. 12, no. 2, pp. 118–123, 2011.

[10] M. Millery, S. Vazquez, V. Walther, N. Humphrey, J. Schlecht, and N. Van Devanter, "Pregnancies in perinatally HIV-infected young women and implications for care and service programs," *Journal of the Association of Nurses in AIDS Care*, vol. 23, no. 1, pp. 41–51, 2011.

[11] A. Sharma, J. G. Feldman, E. T. Golub et al., "Live birth patterns among human immunodeficiency virus-infected women before and after the availability of highly active antiretroviral therapy," *American Journal of Obstetrics and Gynecology*, vol. 196, no. 6, pp. e541–e546, 2007.

[12] L. S. Massad, G. Springer, L. Jacobson et al., "Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV," *AIDS*, vol. 18, no. 2, pp. 281–286, 2004.

[13] J. L. Chen, K. A. Phillips, D. E. Kanouse, R. L. Collins, and A. Miu, "Fertility desires and intentions of HIV-positive men and women," *Family Planning Perspectives*, vol. 33, no. 4, pp. 144–165, 2001.

[14] S. Cliffe, C. L. Townsend, M. Cortina-Borja, and M.-L. Newell, "Fertility intentions of HIV-infected women in the United Kingdom," *AIDS Care*, vol. 23, no. 9, pp. 1093–1101, 2011.

[15] S. Finocchario-Kessler, M. D. Sweat, J. K. Dariotis et al., "Understanding high fertility desires and intentions among a sample of urban women living with HIV in the United States," *AIDS and Behavior*, vol. 14, no. 5, pp. 1106–1114, 2010.

[16] M. R. Loutfy, T. A. Hart, S. S. Mohammed et al., "Fertility desires and intentions of HIV-positive women of reproductive age in Ontario, Canada: a cross-sectional study," *PloS ONE*, vol. 4, no. 12, p. e7925, 2009.

[17] S. M. Craft, R. O. Delaney, D. T. Bautista, and J. M. Serovich, "Pregnancy decisions among women with HIV," *AIDS and Behavior*, vol. 11, no. 6, pp. 927–935, 2007.

[18] B. Nattabi, J. Li, S. C. Thompson, C. G. Orach, and J. Earnest, "A systematic review of factors influencing fertility desires and intentions among people living with HIV/AIDS: implications for policy and service delivery," *AIDS and Behavior*, vol. 13, no. 5, pp. 949–968, 2009.

[19] K. E. Squires, S. L. Hodder, J. Feinberg et al., "Health needs of HIV-infected women in the United States: insights from the women living positive survey," *AIDS Patient Care and STDs*, vol. 25, no. 5, pp. 279–285, 2011.

[20] S. Finocchario-Kessler, M. D. Sweat, J. K. Dariotis et al., "Childbearing motivations, pregnancy desires, and perceived partner response to a pregnancy among urban female youth: does HIV-infection status make a difference?" *AIDS Care*, vol. 24, no. 1, pp. 1–11, 2012.

[21] L. B. Finer and M. R. Zolna, "Unintended pregnancy in the United States: incidence and disparities, 2006," *Contraception*, vol. 84, no. 5, pp. 478–485, 2011.

[22] K. Kikuchi, N. Wakasugi, K. C. Poudel, K. Sakisaka, and M. Jimba, "High rate of unintended pregnancies after

knowing of HIV infection among HIV positive women under antiretroviral treatment in Kigali, Rwanda," *BioScience Trends*, vol. 5, no. 6, pp. 255–263, 2011.

[23] L. J. Koenig, L. Espinoza, K. Hodge, and N. Ruffo, "Young, seropositive, and pregnant: epidemiologic and psychosocial perspectives on pregnant adolescents with human immunodeficiency virus infection," *American Journal of Obstetrics and Gynecology*, vol. 197, no. 3, pp. S123–S131, 2007.

[24] J. Kenny, B. Williams, K. Prime, P. Tookey, and C. Foster, "Pregnancy outcomes in adolescents in the UK and Ireland growing up with HIV," *HIV Medicine*, vol. 13, no. 5, pp. 304–308, 2012.

[25] L. S. Massad, C. T. Evans, T. E. Wilson et al., "Contraceptive use among U.S. women with HIV," *Journal of Women's Health*, vol. 16, no. 5, pp. 657–666, 2007.

[26] S. Finocchario-Kessler, J. K. Dariotis, M. D. Sweat et al., "Do HIV-infected women want to discuss reproductive plans with providers, and are those conversations occurring?" *AIDS Patient Care and STDs*, vol. 24, no. 5, pp. 317–323, 2010.

[27] L. Panozzo, M. Battegay, A. Friedl et al., "High risk behaviour and fertility desires among heterosexual HIV-positive patients with a serodiscordant partner—two challenging issues," *Swiss Medical Weekly*, vol. 133, no. 7-8, pp. 124–127, 2003.

[28] M. A. Lampe, D. K. Smith, G. J. E. Anderson, A. E. Edwards, and S. R. Nesheim, "Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States," *American Journal of Obstetrics and Gynecology*, vol. 204, no. 6, pp. 488.e1–488.e8, 2011.

[29] A. Desgrées du Loû, P. Msellati, A. Yao et al., "Impaired fertility in HIV-1-infected pregnant women: a clinic-based survey in Abidjan, Côte d'Ivoire, 1997," *AIDS*, vol. 13, no. 4, pp. 517–521, 1999.

[30] J. R. Glynn, A. Buvé, M. Caraël et al., "Decreased fertility among HIV-1-infected women attending antenatal clinics in three African cities," *Journal of Acquired Immune Deficiency Syndromes*, vol. 25, no. 4, pp. 345–352, 2000.

[31] R. H. Gray, M. J. Wawer, D. Serwadda et al., "Population-based study of fertility in women with HIV-1 infection in Uganda," *The Lancet*, vol. 351, no. 9096, pp. 98–103, 1998.

[32] L. M. Lee, P. M. Wortley, P. L. Fleming, L. J. Eldred, and R. H. Gray, "Duration of human immunodeficiency virus infection and likelihood of giving birth in a medicaid population in Maryland," *American Journal of Epidemiology*, vol. 151, no. 10, pp. 1020–1028, 2000.

[33] R. H. N. Nguyen, S. J. Gange, F. Wabwire-Mangen et al., "Reduced fertility among HIV-infected women associated with viral load in Rakai District, Uganda," *International Journal of STD and AIDS*, vol. 17, no. 12, pp. 842–846, 2006.

[34] S. Cu-Uvin, J. W. Hogan, D. Warren et al., "Prevalence of lower genital tract infections among human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women," *Clinical Infectious Diseases*, vol. 29, no. 5, pp. 1145–1150, 1999.

[35] S. Cu-Uvin, H. Ko, D. J. Jamieson et al., "Prevalence, incidence, and persistence or recurrence of trichomoniasis among human immunodeficiency virus (HIV)-positive women and among HIV-negative women at high risk for HIV infection," *Clinical Infectious Diseases*, vol. 34, no. 10, pp. 1406–1411, 2002.

[36] C. R. Cohen, "Effect of human immunodeficiency virus type 1 infection upon acute salpingitis: a laparoscopic study," *Journal of Infectious Diseases*, vol. 178, no. 5, pp. 1352–1358, 1998.

[37] K. L. Irwin, A. C. Moorman, M. J. O'Sullivan et al., "Influence of human immunodeficiency virus infection on pelvic inflammatory disease," *Obstetrics and Gynecology*, vol. 95, no. 4, pp. 525–534, 2000.

[38] O. Coll, M. Lopez, R. Vidal et al., "Fertility assessment in non-infertile HIV-infected women and their partners," *Reproductive BioMedicine Online*, vol. 14, no. 4, article 2645, pp. 488–494, 2007.

[39] H. E. Cejtin, A. Kalinowski, P. Bacchetti et al., "Effects of human immunodeficiency virus on protracted amenorrhea and ovarian dysfunction," *Obstetrics and Gynecology*, vol. 108, no. 6, pp. 1423–1431, 2006.

[40] O. C. Ezechi, A. Jogo, C. Gab-Okafor et al., "Effect of HIV-1 infection and increasing immunosuppression on menstrual function," *Journal of Obstetrics and Gynaecology Research*, vol. 36, no. 5, pp. 1053–1058, 2010.

[41] S. D. Harlow, P. Schuman, M. Cohen et al., "Effect of HIV infection on menstrual cycle length," *Journal of Acquired Immune Deficiency Syndromes*, vol. 24, no. 1, pp. 68–75, 2000.

[42] L. S. Massad, C. T. Evans, H. Minkoff et al., "Effects of HIV infection and its treatment on self-reported menstrual abnormalities in women," *Journal of Women's Health*, vol. 15, no. 5, pp. 591–598, 2006.

[43] F. E. Makumbi, G. Nakigozi, S. J. Reynolds et al., "Associations between HIV antiretroviral therapy and the prevalence and incidence of pregnancy in Rakai, Uganda," *AIDS Research and Treatment*, vol. 2011, Article ID 519492, 10 pages, 2011.

[44] L. Myer, R. J. Carter, M. Katyal, P. Toro, W. M. El-Sadr, and E. J. Abrams, "Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study," *PLoS Medicine*, vol. 7, no. 2, Article ID e1000229, 2010.

[45] H. Tweya, C. Feldacker, E. Breeze et al., "Incidence of pregnancy among women accessing antiretroviral therapy in Urban Malawi: a retrospective cohort study," *AIDS and Behavior*, http://www.springerlink.com.libproxy2.umdnj.edu/content/n82815417n281167/.

[46] M. Sandelowski, C. Lambe, and J. Barroso, "Stigma in HIV-positive women," *Journal of Nursing Scholarship*, vol. 36, no. 2, pp. 122–128, 2004.

[47] L. B. Sanders, "Sexual behaviors and practices of women living with HIV in relation to pregnancy," *Journal of the Association of Nurses in AIDS Care*, vol. 20, no. 1, pp. 62–68, 2009.

[48] A. C. Wagner, T. A. Hart, S. Mohammed, E. Ivanova, J. Wong, and M. R. Loutfy, "Correlates of HIV stigma in HIV-positive women," *Archives of Women's Mental Health*, vol. 13, no. 3, pp. 207–214, 2010.

[49] S. Richardson, "Guide for HIV/AIDS clinical care of HIV-infected women through the life cycle," Guide for HIV/AIDS Clinical Care, HRA HIV/AIDS Bureau, 2011.

[50] S. Kathleen, J. Voss, and D. Li, "Female disclosure of HIV-positive serostatus to sex partners: a two-city study," *Women and Health*, vol. 50, no. 6, pp. 506–526, 2010.

[51] T. E. Wilson, J. Feldman, M. Y. Vega et al., "Acquisition of new sexual partners among women with HIV infection: patterns of disclosure and sexual behavior within new partnerships," *AIDS Education and Prevention*, vol. 19, no. 2, pp. 151–159, 2007.

[52] Panel on Antiretroviral Guidelines for Adults and Adolescents, "Guidelines for the use of antiretroviral

agents in HIV-1-infected adults and adolescents," 2012, http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

[53] C. Jasseron, L. Mandelbrot, C. Dollfus et al., "Non-disclosure of a pregnant Woman's HIV status to her partner is associated with non-optimal prevention of mother-to-child transmission," *AIDS and Behavior*, http://www.springerlink.com.libproxy2.umdnj.edu/content/619212838376p285/fulltext.pdf.

[54] S. Wilson, "HIV and pregnancy: challenges in practice," *Practising Midwife*, vol. 14, no. 3, pp. 16–18, 2011.

[55] K. M. Forbes, N. Lomax, L. Cunningham et al., "Partner notification in pregnant women with HIV: findings from three inner-city clinics," *HIV Medicine*, vol. 9, no. 6, pp. 433–435, 2008.

[56] J. D. Makin, B. W. C. Forsyth, M. J. Visser, K. J. Sikkema, S. Neufeld, and B. Jeffery, "Factors affecting disclosure in South African HIV-positive pregnant women," *AIDS Patient Care and STDs*, vol. 22, no. 11, pp. 907–916, 2008.

[57] T. T. Brown, S. R. Cole, X. Li et al., "Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study," *Archives of Internal Medicine*, vol. 165, no. 10, pp. 1179–1184, 2005.

[58] P. C. Tien, M. F. Schneider, S. R. Cole et al., "Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study," *AIDS*, vol. 21, no. 13, pp. 1739–1745, 2007.

[59] C. L. Townsend, M. Cortina-Borja, C. S. Peckham, A. De Ruiter, H. Lyall, and P. A. Tookey, "Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006," *AIDS*, vol. 22, no. 8, pp. 973–981, 2008.

[60] R. Tubiana, J. Le Chenadec, C. Rouzioux et al., "Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 Copies/ ml at Delivery: a case-control study nested in the french perinatal cohort (EPF-ANRS COl)," *Clinical Infectious Diseases*, vol. 50, no. 4, pp. 585–596, 2010.

[61] A. P. Kourtis, C. H. Schmid, D. J. Jamieson, and J. Lau, "Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis," *AIDS*, vol. 21, no. 5, pp. 607–615, 2007.

[62] C. Rudin, A. Spaenhauer, O. Keiser et al., "Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data," *HIV Medicine*, vol. 12, no. 4, pp. 228–235, 2011.

[63] N. Ford, L. Mofenson, K. Kranzer et al., "Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts," *AIDS*, vol. 24, no. 10, pp. 1461–1470, 2010.

[64] L. F. Johnson and D. A. Lewis, "The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis," *Sexually Transmitted Diseases*, vol. 35, no. 11, pp. 946–959, 2008.

[65] F. A. Plummer, "Heterosexual transmission of human immunodeficiency virus type 1 (HIV): interactions of conventional sexually transmitted diseases, hormonal contraception and HIV-1," *AIDS Research and Human Retroviruses*, vol. 14, no. 1, pp. S5–S10, 1998.

[66] L. J. M. Bollen, S. J. Whitehead, P. A. Mock et al., "Maternal herpes simplex virus type 2 coinfection increases the risk of perinatal HIV transmission: possibility to further decrease transmission?" *AIDS*, vol. 22, no. 10, pp. 1169–1176, 2008.

[67] F. Z. Gumbo, K. Duri, G. Q. Kandawasvika et al., "Risk factors of HIV vertical transmission in a cohort of women under a PMTCT program at three peri-urban clinics in a resource-poor setting," *Journal of Perinatology*, vol. 30, no. 11, pp. 717–723, 2010.

[68] M. J. Lee, R. J. Hallmark, L. M. Frenkel, and G. Del Priore, "Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection," *International Journal of Gynecology and Obstetrics*, vol. 63, no. 3, pp. 247–252, 1998.

[69] A. R. Lifson and H. A. Lando, "Smoking and HIV: prevalence, health risks, and cessation strategies," Current HIV/AIDS Reports, 2012.

[70] B. King, S. Dube, R. Kaufmann, L. Shaw, and T. Pechacek, "Vital signs: current cigarette smoking among adults aged ≥18 Years—United States, 2005–2010," *Morbidity and Mortality Weekly Report*, vol. 60, no. 35, pp. 1207–1212, 2011.

[71] F. H. Galvan, E. G. Bing, J. A. Fleishman et al., "The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV cost and services utilization study," *Journal of Studies on Alcohol*, vol. 63, no. 2, pp. 179–186, 2002.

[72] S. C. Kalichman, C. M. Amaral, D. White et al., "Prevalence and clinical implications of interactive toxicity beliefs regarding mixing alcohol and antiretroviral therapies among people living with HIV/AIDS," *AIDS Patient Care and STDs*, vol. 23, no. 6, pp. 449–454, 2009.

[73] J. M. Holmes, K. R. Gerhardstein, and P. T. Griffin, "Brief screening for alcohol use disorders in HIV primary care," *HIV Clinician*, vol. 23, no. 4, pp. 8–13, 2011.

[74] S. C. Kalichman, C. M. Amaral, D. White et al., "Alcohol and adherence to antiretroviral medications: interactive toxicity beliefs among people living with HIV," *Journal of the Association of Nurses in AIDS Care*. In press.

[75] Centers for Disease Control and Prevention, "HIV Surveillance—epidemiology of HIV Infection," 2010, http://www.cdc.gov/hiv/topics/surveillance/resources/slides/general/index.htm.

[76] H. E. Hutton, M. E. McCaul, G. Chander et al., "Alcohol use, anal sex, and other risky sexual behaviors among HIV-infected women and men," *AIDS and Behavior*, http://www.springerlink.com.libproxy2.umdnj.edu/content/5547552wnjp22833.

[77] J. M. Sales, J. L. Brown, A. T. Vissman, and R. J. DiClemente, "The association between alcohol use and sexual risk behaviors among African American women across three developmental periods: a review," *Current Drug Abuse Reviews*, vol. 5, no. 2, pp. 117–128, 2012.

[78] P. Seth, G. M. Wingood, R. J. DiClemente, and L. S. Robinson, "Alcohol use as a marker for risky sexual behaviors and biologically confirmed sexually transmitted infections among young adult African-American women," *Women's Health Issues*, vol. 21, no. 2, pp. 130–135, 2011.

[79] S. K. Whitmore, A. W. Taylor, L. Espinoza, R. L. Shouse, M. A. Lampe, and S. Nesheim, "Correlates of mother-to-child transmission of HIV in the United States and Puerto Rico," *Pediatrics*, vol. 129, no. 1, pp. e74–e81, 2012.

[80] Practice Committee of American Society for Reproductive Medicine, "Smoking and infertility," *Fertility and Sterility*, vol. 90, no. 5, supplement, pp. S254–S259, 2008.

[81] B. G. Armstrong, A. D. McDonald, and M. Sloan, "Cigarette, alcohol, and coffee consumption and spontaneous abortion," *American Journal of Public Health*, vol. 82, no. 1, pp. 85–87, 1992.

[82] J. A. Martin, H. C. Kung, T. J. Mathews et al., "Annual summary of vital statistics: 2006," *Pediatrics*, vol. 121, no. 4, pp. 788–801, 2008.

[83] M. H. Aliyu, H. Weldeselasse, E. M. August, Keith L. G., Salihu H. M., "Cigarette smoking and fetal morbidity outcomes in a large cohort of HIV-infected mothers," *Nicotine & Tobacco Research*, http://ntr.oxfordjournals.org/content/early/2012/05/09/ntr.nts105.abstract.

[84] B. J. Dattel, "Substance abuse in pregnancy," *Seminars in Perinatology*, vol. 14, no. 2, pp. 179–187, 1990.

[85] K. Gouin, K. Murphy, and P. S. Shah, "Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses," *American Journal of Obstetrics and Gynecology*, vol. 204, no. 4, pp. 340.e1–340.e12, 2011.

[86] L. Goldschmidt, G. A. Richardson, D. S. Stoffer, D. Geva, and N. L. Day, "Prenatal alcohol exposure and academic achievement at age six: a nonlinear fit," *Alcoholism*, vol. 20, no. 4, pp. 763–770, 1996.

[87] N. J. Bodsworth, D. A. Cooper, and B. Donovan, "The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state," *Journal of Infectious Diseases*, vol. 163, no. 5, pp. 1138–1140, 1991.

[88] H. H. Thein, Q. Yi, G. J. Dore, and M. D. Krahn, "Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis," *AIDS*, vol. 22, no. 15, pp. 1979–1991, 2008.

[89] C. L. Thio, E. C. Seaberg, R. Skolasky Jr. et al., "HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS)," *The Lancet*, vol. 360, no. 9349, pp. 1921–1926, 2002.

[90] J. Y. Phelps, "Restricting access of human immunodeficiency virus (HIV)-seropositive patients to infertility services: a legal analysis of the rights of reproductive endocrinologists and of HIV-seropositive patients," *Fertility and Sterility*, vol. 88, no. 6, pp. 1483–1490, 2007.

[91] P. Barreiro, J. A. Castilla, P. Labarga, and V. Soriano, "Is natural conception a valid option for HIV-serodiscordant couples?" *Human Reproduction*, vol. 22, no. 9, pp. 2353–2358, 2007.

[92] S. Attia, M. Egger, M. Müller, M. Zwahlen, and N. Low, "Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis," *AIDS*, vol. 23, no. 11, pp. 1397–1404, 2009.

[93] M. S. Cohen, Y. Q. Chen, M. McCauley et al., "Prevention of HIV-1 infection with early antiretroviral therapy," *The New England Journal of Medicine*, vol. 365, no. 6, pp. 493–505, 2011.

[94] S. Cu-Uvin, A. K. DeLong, K. K. Venkatesh et al., "Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load," *AIDS*, vol. 24, no. 16, pp. 2489–2497, 2010.

[95] A. G. Marcelin, R. Tubiana, S. Lambert-Niclot et al., "Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma," *AIDS*, vol. 22, no. 13, pp. 1677–1679, 2008.

[96] P. M. Sheth, C. Kovacs, K. S. Kemal et al., "Persistent HIV RNA shedding in semen despite effective antiretroviral therapy," *AIDS*, vol. 23, no. 15, pp. 2050–2054, 2009.

[97] S. Taylor and S. Davies, "Antiretroviral drug concentrations in the male and female genital tract: implications for the sexual transmission of HIV," *Current Opinion in HIV and AIDS*, vol. 5, no. 4, pp. 335–343, 2010.

[98] S. Kehl, M. Weigel, D. Müller, M. Gentili, A. Hornemann, and M. Sütterlin, "HIV-infection and modern antiretroviral therapy impair sperm quality," *Archives of Gynecology and Obstetrics*, vol. 284, no. 1, pp. 229–233, 2011.

[99] J. D. M. Nicopoullos, P. A. Almeida, J. W. A. Ramsay, and C. Gilling-Smith, "The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing," *Human Reproduction*, vol. 19, no. 10, pp. 2289–2297, 2004.

[100] E. Van Leeuwen, F. W. Wit, S. Repping et al., "Effects of antiretroviral therapy on semen quality," *AIDS*, vol. 22, no. 5, pp. 637–642, 2008.

[101] Q. A. Karim, S. S. A. Karim, J. A. Frohlich et al., "Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women," *Science*, vol. 329, no. 5996, pp. 1168–1174, 2010.

[102] R. M. Grant, J. R. Lama, P. L. Anderson et al., "Preexposure chemoprophylaxis for HIV prevention in men who have sex with men," *The New England Journal of Medicine*, vol. 363, no. 27, pp. 2587–2599, 2010.

[103] N. L. Michael, "Oral preexposure prophylaxis for HIV—another arrow in the quiver," *The New England Journal of Medicine*, vol. 363, no. 27, pp. 2663–2665, 2010.

[104] C. Celum and J. M. Baeten, "Tenofovir-based pre-exposure prophylaxis for HIV prevention: evolving evidence," *Current Opinion in Infectious Diseases*, vol. 25, no. 1, pp. 51–57, 2012.

[105] Committee on Ethics of the American College of Obstetricians and Gynecologists (ACOG), "Human immunodeficiency virus: ethical guidelines for obstetricians and gynecologists. Number 389," 2007, http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Ethics/Human_Immunodeficiency_Virus.

[106] L. Bujan, L. Hollander, M. Coudert et al., "Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREAThE network," *AIDS*, vol. 21, no. 14, pp. 1909–1914, 2007.

[107] E. S. Daar and J. F. Daar, "Human immunodeficiency virus and fertility care: embarking on a path of knowledge and access," *Fertility and Sterility*, vol. 85, no. 2, pp. 298–301, 2006.

[108] Centers for Disease Control and Prevention (CDC), "U. S. medical eligibility criteria for contraceptive use, 2010," *Morbidity and Mortality Weekly Reports. Recommendations and Reports*, vol. 59, no. 4, pp. 1–86, 2010.

[109] World Health Organization, *Medical Eligibility Criteria for Contraceptive Use*, WHO, 4th edition, 2009.

[110] B. A. Richardson, C. S. Morrison, C. Sekadde-Kigondu et al., "Effect of intrauterine device use on cervical shedding of HIV-1 DNA," *AIDS*, vol. 13, no. 15, pp. 2091–2097, 1999.

[111] E. M. Stringer, C. Kaseba, J. Levy et al., "A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus," *American Journal of Obstetrics and Gynecology*, vol. 197, no. 2, pp. 144.e1–144.e8, 2007.

[112] S. Y. El-Ibiary and J. M. Cocohoba, "Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives," *European Journal of Contraception and Reproductive Health Care*, vol. 13, no. 2, pp. 123–132, 2008.

[113] M. A. Vogler, K. Patterson, L. Kamemoto et al., "Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: pharmacokinetic results of ACTG trial A5188," *Journal of Acquired Immune Deficiency Syndromes*, vol. 55, no. 4, pp. 473–482, 2010.

[114] S. E. Cohn, J. G. Park, D. H. Watts et al., "Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 2, pp. 222–227, 2007.

[115] World Health Organization, "Hormonal contraception and HIV: technical Statement," 2012, http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.08_eng.pdf.

[116] C. S. Morrison, P. L. Chen, I. Nankya et al., "Hormonal contraceptive use and HIV disease progression among women in Uganda and Zimbabwe," *Journal of Acquired Immune Deficiency Syndromes*, vol. 57, no. 2, pp. 157–164, 2011.

[117] C. B. Polis, M. J. Wawer, N. Kiwanuka et al., "Effect of hormonal contraceptive use on HIV progression in female HIV seroconverters in Rakai, Uganda," *AIDS*, vol. 24, no. 12, pp. 1937–1944, 2010.

[118] E. M. Stringer, M. Giganti, R. J. Carter, W. El-Sadr, E. J. Abrams, and J. S. A. Stringer, "Hormonal contraception and HIV disease progression: a multicountry cohort analysis of the MTCT-Plus Initiative," *AIDS*, vol. 23, supplement 1, pp. S69–S77, 2009.

[119] E. M. Stringer, J. Levy, M. Sinkala et al., "HIV disease progression by hormonal contraceptive method: secondary analysis of a randomized trial," *AIDS*, vol. 23, no. 11, pp. 1377–1382, 2009.

[120] H. E. Cejtin, L. Jacobson, G. Springer et al., "Effect of hormonal contraceptive use on plasma HIV-1-RNA levels among HIV-infected women," *AIDS*, vol. 17, no. 11, pp. 1702–1704, 2003.

[121] B. A. Richardson, P. A. Otieno, D. Mbori-Ngacha, J. Overbaugh, C. Farquhar, and G. C. John-Stewart, "Hormonal contraception and HIV-1 disease progression among post-partum Kenyan women," *AIDS*, vol. 21, no. 6, pp. 749–753, 2007.

[122] J. M. Baeten, S. Benki, V. Chohan et al., "Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women," *AIDS*, vol. 21, no. 13, pp. 1771–1777, 2007.

[123] L. Lavreys, V. Chohan, J. Overbaugh et al., "Hormonal contraception and risk of cervical infections among HIV-1-seropositive Kenyan women," *AIDS*, vol. 18, no. 16, pp. 2179–2184, 2004.

[124] C. S. Morrison, P. L. Chen, C. Kwok et al., "Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling," *AIDS*, vol. 24, no. 11, pp. 1778–1781, 2010.

[125] R. Heffron, D. Donnell, H. Rees et al., "Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study," *The Lancet Infectious Diseases*, vol. 12, no. 1, pp. 19–26, 2012.

[126] C. A. Blish and J. M. Baeten, "Hormonal Contraception and HIV-1 Transmission," *American Journal of Reproductive Immunology*, vol. 65, no. 3, pp. 302–307, 2011.

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Research Article

Reproductive Counseling by Clinic Healthcare Workers in Durban, South Africa: Perspectives from HIV-Infected Men and Women Reporting Serodiscordant Partners

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Background. Understanding HIV-infected patient experiences and perceptions of reproductive counseling in the health care context is critical to inform design of effective pharmaco-behavioral interventions that minimize periconception HIV risk and support HIV-affected couples to realize their fertility goals. *Methods*. We conducted semistructured, in-depth interviews with 30 HIV-infected women (with pregnancy in prior year) and 20 HIV-infected men, all reporting serodiscordant partners and accessing care in Durban, South Africa. We investigated patient-reported experiences with safer conception counseling from health care workers (HCWs). Interview transcripts were reviewed and coded using content analysis for conceptual categories and emergent themes. *Results*. The study findings indicate that HIV-infected patients recognize HCWs as a resource for periconception-related information and are receptive to speaking to a HCW prior to becoming pregnant, but seldom seek or receive conception advice in the clinic setting. HIV nondisclosure and unplanned pregnancy are important intervening factors. When advice is shared, patients reported receiving a range of information. Male participants showed particular interest in accessing safer conception information. *Conclusions*. HIV-infected men and women with serodiscordant partners are receptive to the idea of safer conception counseling. HCWs need to be supported to routinely initiate accurate safer conception counseling with HIV-infected patients of reproductive age.

1. Introduction

Current HIV prevention strategies (condoms and abstinence) force HIV-serodiscordant couples to choose between risking HIV transmission to a partner, or accepting childlessness [1–12]. Behavioral strategies (home artificial insemination, sex without condoms limited to peak fertility), male circumcision [13–15], antiretroviral therapy (ART) for the infected partner [16–18], and preexposure antiretroviral prophylaxis (PrEP) for the negative partner [19–22] create opportunities for HIV-serodiscordant couples to realize fertility goals and minimize periconception HIV transmission [23–27]. Prior to effective HIV treatment, the prevailing professional recommendation was for people living with HIV to avoid having children [28, 29]. In 2001, the U.S. Centers for Disease Control recommended that healthcare providers support the fertility desires of people living with HIV [30]. South Africa's constitution protects the right

to reproductive choice for HIV-infected persons, and the most recent guidelines from the Southern African HIV Clinicians Society offer risk-reduction strategies for HIV-serodiscordant couples who choose to conceive [31, 32].

Cross-sectional studies indicate that people living with HIV are receptive to safer conception advice from providers [33–36], but that healthcare workers (HCWs) are not routinely engaging in conversations about fertility desires or plans, a crucial first piece of any reproductive health intervention [31, 34, 35, 37]. In Cape Town, over 30% of HIV-infected women and 65% of HIV-infected men attending public sector clinics were interested in having additional children, yet only 19% and 6%, respectively, had discussed this with a HCW [38]. Among HIV-infected women in Johannesburg, with plans to conceive in the next year, 40% had ever had a conversation about fertility plans with a provider [34]. Conversations with HCWs about conception plans were also infrequent in Argentina [37], Brazil [39], and the United States [35]. Barriers to these conversations include a combination of patient (e.g., fear of judgment, lack of pregnancy planning), provider (e.g., limited experience, knowledge, or skills), and structural factors (e.g., competing healthcare demands, limited resources, poor integration of family planning and HIV services) [31, 35–37, 40, 41]. While some conversations may be initiated with HIV lay counselors, they may not have the skills to address clinical issues beyond their focused training [42, 43].

Data demonstrating that ARVs minimize HIV transmission suggest that periconception risk-reduction interventions will require HCW involvement [16, 19–22, 27]. In our conceptual framework for periconception risk behavior, HCWs have the potential to minimize risk behavior through providing information about HIV risk, offering prevention strategies, and promoting adherence to risk reduction strategies [44]. There are no data on practices in KwaZulu-Natal, the most HIV-affected province in South Africa, where 41% of pregnant women attending antenatal clinics are HIV positive [45]. A better understanding of current HCW knowledge, attitudes, and practices will enhance the provision of reproductive counseling for HIV-infected individuals by allowing for development of interventions that capitalize on HCW strengths and address weaknesses.

We present qualitative data resulting from interviews with 30 HIV-infected women and 20 HIV-infected men with serodiscordant sexual partners in Durban, South Africa. We previously reported on periconception risk behavior within this sample [33] and here focus on participant reports of their experiences with HCW provision of reproductive counseling. These data offer early insight into current HCW practices and may contribute to development of feasible safer conception interventions.

2. Methods

2.1. Study Setting, Patient Selection, Inclusion and Exclusion Criteria. Participants were recruited from the antiretroviral (ARV) and preventing maternal-to-child-transmission (PMTCT) clinics within a state-aided (public/private partnership) general hospital serving a predominantly urban population from the greater Durban area where district antenatal clinic HIV prevalence is estimated at 41.5% [45]. In 2011, the ARV clinic was providing care and treatment to 4734 patients on ART. Sixty percent of these patients are women; the majority (>90%) are black South Africans. Patients pay approximately 25 USD per month for comprehensive HIV services, which includes the cost of ARVs. Pregnant patients pay approximately 35 USD per visit to access antenatal care, which includes PMTCT clinic services. In 2010, 200 HIV-infected pregnant women enrolled in this program.

Male participants were recruited from the ARV clinic and female participants were recruited from the ARV and PMTCT clinics. Inclusion criteria were (1) age 18–45 years; (2) HIV-positive; (3) pregnancy in the prior 12 months, including currently pregnant (for women); (4) partner of unknown or seronegative HIV status (prior to referent pregnancy) by participant report (father of the referent pregnancy for women, current sexual partner for men); (5) fluent in English or isiZulu; (6) able to give informed consent. Initial attempts to recruit men with partner pregnancy in the past year were unsuccessful, men were subsequently recruited independent of recent partner pregnancy. It is not clear if initial recruitment challenges were due to sensitivities of reporting partner pregnancy (in a setting where condoms are promoted strongly) or a paucity of men with recent partner pregnancy.

2.2. Procedures. We conducted in-depth, qualitative, individual interviews to explore reproductive decision-making, sexual transmission risk understanding and practices, and periconception risk understanding and practices [33]. Here, we focus on data from the questions "What have health care workers advised you about having children (after knowing your status)?" and "What advice have you received around getting pregnant/having children safely (since knowing your status)?"

Participants were recruited from March through July 2010 via purposive sampling from patients awaiting clinical consultation. After obtaining informed consent, a gender-concordant research assistant trained in qualitative interviewing techniques interviewed participants in a private setting in isiZulu or English. Interviews lasted approximately 30–90 minutes and were recorded, translated, and transcribed. Participants did not receive compensation for participation.

Transcripts were independently reviewed and coded, and resultant conceptual categories and emergent themes were discussed by the research team using content analysis [46, 47]. Several authors reviewed coding categories and emergent themes with the research assistants in order to explore additional themes and confirm accuracy of interpretation.

Ethics approvals were obtained from the McCord Hospital Research Ethics Committee (Durban, South Africa) and from the Partners Healthcare Institutional Review Board (Boston, USA).

3. Results

3.1. Demographics. Baseline demographic data, HIV history, reported partner HIV status, and reproductive history for 30 female and 20 male participants are shown in Table 1. Women and men averaged 30 (SD 4) and 34 (SD 6) years of age, respectively, and had been diagnosed with HIV for a mean of 3 years (SD 2 women, SD 5 men). Seventy-three percent of women and 60% of men had completed secondary school, while 63% of women and 75% of men reported current employment. 73% of women were diagnosed with HIV prior to the referent pregnancy. Women had an average of 2 (SD 1) pregnancies (including current), 1.1 (SD 0.7) prior live births, 0.9 (SD 0.6) living children, and 18 (60%) were pregnant at the time of interview. We have previously detailed the complexities of pregnancy intention in this sample, but about a third (11) of women described the referent pregnancy as explicitly planned [33]. Men had an average of 0.9 (SD 1) living children; three (16%) reported partner pregnancy in the past year.

3.2. Overview. We have presented a conceptual framework for considering factors that impact periconception risk behavior [44]. Structural, individual, and dyadic domains affect access to risk reduction information (e.g., knowledge that ARVs can reduce sexual transmission risk), motivation (e.g., to adhere to prevention strategies), and ability to implement behavioral change (e.g., partnership dynamics and discussions of safer sex practices). Within this framework, HCWs have the potential to minimize risk behavior through providing HIV-affected couples with information about HIV transmission and conception, supporting disclosure, providing ARVs as prevention, and promoting adherence to HIV risk reduction strategies [44]. Here, we present data exploring participant experiences with reproductive counseling from HCWs. We present themes suggesting that, in this sample, HIV-infected men and women in serodiscordant partnerships (1) are aware of and receptive to the idea that one should speak to an HCW prior to becoming pregnant, (2) seldom seek or receive conception advice from healthcare workers, and (3) when advice is shared, patients receive a range of information around safer conception. In addition, (4) men are eager for safer conception advice.

3.2.1. Aware of and Open to Safer Conception and Pregnancy Information from HCWs. Most participants indicated that they had been informed by a HCW that they should seek advice when they were ready to conceive. In some cases, participants communicated that this advice might help minimize transmission to a child, and in some cases to a partner. This awareness was related to general information shared by counselors during routine ARV adherence training sessions (group adherence training sessions prior to ART initiation are routine in South Africa), regardless of the participant's fertility goals at the time.

> *They [healthcare workers during the training session] told me that when I have told her [disclosed to partner], we should come here [to the clinic] together so that they will explain to both of us. They tell us that we should come back with our partners so that the doctor tells us what to do in order for the virus not to be transferred to the child.* (Participant B03, 26-year-old man)

> *They [counselors] said that we should come with our partners so that you explain to the doctor that you want to have a child so that he tells you what to do, and that was it.* Did they say anything more? *No, they only said that we should consult a doctor with your partner if you want to have children.* (Participant B15, 29-year-old man)

In addition to knowing that they should tell a HCW if they wanted to have children, participants were open to seeking this advice from healthcare workers.

> *With us black people, if it happens that you get the virus and you die not having a child, your name just disappears and you are never mentioned. That would be difficult. So if it happens that you do get HIV then you should go to the clinic and talk to them [healthcare workers] so that they help you to get a child in a safe way.* (Participant B04, 28-year-old man)

> *We want to have a child together because we love each other and we are so close to each other… I will probably go to special doctors when I am ready for that so that I hear from them what it is that I have to do in order to have a child since I have the virus and my partner does not.* (Participant B16, 36-year-old man)

> *If you want to have children you need to consult the doctor… then they will advise you what to do.* (Participant A27, 34-year-old woman)

3.2.2. Seldom Seek Safer Conception Information Prior to Conception. While most participants were aware that they should approach a healthcare worker prior to conception, few sought, or received safer conception advice. Participants described several barriers to accessing reproductive counseling prior to conception including fear of judgment from nurses and financial challenges.

> *They did not tell us that we should no longer have children, but you could see that is what they meant. The other day, one of the nurses made a comment and asked "why don't we go for family planning" because they do not want to see us coming back to take the treatment [ARVs for PMTCT] again.* (Participant A26, 23-year-old woman)

> *I spoke to the doctor who said it is safe to have more children if I want to. He said I need to see*

Table 1: Study population characteristics.

Characteristics	Women $n = 30$ mean ± S.D. number (%)	Men $n = 20$ mean ± S.D. number (%)
Age (years)	30 ± 4	34 ± 6
Completed matric or above[†]	22 (73%)	12 (60%)
Employed	19 (63%)	15 (75%)
Years since HIV diagnosis	3 ± 2	3 ± 5
Currently on ART/ARVs	21 (70%)	17/20 (85%)
HIV-negative (versus unknown status) partner[‡]	14 (46%)	13 (65%)
Disclosed HIV status to partner*	23 (79%)	15 (78%)
Pregnancy or partner pregnancy in the past year	30 (100%)	3 (16%)
Pregnancy or partner pregnancy after HIV-diagnosis	22 (73%)	2 (11%)
Pregnancies, including current	2.1 ± 1.1	—
Live births	1.1 ± 0.7	—
Currently living children	0.9 ± 0.6	0.9 ± 1.0

[†]Completed final exams for high school (secondary school).
[‡]By participant report.
*Women—father of referent pregnancy. Men—current or most recent sexual partner.

> *him before I fall pregnant. He said I can come to him, but I didn't because he was expensive as he is a gynecologist.* (Participant A13, 32-year-old woman)

Additional barriers may be related to dyadic factors. For example, participants described that they were told to seek reproductive counseling at the ARV clinic with their partners. However, about a third of participants had not disclosed his/her HIV status to their partner, making this scenario unlikely. Further, about a third of the women in this sample described the referent pregnancy as unplanned.

3.2.3. Range in Quality of Information Shared by Providers about Safer Conception in the Context of HIV Infection. Participants reported a range of information received from providers. At one end of the spectrum, some participants had not received advice about options for having children since their HIV diagnosis, including in the setting of expressing plans for having children.

> *They [healthcare workers] haven't advised me: they have asked me about it but they have never given me any advice. They asked me if I am planning on having more children and I told them, "Yes, I am planning on having one more." I have never received any advice.* (Participant A28, 24-year-old woman)

> What advice have you received from health care workers… around having children after knowing your status? *Except that I have to practice safe sex, there is nothing* (Participant A30, 31-year-old woman)

Others had received helpful safer conception information from doctors or nurses at PMTCT, ARV, and gynecology clinics. Risk reduction strategies that participants had learned included artificial insemination, intercourse timed to peak fertility, manual insemination (for male—uninfected couples—the uninfected male ejaculates into a condom or other container and the semen is inserted into the woman's vaginal canal via a syringe or reversed condom), sperm washing, and intercourse with lubrication (to avoid abrasions).

> *They told me that I can go to one of those private hospitals to ask about sperm washing… One of the times when I came into the clinic there was a poster on the wall saying "if you want to have a child, speak to either a doctor or a nurse." So I asked the doctor, "do you think is it possible for me to have a child even if I'm positive?" But I had to go to one of those private hospitals to look into that thing [sperm washing].* (Participant B05, 31-year-old man)

> *A doctor gave us a [syringe] which we had to use after sex to withdraw sperm [from the condom to insert into the woman]. … We are both aware that I am positive and so we would use a condom all the time … and we received advice from the doctor on how to use the syringe that he gave us so that he [partner] does not get infected.* (Participant A25, 32-year-old woman)

One participant suggested the importance of a lower plasma HIV viral load prior to conception, but it was not clear where she and her partner had learned this information. ART as prevention was not a component of the South African Department of Health Treatment Guidelines at the time of this study (or now) [48].

> *After finding out that my viral load was very low, even undetectable, he [husband] decided that let's take a chance and try and see what is going to happen. He said he has taken that decision, it's not that I am forcing him to take it. Then we just took a chance.* (Participant A04, 28-year-old woman)

Some participants explained that the advice they had received about whether or not they, as HIV-infected individuals, could have children evolved over time—or varied with different providers.

> *So far they told me... that I cannot have children. But then they changed [and said] that I can have children, and that is what I am not sure of.* (Participant B11, 33-year-old man)

3.2.4. Men Are Eager to Learn about Safer Conception. From our sample, many male participants had engaged with a HCW around discussions of safer conception or had sought out information from the internet, relatives, or other news sources.

> *No [I have not had a conversation with a HCW], but I've done research and they said that one can do artificial insemination but I am not sure if it is done on humans. ... Artificial insemination means that a person can be impregnated by a man, but... technology can be used to make a baby without them having sex... The child is yours because the semen is taken from you and can be injected into the women and a baby grows inside the woman, the genes of that child are yours.* (Participant B13, 28-year-old man)

Several male participants became quite interested in safer conception options during the interview and planned to seek out additional advice from a HCW. One participant (B12, 35-year-old man) responded to a question about fertility desire by saying, "*so in the situation that I am in now I do not think I want to have children again*," but by the end of the interview he asks:

> *Is it possible to have children if I am positive and my partner is negative?*

Another participant initially stated, "*I have two kids at the moment. Even before I was diagnosed [with HIV], we were not planning to have more ... Two is enough.*" However, by the end of the interview, he asks:

> *I want to know if ... I decide to have kids how is that possible? ... Maybe I'll try to find more ways to get information about how to have kids when you're HIV positive.* (Participant B14, 39-year-old man)

Women were not particularly eager for advice. However, this may simply reflect the study sample given that fewer women were planning a future pregnancy and many were still close to or in the midst of a current pregnancy.

4. Discussion

These qualitative data suggest that HIV-infected patients are increasingly aware of reproductive counseling opportunities. Many participants understood that HCWs may have valuable advice to offer to facilitate safer conception and were open to seeking this advice. While few participants had sought advice, some participants had received safer conception advice from healthcare encounters.

Prior studies suggest that the majority of HIV-infected patients are not receiving reproductive counseling and are reluctant to engage with healthcare workers to discuss reproductive plans [12, 35, 36, 39, 49–51]. Schwartz et al. [34, page 73] presented data collected during 2009 and reported that only 41% of HIV-infected women reported that an "ART healthcare provider had spoken with them about their options should they want to conceive in the future". In work by Cooper et al., collected in 2006, 19% of women and 6% of men had "consulted a doctor, nurse, or counselor in HIV care about fertility intentions" [38, page S44]. The fact that many participants, including men, in this small sample knew that HCWs may have advice to offer captures data not mentioned in prior studies. These data suggest that clinical settings may be adapting to accommodate the fertility goals of people living with HIV.

Many participants reported the expectation that they could access detailed counseling if they returned to the clinic when they were ready to have a child. From work by our group and others, several facts of periconception practice make this clinical approach precarious. Waiting to talk to a provider until one is ready to have a child eliminates the opportunity to discuss the risks of having children in order to *inform* the decision to have biologic children [24, 52, 53]. Many men and women living with HIV do not know their partner's status and/or have not disclosed to their partners. Prior to testing and disclosure, it is impossible for an individual or a couple to assess sexual transmission risk in the context of conception. Continued efforts to promote couple-based testing and supported disclosure are critical [54]. For those who decide to have children, a preconception conversation with a healthcare worker should include an assessment of the HIV-infected partner's health; the HIV status of the partner; if the woman is positive, a discussion of the risks of pregnancy when HIV infected; risks of transmission to a partner with various periconception risk reduction strategies; fertility assessment; the increased risk of transmission and acquisition during unprotected sex during pregnancy; the risks of perinatal transmission [44].

Furthermore, asking individuals or couples to return when they are ready to have children presupposes conception planning. However, many pregnancies are not explicitly planned [55, 56]. Providing up-front information about the options for safer conception may communicate the importance of preconception planning—to protect the future child and the partner. Recent data from Johannesburg (South Africa) suggest high fertility intentions at ART initiation [34], reflecting the importance of providing safer conception information at treatment initiation and in followup. In addition, decisions about conception are often dyadic. A partner

(who is not attending clinic) may make decisions about having children—if his or her partner has not been educated it is impossible for them to have an informed conversation about the risks and options for safer conception. In addition, life transitions may be quick and there may be plans for pregnancy long before a next visit with a provider [57].

Expecting a patient to raise the issue of fertility plans on his or her own may be problematic. While not a theme in our data, published data suggest that women and men living with HIV hesitate to reveal fertility plans to HCWs for fear of judgment [36, 58]. It is not part of routine clinical practice to expect patients to tell providers when they are ready to discuss health behavior change (e.g., smoking, substance abuse, exercise, sexual behavior)—the onus is on the provider to actively inquire about behaviors that compromise health. Routine assessment of fertility goals and plans should be incorporated into clinical care for people living with HIV, with subsequent recommendations for safer conception or effective contraception options, depending on fertility goals. How to execute this in overburdened healthcare systems is a challenge but may require increased training in fertility intention assessment and comprehensive reproductive counseling for counselors.

Participants had learned of safer conception strategies from HCWs including artificial insemination, intercourse timed to peak fertility, sperm washing, home manual insemination, and intercourse with lubrication to avoid abrasions. The frequency with which sperm washing and artificial insemination was raised is interesting since these are some of the least accessible (geographically, economically) strategies for reducing transmission risk. Simpler risk reduction strategies such as delaying conception until the infected partner is on treatment with suppressed HIV RNA viral load, timing sex without condoms to peak fertility, circumcision for the male partner if he is uninfected, and manual insemination are likely to be more feasible. Our semistructured interview guide was not designed to probe specifically about particular techniques and it is possible that participants were more likely to recall discussions about and have faith in high-tech concepts such as sperm washing compared to behavioral modifications such as timing unprotected sex to peak fertility. In addition, patients may have received limited information, perhaps due to insufficient clinician training on this topic. The WHO guidelines for serodiscordant couples offer some safer conception recommendations, in addition, a more comprehensive guideline was recently published by the Southern African HIV Clinicians Society and will be helpful for clinicians [32, 54]. HCW training on the interpretation and application of these guidelines should be a priority for promoting comprehensive reproductive health counseling.

We found that, in this sample, male participants were eager to engage with HCWs in order to seek reproductive counseling. Prior data suggests that providers may have less insight into male reproductive intentions [31] and that men are less likely to seek advice from providers [38]. We previously published on the important role of men in conception decisions from an earlier analysis of these data [33], an observation which has been reported by others [9, 11, 12, 36, 59–61]. As reproductive counseling is integrated into HIV care, it will be crucial to increase male involvement. Interventions to engage men in contraception and family planning have been effective in several sub-Saharan African settings [61–63]. In addition, the dyadic nature of conception decisions and periconception risk behavior emphasizes the importance of a couple-oriented counseling approach when feasible [44].

The main limitations of the data are inherent to qualitative research—findings from this small qualitative sample are meant to generate hypotheses to pursue in future larger scale research. In addition, our participants were attending clinical services at a semiprivate hospital and may not represent the broader population who access public sector care or those who do not access any healthcare. While this clinic does not have a formal program for safer conception counseling, several of the authors previously worked at this clinic which may have heightened some of the clinic providers' awareness around reproductive counseling for people living with HIV. Finally, patient perspectives of past experiences with provider counseling may not accurately reflect what occurred; provider perspectives are also needed to understand current practices.

5. Conclusion

These are the first data to explore patient experiences with provider provision of reproductive counseling in KwaZulu Natal, where 41% of women attending antenatal clinics are HIV infected [45]. This work suggests that men and women living with HIV are aware that safer conception options may be available and are interested in accessing this information. Further, there is a clear need to expand the quality and reach of periconception risk reduction information to both providers and patients. These data serve as important hypothesis generation to guide future research as reproductive counseling interventions are developed.

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References

[1] J. L. Chen, K. A. Phillips, D. E. Kanouse, R. L. Collins, and A. Miu, "Fertility desires and intentions of HIV-positive men and women," *Perspectives on Sexual and Reproductive Health*, vol. 33, no. 4, pp. 144–165, 2001.

[2] L. C. G. Frodsham, F. Boag, S. Barton, and C. Gilling-Smith, "Human immunodeficiency virus infection and fertility care

in the United Kingdom: demand and supply," *Fertility and Sterility*, vol. 85, no. 2, pp. 285–289, 2006.

[3] L. Panozzo, M. Battegay, A. Friedl et al., "High risk behaviour and fertility desires among heterosexual HIV-positive patients with a serodiscordant partner—two challenging issues," *Swiss Medical Weekly*, vol. 133, no. 7-8, pp. 124–127, 2003.

[4] I. Heard, R. Sitta, F. Lert et al., "Reproductive choice in men and women living with HIV: evidence from a large representative sample of outpatients attending French hospitals (ANRS-EN12-VESPA study)," *AIDS*, vol. 21, supplement 1, pp. S77–S82, 2007.

[5] L. Myer, C. Morroni, and K. Rebe, "Prevalence and determinants of fertility intentions of HIV-infected women and men receiving antiretroviral therapy in South Africa," *AIDS Patient Care and STDs*, vol. 21, no. 4, pp. 278–285, 2007.

[6] S. G. Brubaker, E. A. Bukusi, J. Odoyo, J. Achando, A. Okumu, and C. R. Cohen, "Pregnancy and HIV transmission among HIV-discordant couples in a clinical trial in Kisumu, Kenya," *HIV Medicine*, vol. 12, no. 5, pp. 316–321, 2011.

[7] A. Kaida, I. Andia, M. Maier et al., "The potential impact of antiretroviral therapy on fertility in sub-Saharan Africa," *Current HIV/AIDS Reports*, vol. 3, no. 4, pp. 187–194, 2006.

[8] M. Maier, I. Andia, N. Emenyonu et al., "Antiretroviral therapy is associated with increased fertility desire, but not pregnancy or live birth, among HIV+ women in an early HIV treatment program in rural Uganda," *AIDS and Behavior*, vol. 13, no. 1, pp. S28–S37, 2009.

[9] J. Beyeza-Kashesya, A. M. Ekstrom, F. Kaharuza, F. Mirembe, S. Neema, and A. Kulane, "My partner wants a child: a cross-sectional study of the determinants of the desire for children among mutually disclosed sero-discordant couples receiving care in Uganda," *BMC Public Health*, vol. 10, article 247, 2010.

[10] J. Homsy, R. Bunnell, D. Moore et al., "Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study," *PLoS ONE*, vol. 4, no. 1, Article ID e4149, 2009.

[11] S. Nakayiwa, B. Abang, L. Packel et al., "Desire for children and pregnancy risk behavior among HIV-infected men and women in Uganda," *AIDS and Behavior*, vol. 10, supplement 1, pp. S95–S104, 2006.

[12] O. Awiti Ujiji, A. M. Ekström, F. Ilako, D. Indalo, and B. Rubenson, "'I will not let my HIV status stand in the way.' Decisions on motherhood among women on ART in a slum in Kenya- a qualitative study," *BMC Women's Health*, vol. 10, article 13, 2010.

[13] B. Auvert, D. Taljaard, E. Lagarde, J. Sobngwi-Tambekou, R. Sitta, and A. Puren, "Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial," *PLoS Medicine*, vol. 2, no. 11, article e298, 2005.

[14] R. C. Bailey, S. Moses, C. B. Parker et al., "Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial," *The Lancet*, vol. 369, no. 9562, pp. 643–656, 2007.

[15] R. H. Gray, G. Kigozi, D. Serwadda et al., "Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial," *The Lancet*, vol. 369, no. 9562, pp. 657–666, 2007.

[16] M. S. Cohen, Y. Q. Chen, M. McCauley et al., "Prevention of HIV-1 infection with early antiretroviral therapy," *The New England Journal of Medicine*, vol. 365, no. 6, pp. 493–505, 2011.

[17] D. Donnell, J. M. Baeten, J. Kiarie et al., "Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis," *The Lancet*, vol. 375, no. 9731, pp. 2092–2098, 2010.

[18] S. Attia, M. Egger, M. Müller, M. Zwahlen, and N. Low, "Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis," *AIDS*, vol. 23, no. 11, pp. 1397–1404, 2009.

[19] Q. A. Karim, S. S. A. Karim, J. A. Frohlich et al., "Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women," *Science*, vol. 329, no. 5996, pp. 1168–1174, 2010.

[20] R. M. Grant, J. R. Lama, P. L. Anderson et al., "Preexposure chemoprophylaxis for HIV prevention in men who have sex with men," *The New England Journal of Medicine*, vol. 363, no. 27, pp. 2587–2599, 2010.

[21] J. M. Baeten, D. Donnell, P. Ndase et al., "ARV PrEP for HIV-1 prevention among hetersexual men and women," in *Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections (CROI '12)*, Washington, Seattle, USA, 2012.

[22] M. C. Thigpen, P. M. Kebaabetswe, D.K. Smith et al., "Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study," in *Proceedings of the 6th IAS International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention*, Rome, Italy, 2011.

[23] P. Barreiro, J. A. Castilla, P. Labarga, and V. Soriano, "Is natural conception a valid option for HIV-serodiscordant couples?" *Human Reproduction*, vol. 22, no. 9, pp. 2353–2358, 2007.

[24] L. T. Matthews and J. S. Mukherjee, "Strategies for harm reduction among HIV-affected couples who want to conceive," *AIDS and Behavior*, vol. 13, supplement 1, pp. S5–S11, 2009.

[25] L. T. Matthews, J. M. Baeten, C. Celum, and D. R. Bangsberg, "Periconception pre-exposure prophylaxis to prevent HIV transmission: benefits, risks, and challenges to implementation," *AIDS*, vol. 24, no. 13, pp. 1975–1982, 2010.

[26] M. A. Lampe, D. K. Smith, G. J. E. Anderson, A. E. Edwards, and S. R. Nesheim, "Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States," *American Journal of Obstetrics and Gynecology*, vol. 204, no. 6, pp. 488.e1–488.e8, 2011.

[27] P. L. Vernazza, I. Graf, U. Sonnenberg-Schwan, M. Geit, and A. Meurer, "Pre-exposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child," *AIDS*, vol. 25, no. 16, pp. 2005–2008, 2011.

[28] CDC, "Recommendations for assisting in the prevention of perinatal transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus and acquired immunodeficiency syndrome," *MMWR*, vol. 34, no. 48, pp. 721–726, 731.

[29] Ethics Committee of the American Society for Reproductive Medicine, "Special considerations regarding human immunodeficiency virus and assisted reproductive technologies," *Fertility and Sterility*, vol. 62, Supplement 1, p. 85S, 1994.

[30] CDC, "Revised guidelines for HIV counseling, testing, and referral," *MMWR*, vol. 50, no. 19, pp. 1–57, 2001.

[31] J. Harries, D. Cooper, L. Myer, H. Bracken, V. Zweigenthal, and P. Orner, "Policy maker and health care provider perspectives on reproductive decision-making amongst HIV-infected individuals in South Africa," *BMC Public Health*, vol. 7, article 282, 2007.

[32] L. G. Bekker, V. Black, L. Myer et al., "Guideline on safer conception in fertile HIV-infected individuals and couples," *Southern African Journal of HIV Medicine*, no. 40, pp. 31–44, 2011.

[33] L. T. Matthews, T. Crankshaw, J. Giddy et al., "Decision-making and periconception practices among HIV-positive men and women attending HIV services in Durban, South Africa," *AIDS and Behavior*. In press.

[34] S. R. Schwartz, S. H. Mehta, T. E. Taha, H. V. Rees, F. Venter, and V. Black, "High pregnancy intentions and missed opportunities for patient-provider communication about fertility in a South African cohort of HIV-positive women on antiretroviral therapy," *AIDS and Behavior*, vol. 16, no. 1, pp. 69–78, 2011.

[35] S. Finocchario-Kessler, J. K. Dariotis, M. D. Sweat et al., "Do HIV-infected women want to discuss reproductive plans with providers, and are those conversations occurring?" *AIDS Patient Care and STDs*, vol. 24, no. 5, pp. 317–323, 2010.

[36] D. Cooper, J. Harries, L. Myer, P. Orner, and H. Bracken, "'Life is still going on': reproductive intentions among HIV-positive women and men in South Africa," *Social Science and Medicine*, vol. 65, no. 2, pp. 274–283, 2007.

[37] M. L. Gogna, M. M. Pecheny, I. Ibarlucía, H. Manzelli, and S. B. López, "The reproductive needs and rights of people living with HIV in Argentina: health service users' and providers' perspectives," *Social Science and Medicine*, vol. 69, no. 6, pp. 813–820, 2009.

[38] D. Cooper, J. Moodley, V. Zweigenthal, L. G. Bekker, I. Shah, and L. Myer, "Fertility intentions and reproductive health care needs of people living with HIV in Cape Town, South Africa: implications for integrating reproductive health and HIV Care services," *AIDS and Behavior*, vol. 13, supplement 1, pp. S38–S46, 2009.

[39] V. Paiva, E. Ventura Filipe, N. Santos, T. Novaes Lima, and A. Segurado, "The right to love: the desire for parenthood among men living with HIV," *Reproductive Health Matters*, vol. 11, no. 22, pp. 91–100, 2003.

[40] L. Myer, K. Rebe, and C. Morroni, "Missed opportunities to address reproductive health care needs among HIV-infected women in antiretroviral therapy programmes," *Tropical Medicine and International Health*, vol. 12, no. 12, pp. 1484–1489, 2007.

[41] M. B. Laws, Y. S. Bradshaw, S. A. Safren et al., "Discussion of sexual risk behavior in HIV care is infrequent and appears ineffectual: a mixed methods study," *AIDS and Behavior*, vol. 15, no. 4, pp. 812–822, 2011.

[42] C. Sprague, M. F. Chersich, and V. Black, "Health system weaknesses constrain access to PMTCT and maternal HIV services in South Africa: a qualitative enquiry," *AIDS Research and Therapy*, vol. 8, article 10, 2011.

[43] H. van Rooyen, K. Durrheim, and G. Lindegger, "Advice-giving difficulties in voluntary counselling and testing: a distinctly moral activity," *AIDS Care*, vol. 23, no. 3, pp. 281–286, 2011.

[44] T. Crankshaw, L. T. Matthews, J. Giddy et al., "A conceptual framework for periconception HIV transmission risk reduction among HIV serodiscordant couples," *Reproductive Health Matters*. In press.

[45] National Department of Health, South Africa, *National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa*, National Department of Health, Pretoria, South Africa, 2010.

[46] A. Strauss and J. M. Corbin, *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory*, Sage, Thousand Oaks, Calif, USA, 1998.

[47] P. R. Ulin, E. T. Robinson, and E. E. Tolley, *Qualitative Methods in Public Health: A Field Guide For Applied Research*, Jolley-Bass, San Francisco, Calif, USA, 2005.

[48] National Department of Health, South Africa, Clinical guidelines for the managment of HIV & AIDS in adults and adolescents, 2010.

[49] A. Kaida, F. Laher, S. A. Strathdee et al., "Childbearing intentions of HIV-positive women of reproductive age in Soweto, South Africa: the influence of expanding access to haart in an hiv hyperendemic setting," *American Journal of Public Health*, vol. 101, no. 2, pp. 350–358, 2011.

[50] P. Orner, D. Cooper, L. Myer, V. Zweigenthal, L. G. Bekker, and J. Moodley, "Clients' perspectives on HIV/AIDS care and treatment and reproductive health services in South Africa," *AIDS Care*, vol. 20, no. 10, pp. 1217–1223, 2008.

[51] D. McCarraher, C. Cuthbertson, D. Kung'U, C. Otterness, L. Johnson, and G. Magiri, "Sexual behavior, fertility desires and unmet need for family planning among home-based care clients and caregivers in Kenya," *AIDS Care*, vol. 20, no. 9, pp. 1057–1065, 2008.

[52] P. Barreiro, J. Del Romero, M. Leal et al., "Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy," *Journal of Acquired Immune Deficiency Syndromes*, vol. 43, no. 3, pp. 324–326, 2006.

[53] R. J. Chadwick, J. E. Mantell, J. Moodley, J. Harries, V. Zweigenthal, and D. Cooper, "Safer conception interventions for HIV-affected couples: implications for resource-constrained settings," *Topics in Antiviral Medicine*, vol. 19, no. 4, pp. 148–155, 2011.

[54] Wold Health Organization, *Guidance on Couples HIV Testing and Counselling Including Antiretroviral Therapy For Treatment and Prevention in Serodiscordant Couples*, World Health Organization, Geneva, Switzerland, 2012.

[55] C. MacPhail, A. E. Pettifor, S. Pascoe, and H. V. Rees, "Contraception use and pregnancy among 15–24 year old South African women: a nationally representative cross-sectional survey," *BMC Medicine*, vol. 5, article 31, 2007.

[56] Department of Health South Africa, *Medical Research Council, and OrcMacro, South Africa Demographic and Health Survey 2003*, Department of Health, Pretoria, South Africa, 2007.

[57] A. Harrison and L. F. O'Sullivan, "In the absence of marriage: long-term concurrent partnerships, pregnancy, and HIV risk dynamics among South African young adults," *AIDS and Behavior*, vol. 14, no. 5, pp. 991–1000, 2010.

[58] G. Wagner, S. Linnemayr, C. Kityo, and P. Mugyenyi, "Factors associated with intention to conceive and its communication to providers among HIV clients in Uganda," *Maternal and Child Health Journal*, pp. 1–9, 2011.

[59] S. Yeatman, "HIV infection and fertility preferences in rural Malawi," *Studies in Family Planning*, vol. 40, no. 4, pp. 261–276, 2009.

[60] D. J. Smith and B. C. Mbakwem, "Life projects and therapeutic itineraries: marriage, fertility, and antiretroviral therapy in Nigeria," *AIDS*, vol. 21, supplement 5, pp. S37–S41, 2007.

[61] UNDP/UNFPA/WHO/ World Bank Special Programme of Research, Development and Research Training in Human Reproduction, "Programming for male involvement in reproductive health," Report of the Meeting of WHO Regional Advisors in Reproductive Health WHO/PAHO, WHO, Washington, DC, USA, 2001.

[62] D. Shattuck, B. Kerner, K. Gilles, M. Hartmann, T. Ng'ombe, and G. Guest, "Encouraging contraceptive uptake by motivating men to communicate about family planning: the Malawi

Male Motivator project," *American Journal of Public Health*, vol. 101, no. 6, pp. 1089–1095, 2011.

[63] A. Terefe and C. P. Larson, "Modern contraception use in Ethiopia: does involving husbands make a difference?" *American Journal of Public Health*, vol. 83, no. 11, pp. 1567–1571, 1993.

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Review Article

Contraception for the HIV-Positive Woman: A Review of Interactions between Hormonal Contraception and Antiretroviral Therapy

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Background. Preventing unintended pregnancy in HIV-positive women can significantly reduce maternal-to-child HIV transmission as well as improve the woman's overall health. Hormonal contraceptives are safe and effective means to avoid unintended pregnancy, but there is concern that coadministration of antiretroviral drugs may alter contraceptive efficacy. *Materials and Methods*. We performed a literature search of PubMed and Ovid databases of articles published between January 1980 and February 2012 to identify English-language reports of drug-drug interactions between hormonal contraceptives (HCs) and antiretroviral drugs (ARVs). We also reviewed the FDA prescribing information of contraceptive hormone preparations and antiretrovirals for additional data and recommendations. *Results*. Twenty peer-reviewed publications and 42 pharmaceutical package labels were reviewed. Several studies of combined oral contraceptive pills (COCs) identified decreased serum estrogen and progestin levels when coadministered with certain ARVs. The contraceptive efficacy of injectable depot medroxyprogesterone acetate (DMPA) and the levonorgestrel intrauterine system (LNG-IUS) were largely unaffected by ARVs, while data on the contraceptive patch, ring, and implant were lacking. *Conclusions*. HIV-positive women should be offered a full range of hormonal contraceptive options, with conscientious counseling about possible reduced efficacy of COCs and the contraceptive implant when taken with ARVs. DMPA and the LNG-IUS maintain their contraceptive efficacy when taken with ARVs.

1. Introduction

The face of the HIV/AIDS epidemic has changed dramatically since its emergence in the 1980s. Far from its origins as an illness of homosexual men, HIV/AIDS is increasingly affecting women around the world: in 2008, women made up nearly half of the global population of those infected with HIV (15.7 million women, 33.4 million total) [1]. While spread of the epidemic has slowed, addressing the health needs of women infected with HIV remains an important priority. Recent efforts have largely focused on expanding access to HIV diagnosis and counseling, as well as treatment with highly-active antiretroviral therapy (HAART). Providing reproductive health services to women living with HIV is crucial to improving their overall health. Preventing unplanned or mistimed pregnancy allows a woman with HIV to optimize her own health and has the potential to decrease maternal-to-child transmission of HIV. The World Health Organization (WHO) reports that approximately 90% of children living with HIV acquired the infection perinatally—during pregnancy, birth, or breastfeeding [1]. In a model comparing interventions to decrease maternal-to-child transmission (MTCT) of HIV, increasing use of contraception was found to prevent 28.6% more HIV-positive births than increasing use of peripartum nevirapine [2]. Effective contraception thus offers great opportunity to slow the spread of perinatally acquired HIV, though sexual transmission of HIV may still occur between serodiscordant couples.

As access to both modern methods of contraception and antiretroviral drugs (ARVs) expands, women with HIV enter the largely uncharted territory of potential drug interactions. In this paper we will summarize the available literature regarding coadministration of ARVs and hormonal contraception, with a focus on whether ARVs lead to alterations in hormonal contraceptive efficacy.

Modern hormonal birth control methods available in the United States include daily pills (combined oral contraceptives (COCs) that contain estrogen and a progestin, as well as progestin-only pills (POPs)), a weekly combined hormonal patch, a monthly combined hormonal vaginal ring, injectable depot medroxyprogesterone acetate (DMPA) given every three months, a three-year etonogestrel (progestin) implantable rod, and a five-year levonorgestrel intrauterine system (LNG-IUS). The latter two are often described as long-acting reversible contraceptives (LARCs). All of these methods are highly effective at preventing pregnancy, with the typical-use failure rate ranging from 0.1% (LNG-IUS) to 8% (POPs, COCs, ring) [3]. Hormonal emergency contraceptives (ECs) are also available, which reduce the risk of pregnancy by 89% when taken within 72 hours of unprotected sex [3]. Contraceptive hormones are metabolized by the hepatic cytochrome (CYP) P450 pathway, which is also responsible for the metabolism of many ARVs [4]. Orally administered contraceptive hormones are subject to extensive first-pass gut and hepatic metabolism, which necessitates higher estrogen and progestin doses than those required when these hormones are given via routes that lead to minimal first-pass metabolism [5]. Whether novel delivery systems (i.e., transdermal or transvaginal) affect the pharmacokinetics of contraceptive hormones, and how these drugs will interact with ARVs, remains unclear. It is also uncertain how LARC methods interact with HAART regimens.

Contraceptive steroids mainly work by negative feedback inhibition of the hypothalamic-pituitary-ovarian (HPO) axis, with additional effects on cervical mucus and the endometrium. Exogenous estrogen and progestin both profoundly suppress pulsatile secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [6, 7]. However, most of the contraceptive effects (i.e., ovulation suppression, thinning of the endometrium, and cervical mucus thickening) are due primarily to progestin and are dose-dependent [6, 8]. Ethinyl estradiol (EE), the estrogenic component of most currently marketed COCs, is primarily metabolized through the hepatic CYP pathway. Specifically, hydroxylation of EE is catalyzed by the hepatic enzymes CYP3A4 and CYP2C9. Wide variation in the levels of these enzymes among individuals is thought to contribute significantly to large intersubject variability of EE pharmacokinetics [9]. The contraceptive progestins available today also vary widely in their metabolism and pharmacokinetics, with large intersubject and intrasubject variability [10].

Modern management of HIV typically involves a combination of ARVs, commonly described as highly active antiretroviral therapy (HAART), since monotherapy can lead to the development of viral resistance to drug therapy. In treatment-naïve patients, a starting regimen typically includes two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), two NRTIs and a nonnucleoside reverse transcriptase inhibitor (NNRTI), or three NRTIs [11]. Table 1 lists the five preferred regimens described by the Department of Health and Human Services (DHHS). Ritonavir, a protease inhibitor, is rarely used for its own antiretroviral activity, but is used for its inhibitory effect on CYP3A4, the liver enzyme that normally metabolizes protease inhibitors. A low dose of ritonavir is used to enhance, or "boost," other protease inhibitors, thereby improving ARV efficacy.

This paper will examine the available evidence regarding drug interactions between ARVs and all types of hormonal contraception (HC), including transdermal and transvaginal routes as well as LARC options. Pertinent pharmacokinetic (PK) parameters, such as the maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), half-life ($t_{1/2}$), and the area under the concentration-time curve (AUC), will be discussed for each drug interaction, when available. We will also include recommendations made in the Centers for Disease Control and Prevention Medical Eligibility Criteria (CDC MEC). This tool provides evidence-based recommendations about appropriate use of contraceptives in women with various medical comorbidities, including HIV. The document cross-references contraceptive methods and medical conditions, assigning a recommendation category to each combination of these. These categories are as follows: Category 1—a condition for which there is no restriction for use of the contraceptive method; Category 2—a condition for which the advantages of using the method generally outweigh the theoretical or proven risks; Category 3—a condition for which the theoretical or proven risks usually outweigh the advantages of using the method; Category 4—a condition that represents an unacceptable health risk if the contraceptive method is used [35].

2. Materials and Methods

We performed a literature search using PubMed and Ovid databases to identify English-language articles published from January 1980 to February 2012. Search terms included contraception, hormonal contraception, contraceptives, hormonal contraceptives, birth control, HIV, family planning, and the generic names of individual ARVs and HC components: abacavir, amprenavir, atazanavir, darunavir, delavirdine, didanosine, efavirenz, emtricitabine, enfuvirtide, etravirine, fosamprenavir, indinavir, lamivudine, lopinavir, maraviroc, nelfinavir, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, tenofovir, tipranavir, zalcitabine, zidovudine, ethinyl estradiol, ethynodiol diacetate, etonogestrel, levonorgestrel, depot medroxyprogesterone acetate, norethindrone, desogestrel, drospirenone, norgestrel, norgestimate, mifepristone, and ulipristal. We included randomized and nonrandomized trials, observational studies, and case reports that provided pharmacokinetic data for any of the hormonal contraceptives. Hand searches of relevant journals, references

Table 1: DHHS preferred antiretroviral regimens for antiretroviral therapy-naïve patients [11].

NNRTI-based regimen	Efavirenz (NNRTI) + tenofovir (NRTI) + emtricitabine (NRTI)
PI-based regimens	Atazanavir/ritonavir (PI) + tenofovir (NRTI) + emtricitabine (NRTI) Darunavir/ritonavir (once daily) (PI) + tenofovir (NRTI) + emtricitabine (NRTI)
INSTI-based regimen	Raltegravir (II) + tenofovir (NRTI) + emtricitabine (NRTI)
Preferred regimen for pregnant women	Lopinavir/ritonavir (twice daily) (PI) + zidovudine (NRTI) + lamivudine (NRTI)

Abbreviations. NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleos(t)ide reverse transcriptase inhibitor; PI: protease inhibitor; INSTI (II): integrase strand transfer inhibitor.

from review articles, and conference abstracts were performed, and pharmaceutical package labels for individual drugs/methods were also reviewed. Results are presented according to type of contraceptive method.

3. Results

A total of 20 published studies or abstracts were identified and included, as were 42 FDA-mandated package labels published by pharmaceutical companies. Package labels that did not include any data about drug interactions between hormonal contraceptives and ARVs are not reported.

3.1. Combined (Estrogen + Progestin) Methods

3.1.1. Combined Oral Contraceptives (COCs). A review of the FDA labeling of a selection of COC yields mixed advice about interactions with antiretroviral drugs. Labels for three COCs (EE/norgestrel (Lo/Ovral), EE/levonorgestrel (Alesse), and EE/norgestimate (Ortho Tri-Cyclen)) mention possible interaction with protease inhibitors (PI) and refer providers to the PI label for additional information [36–38]. Labels for two other COCs (EE/drospirenone (Yaz) and EE/desogestrel (Mircette)) warn of potential decreased contraceptive efficacy when taken with enzyme-inducing drugs such as anticonvulsants or rifampin, but there is no reference to specific studies about potential interactions with ARV [39, 40].

The package labels of various ARVs offer some more detailed information. Of the ten PIs available in the United States, all package labels provide data regarding interactions between the PI and COCs. Seven PIs (amprenavir, darunavir, lopinavir, nelfinavir, tipranavir, saquinavir, and ritonavir) were associated with decreases in pharmacokinetic parameters of both estrogen and progestin components of the coadministered COC, and the labels consequently recommended that women use an additional barrier method or rely on nonhormonal contraceptives [13, 14, 41–45]. These conclusions emphasized the decrease in serum EE concentrations as a reason to avoid COCs, despite the fact that most contraceptive activity of COCs is provided by the progestin.

Atazanavir has differing effects on COC metabolism, depending on whether or not it is coadministrated with ritonavir. When women took EE/norethindrone (NET) and atazanavir alone on days 16 to 29 of the COC cycle, there was an increase in the serum concentrations of both EE and norethindrone (Table 2) [12]. However, when atazanavir combined with ritonavir was coadministrated with EE/norgestimate on days 29 to 42 after a full cycle of the COC, concentrations of EE were decreased while levels of norgestimate were increased. The manufacturer of atazanavir advises that women use a pill with at least 35 mcg EE in the setting of ritonavir-boosted atazanavir, but to use a pill with no more than 30 mcg of EE if atazanavir was the sole protease inhibitor [12]. These recommendations are potentially confusing for practitioners seeking clinical advice.

The earliest peer-reviewed study identified in our paper was a 1998 open-label trial of ritonavir and a COC containing EE/ethynodiol diacetate [16]. A total of 23 healthy, HIV-negative women were included in the analysis, each of whom received a dose of the COC on study days 1 and 29. From day 16 to 29, subjects took escalating doses of ritonavir to a maximum dose of 500 mg every 12 hours. Serial blood samples were collected over 48 hours following each dose of COC. Compared to the COC dose given on study day 1, the dose given on day 29 resulted in a 32% lower EE mean C_{max} ($P < 0.001$) and 41% lower mean AUC ($P < 0.001$). The authors noted that one subject who missed the morning dose of ritonavir on day 29 still showed a 31% decrease in EE AUC, "suggesting enzyme induction rather than altered absorption as the probable cause of the interaction" [16].

Mildvan et al. studied the interactions between steady-state nevirapine and a single dose of EE/NET [18]. Fourteen HIV-positive women aged 26 to 47 years with a stable ARV regimen for at least 4 weeks were enrolled, and 10 completed the study. Subjects received one dose of the study COC on day 0, followed by intense plasma sampling over the next 48 hours. They then received nevirapine for the next 28 days, with typical escalation of the dose from week 2 to week 3 (Table 2). They received a second dose of the COC on day 30 along with the scheduled dose of nevirapine, followed by additional plasma sampling. Participants continued ARV therapy during the study period. Compared to the COC taken alone, EE administered with nevirapine had a 29% decrease in median AUC ($P = 0.014$), but no change in C_{max}, and a decrease in mean terminal half-life from 16.6 hours to 12.5 hours ($P = 0.010$). Norethindrone demonstrated an 18% decrease in median AUC when COC was given with nevirapine, compared to the COC given alone ($P = 0.016$). The authors concluded that nevirapine increases the systemic clearance of EE and NET, with the potential of lowering concentrations to subtherapeutic levels. The authors provide no definition of what constitutes a subtherapeutic level of EE or norethindrone. They suggest that, in the absence of

Table 2: Summary of pharmacokinetic interactions (results are given as geometric mean ratios of HC + ARV to HC alone, with 90% confidence intervals, unless otherwise specified).

Drug *Subclass*	Source and number of patients	Effect on hormonal contraceptives
Atazanavir (Reyataz) *Protease inhibitor*	Reyataz package label [12]	
	$N = 19$	EE 35 mcg/NET (0.5 mg/0.75 mg/1 mg) (day 1–29) + ATV 400 mg daily (day 16–29) (i) EE C_{max} increased 15% (0.99–1.32) (ii) EE AUC increased 48% (1.31–1.68) (iii) EE C_{min} increased 91% (1.57–2.33) (iv) NET C_{max} increased 67% (1.42–1.96) (v) NET AUC increased 110% (1.68–2.62) (vi) NET C_{min} increased 362% (2.57–5.09)
	$N = 14$	EE 35 mcg/NGM (0.18 mg/0.215 mg/0.25 mg) (day 1–28), then EE 25 mcg/NGM (0.18 mg/0.215 mg/0.25 mg) (day 29–42) + ATV/r 300/100 daily (day 29–42) (i) EE C_{max} decreased 16% (0.74–0.95) (ii) EE AUC decreased 19% (0.75–0.87) (iii) EE C_{min} decreased 37% (0.55–0.71) (iv) 17-deacetyl norgestimate C_{max} increased 68% (1.51–1.88) (v) 17-deacetyl norgestimate AUC increased 85% (1.67–2.05) (vi) 17-deacetyl norgestimate C_{min} increased 102% (1.77–2.31)
Nelfinavir (Viracept) *Protease inhibitor*	Viracept package label [13]	
	$N = 12$	EE 35 mcg/NET 0.4 mg (day 1–15) + NFV 750 mg q 8 h for 7 days (i) Decreased EE C_{max} by 28% (ii) Decreased EE AUC by 47% (iii) Decreased EE C_{min} by 62% (iv) No effect on NET C_{max} (v) Decreased NET AUC by 18% (vi) Decreased NET C_{min} by 46%
Lopinavir/ritonavir (Kaletra) *Protease inhibitor*	Kaletra package label [14]	
	$N = 12$	EE 35 mcg/NET 1 mg po daily (21 days) + LPV/r 400/100 po bid (14 days) (i) EE C_{max} decreased 41% (0.52–0.66) (ii) EE AUC decreased 42% (0.54–0.62) (iii) EE C_{min} decreased 58% (0.36–0.49) (iv) NET C_{max} decreased 16% (0.75–0.94) (v) NET AUC decreased 17% (0.73–0.94) (vi) NET C_{min} decreased 32% (0.54–0.85)
	Vogler et al. [15]	
		EE 35 mcg/NET 1 mg po (day 1) EE/NGM patch (day 3–24, new patch every 7 days) + LPV/r (400/100 bid) and stable NRTIs (treatment arm) or no ARV or NRTIs only (control arm) (i) COC (a) EE AUC decreased 55% ($P = 0.003$) (b) EE C_{48} decreased 76% ($P = 0.023$)

Table 2: Continued.

Drug *Subclass*	Source and number of patients	Effect on hormonal contraceptives
	$N = 8$ (treatment arm) $N = 24$ (control arm)	(ii) Patch (a) EE AUC decreased 45% ($P = 0.064$) (b) EE C_{min} decreased 28% ($P = 0.395$) (c) NGMN AUC increased 83% ($P = 0.036$) (d) NGMN C_{min} increased 134% ($P = 0.036$)
Ritonavir (Norvir) *Protease inhibitor*	Ouellet et al. [16]	
	$N = 23$	Day 1: EE 50 mcg/ethynodiol diacetate 1 mg Day 15: RTV 300 mg q 12 h Day 16: RTV 400 mg q 12 h Days 17–30: RTV 500 mg q 12 h Day 29: 2nd dose of EE 50 mcg/ethynodiol diacetate 1 mg Ratio of means with 95% CI (i) EE C_{max} decreased 32% (0.612–0.758, $P < 0.001$) (ii) EE AUC decreased 40% (0.506–0.694, $P < 0.001$) (iii) Ethynodiol diacetate levels not measured
Nevirapine (Viramune) *NNRTI*	Viramune package label [17]	
	$N = 10$	EE 35 mcg/NET 1 mg + NVP 200 mg daily × 14 days, then bid × 14 days (i) EE C_{max}—no change (ii) EE AUC decreased 20% (iii) EE C_{min} undetectable (iv) NET C_{max} decreased 16% (v) NET AUC decreased 19% (vi) NET C_{min} undetectable
	$N = 32$	DMPA 150 mg IM q 3 months + NVP 200 mg po daily × 14 days, then 200 mg po bid × 14 days (i) No change in DMPA AUC, C_{max}, or C_{min}
	Mildvan et al. [18]	
	$N = 10$	Day 0: EE 35 mcg/NET 1 mg Day 2–15: NVP 200 mg po daily Day 16–29: NVP 200 mg bid Day 30: NVP 200 mg bid + EE 35 mcg/NET 1 mg (i) EE C_{max} decreased 2% (0.78–1.17, $P = 0.770$) (ii) EE AUC decreased 22% (0.54–1.02, $P = 0.014$) (iii) EE $t_{1/2}$ (12.5 ± 3.8 hrs versus 16.9 ± 4.8 hrs, $P = 0.010$) (iv) NET C_{max} decreased 14% (0.72–1.01, $P = 0.123$) (v) NET AUC decreased 18% (0.67–0.96, $P = 0.016$) (vi) NET $t_{1/2}$ 11.5 ± 3.7 hrs versus 12.3 ± 5.3 hrs ($P = 0.389$)
Efavirenz (Sustiva) *NNRTI*	Sustiva package label [19]	
	$N = 21$	EE 35 mcg/NGM 0.25 mg × 14 days + EFV 600 mg daily × 14 days (i) No change in EE C_{max}, AUC, C_{min} (ii) NGMN C_{max} decreased 46% (39%–52%) (iii) NGMN AUC decreased 64% (62%–67%) (iv) NGMN C_{min} decreased 82% (79%–85%) (v) LNG C_{max} decreased 80% (77%–83%)

Table 2: Continued.

Drug *Subclass*	Source and number of patients	Effect on hormonal contraceptives
		(vi) LNG AUC decreased 83% (79%–87%)
		(vii) LNG C_{min} decreased 86% (80%–90%)
		ENG implant: decreases ENG (no data provided)
	Sevinsky et al. [20]	
		Cycle 1: EE 25 mcg/NGM 0.18 mg (day 1–7), 0.215 mg (day 8–14), 0.25 mg (day 15–21)
		Cycle 2: EE 35 mcg/NGM 0.25 mg (day 22–56)
		Cycle 3: EE 35 mcg/NGM 0.25 mg (day 57–77) + EFV 600 mg daily (day 57–70)
		(i) EE C_{max} increased 6% (0.95–1.19)
	$N = 28$	(ii) EE AUC decreased 10% (0.80–1.01)
		(iii) EE C_{min} decreased 8% (0.75–1.14)
		(iv) NGMN C_{max} decreased 46% (0.48–0.61)
		(v) NGMN AUC decreased 64% (0.33–0.38)
		(vi) NGMN C_{min} decreased 82% (0.15–0.21)
Tenofovir (Viread) *NRTI*	Viread package label [17]	
		EE 35 mcg/NGM 0.18 mg + TDF
	$N = 20$	(i) No change in EE C_{max}, AUC, C_{min}
		(ii) No change in NGM C_{max}, AUC, C_{min}
Etravirine (Intelence) *NNRTI*	Intelence package label [21]	
		EE 35 mcg/NET 1 mg po daily + ETR 200 mg po bid
		(i) EE C_{max} increased 33% (1.21–1.46)
		(ii) EE AUC increased 22% (1.13–1.31)
	$N = 16$	(iii) EE C_{min} increased 9% (1.01–1.18)
		(iv) NET C_{max} increased 5% (0.98–1.12)
		(v) NET AUC decreased 5% (0.90–0.99)
		(vi) NET C_{min} decreased 22% (0.68–0.90)
	Schöller-Gyüre et al. [22]	
		Days 1–21: EE 35 mcg/NET 1 mg po daily
		Days 1-15: ETR 200 mg po bid
		(i) EE C_{max} increased 33% (1.21–1.46)
		(ii) EE AUC increased 22% (1.13–1.31)
	$N = 24$	(iii) EE C_{min} increased 9% (1.01–1.18)
		(iv) NET C_{max} increased 5% (0.98–1.12)
		(v) NET AUC decreased 5% (0.90–0.99)
		(vi) NET C_{min} decreased 22% (0.68–0.90)
Raltegravir (Isentress) *Integrase inhibitor*	Anderson et al. [23]	
		EE 35 mcg/NGM 0.18 mg/0.215 mg/0.25 mg po daily + RAL 400 mg po bid or placebo (day 1–21)
		(i) EE C_{max} increased 6% (0.98–1.14, $P = 0.2351$)
	$N = 19$	(ii) EE AUC decreased 2% (0.93–1.04, $P = 0.5843$)
		(iii) NGMN AUC increased 14% (1.008–1.21, $P = 0.0011$)
		(iv) NGMN C_{max} increased 29% (1.23–1.37, $P < 0.0001$)

Table 2: Continued.

Drug *Subclass*	Source and number of patients	Effect on hormonal contraceptives
"Quad" regimen: elvitegravir + cobicistat + emtricitabine + tenofovir	German et al. [24]	
	$N = 15$	EE 25 mcg/NGM 1 mg (day 1–21) + Quad (day 12–21): (i) EE AUC decreased 25% (ii) NGMN AUC increased 100% (iii) NGMN C_{max} increased 100%
Depot medroxyprogesterone acetate (Depo-Provera) *Injectable progesterone*	Cohn et al. [25]	
	$N = 70$	Group A (control)—no PI or NNRTIs Group B—NFV + NRTIs Group C—EFV + NRTIs Group D—NVP + NRTIs (i) All received DMPA on day 1. PK samples were drawn day 0 and after 4 weeks. (ii) No change in MPA C_{max}, AUC, C_{min}, or terminal half-life when coadministered with HAART regimens containing nelfinavir, efavirenz, or nevirapine (iii) MPA C_{max} range (including all groups): 0.32–3.7 ng/mL (iv) MPA C_{min} range (including all groups): 0.04–1.31 ng/mL (v) MPA AUC_{0-12} values are not reported
	Nanda et al. [26]	
	$N = 30$	Treatment group: 15 women on AZT/3TC/EFV Control group: 15 HIV+ women not on HAART Both groups received DMPA 150 mg IM on day 1 and had serum drawn every 2 weeks for 12 weeks total to assess MPA and serum progesterone levels (i) DMPA $AUC_{0-84\,d}$ increased 1% (0.85–1.20) (ii) DMPA C_{max} increased 1% (0.84–1.22) (iii) DMPA C_{min} decreased 10% (0.77–1.06)
Etonogestrel implant (Implanon) *Progesterone implant*	Matiluko et al. [27]	
	$N = 1$	Month 0: implant placed Month 13: HIV diagnosed, started AZT/3TC/EFV Month 16: diagnosed with ruptured ectopic pregnancy
	Lakhi and Govind [28]	
	$N = 2$	Patient 1 (i) July 2004: implant placed. (ii) January 2007: started EFV/FTC/TDF (iii) May 2007: diagnosed with intrauterine pregnancy Patient 2 (i) Conceived with implant in place after starting EFV/LPV (no timeline provided)

Table 2: Continued.

Drug *Subclass*	Source and number of patients	Effect on hormonal contraceptives
	McCarty et al. [29]	
	$N = 1$	June 2005: diagnosed with HIV August 2005: started AZT/3TC/EFV November 2005: implant placed April 2008: diagnosed with right ectopic pregnancy January 2009: diagnosed with left ectopic pregnancy
	Leticee et al. [30]	
	$N = 2$	Patient 1 (i) November 2002: started AZT/3TC/EFV (ii) January 2004: implant placed (iii) April 2006: diagnosed with intrauterine pregnancy, with conception estimated in Dec. 2005 based on ultrasound (23 months after implant placement) Patient 2 (i) 2001: HIV diagnosed (ii) July 2005: implant placed (iii) April 2007: started on EFV/TDF/FTC (iv) October 2007: pregnant after condom rupture
Levonorgestrel Intrauterine system (Mirena) *Progesterone IUD*	Heikinheimo et al. [31]	
	$N = 12$	LNG-IUS placed between cycle day 1–7. Serum drawn immediately before LNG-IUS insertion and at 1 week, 3 months, 6 months, and 12 months. No difference in serum LNG levels in HIV-positive women on HAART compared to HIV-positive women not on HAART (data presented graphically), and consistent with HIV negative historical controls
	Lehtovirta et al. [32]	
	$N = 6$	Retrospective review of 6 HIV-positive women with LNG-IUS. Two were treated with HAART, and 4 were on no ARVs. Mean duration of LNG-IUS use = 45 months (range 12–72 months). No PK assessments were performed. No pregnancies or adverse events were reported
	Heikinheimo et al. [33]	
	$N = 40$	Case-control study of 15 HIV-positive women using LNG-IUS and 25 HIV-positive women not using LNG-IUS was conducted. 54% of LNG-IUS users and 56% of controls were on HAART at beginning of followup, 73% and 76% were on HAART at the end of followup. No PK assessments were performed. No pregnancies and no differences in CD4 counts or HIV VL were seen between the two groups
Levonorgestrel emergency contraception (Plan B)	Carten et al. [34]	
	$N = 24$	Day 1: LNG 0.75 mg orally, PK blood sampling immediately before and for 12 hours after LNG dose Days 4–17: EFV 600 mg qhs Day 18: LNG 0.75 mg orally, PK blood sampling immediately before and for 12 hours after LNG dose (i) LNG $AUC_{0-12\,h}$ decreased 48% (0.36–0.48, $P < 0.0001$) (ii) LNG C_{max} decreased 45% (0.49–0.63, $P < 0.0001$) (iii) LNG C_{min} decreased 69% (0.26–0.36, $P < 0.0001$)

Abbreviations. EE: ethinyl estradiol, NET: norethindrone, NGM: norgestimate, NGMN: norelgestromin, LNG: levonorgestrel, ENG: etonogestrel, DMPA: depot medroxyprogesterone acetate, MPA: medroxyprogesterone acetate, C_{max}: maximum serum concentration, AUC: area under the concentration-time curve, C_{min}: minimum serum concentration, $t_{1/2}$: half-life, ATV: atazanavir, NFV: nelfinavir, LPV/r: lopinavir/ritonavir, NVP: nevirapine, ATV/r: atazanavir/ritonavir, EFV: efavirenz, AZT: zidovudine, 3TC: lamivudine, FTC: emtricitabine, TDF: tenofovir, LPV: lopinavir, ETR: etravirine.

more reassuring data, COCs should not be considered as a primary method of contraception in HIV-positive women taking nevirapine [18].

An open-label study of interactions between saquinavir and a low-dose COC containing EE/gestodene showed no effect on the pharmacokinetics of saquinavir [46]. Pharmacokinetic parameters for EE and gestodene were not assessed in this study, so it is unclear whether saquinavir impacts the efficacy of COCs.

The potential interactions between maraviroc (a CCR5 coreceptor antagonist, which blocks the ability of the HIV virus to enter a cell) and a COC were investigated in a double-blind, placebo-controlled, crossover study. Fifteen healthy HIV-negative women were given daily doses of EE/levonorgestrel (LNG) and either maraviroc (100 mg twice daily) or placebo [47]. There was no significant difference in the AUC or C_{max} for EE, LNG, or maraviroc between the two study arms, indicating that maraviroc has no effect on the pharmacokinetics of these hormones.

Schöller-Gyüre et al. studied EE/NET and concomitant use of etravirine (an NNRTI) in healthy HIV-negative women [22]. Participants took COC for two consecutive cycles (21 days of active pills followed by a pill-free week), then added etravirine during the first 15 days of cycle 3. Pharmacokinetic assessments performed on day 15 of COC cycles 2 and 3 revealed a 22% increase in EE AUC, a 33% increase in EE C_{max}, and a 9% increase in EE C_{min} when the COC was given with etravirine, while norethindrone had a 22% decrease in C_{min} but exhibited no change in AUC or C_{max}. Serum levels of LH, FSH, and progesterone were also measured on days 1 and 14 of cycle 3. There were no significant changes in any of these levels when etravirine was added compared to when the COC was taken alone. There was no serologic evidence of ovulation in any of the study participants. Ultimately, the authors concluded that COC could be used safely by women taking etravirine as their contraceptive efficacy appears to be maintained [22].

A recent study evaluated the effect of the PIs lopinavir and ritonavir on the pharmacokinetics of orally and transdermally administered hormonal contraceptives in HIV-infected women [15]. Participants in the treatment arm were taking a stable lopinavir/ritonavir dose in combination with dual NRTI therapy, while those in the control arm were taking NRTIs only or no ARV therapy at all. Women in the treatment and control arms all received a single dose of a COC containing EE/NET five to seven days after the start of menses, followed by serial blood samples. Participants applied the contraceptive patch (EE/norelgestromin) 48 hours after taking the single-dose COC, and serial blood sampling for PK parameters and progesterone was performed. There was a 55% decrease in EE AUC ($P = 0.003$) and a 76% decrease in serum EE concentration 48 hours after COC ingestion ($P = 0.023$) in the PI treatment arm compared to controls. (Results for the contraceptive patch in this study are discussed below.) Norelgestromin levels were not assessed in patients taking the COC, making any conclusions about COC contraceptive efficacy when coadministrated with lopinavir/ritonavir impossible.

Raltegravir is an HIV integrase strand transfer inhibitor which prevents the integration of HIV DNA into the host genome; it is not known to affect the activity of any CYP isoenzymes [48]. A randomized two-arm crossover study investigating interactions between raltegravir and a triphasic COC containing EE/norgestimate found no difference in EE PK parameters between the two groups. There were small decreases in the C_{min} and AUC of norelgestromin, the active metabolite of norgestimate, but these were not felt to be clinically significant [23].

Efavirenz is an NNRTI that is a potent inhibitor of CYP3A4 as well as a known teratogen [19]. Because efavirenz has been associated with neural tube defects, especially when exposure occurs in the first trimester, effective contraception is particularly important for HIV-positive women taking this drug. A study of healthy HIV-negative women evaluated the pharmacokinetic interaction between once-daily efavirenz and a COC containing EE/norgestimate [20]. Participants completed one 28-day cycle with a 25 mcg EE/triphasic norgestimate COC. All participants who had acceptable baseline safety evaluations during this first cycle took a higher-dose (35 mcg) EE/monophasic norgestimate (0.25 mg) COC for cycles 2 and 3, with 14 days of efavirenz taken during cycle 3 (days 57–70). Pharmacokinetic blood samples for EE (days 14, 42, and 70), norelgestromin (the active metabolite of norgestimate; days 42 and 70), and efavirenz (day 70) were drawn throughout the study. There was no difference in EE AUC between cycle 2 (35 mcg EE/0.25 mg norgestimate) and cycle 3 (35 mcg EE/0.25 mg norgestimate + 600 mg efavirenz), while there was a significant decrease in norelgestromin C_{max} (46%), AUC (64%), and C_{min} (82%) in cycle 3 compared to cycle 2. Despite the decrease in norelgestromin concentrations, serum progesterone levels remained low throughout all cycles, suggesting that ovulation was successfully suppressed during efavirenz administration.

Many ARVs are now formulated in combination pills to facilitate adherence with therapy. A new example of such a formulation is the "Quad" regimen, which contains elvitegravir (an investigational integrase inhibitor), cobicistat (an investigational pharmacoenhancer that has no antiretroviral activity itself, but is used to inhibit elvitegravir metabolism), and a common NRTI backbone of emtricitabine and tenofovir. In a Phase 1, open-label, fixed sequence study, 15 HIV-negative healthy women were given a COC containing EE/norgestimate for two 28-day cycles [24]. On days 12 to 21 of the second cycle, they were also given the Quad regimen. Serum sampling for EE and norelgestromin PK parameters was performed on day 21 of each cycle, and samples for PK of elvitegravir and cobicistat were performed on day 21 of the second cycle only. While there was a 25% decrease in EE AUC from the first to the second cycle, the AUC and C_{max} of norelgestromin doubled. There was no change in serum progesterone or FSH levels measured on day 21 of the treatment cycle compared to day 21 of the baseline cycle. Levels of LH were lower when the COC was given with the Quad regimen compared to the COC alone. Ultimately, the authors concluded that the contraceptive efficacy of the COC was maintained, but recommended that a COC with at least

30 mcg EE is considered in women taking the Quad regimen to offset the decreased EE levels noted when the two were taken together.

The CDC MEC lists all combined hormonal contraceptive methods (COC, patch, and vaginal ring) as Category 1 for women with HIV or AIDS [35]. In a separate discussion of drug interactions between hormonal contraceptives and ARVs, it is noted that some NNRTIs and ritonavir-boosted PIs are associated with decreased levels of contraceptive hormones that could compromise contraceptive effectiveness. Consequently, the CDC lists combined hormonal methods as Category 2 for women taking NNRTIs, and Category 3 for women taking ritonavir-boosted PIs. The lack of data regarding clinical outcomes such as escape ovulation or unintended pregnancy makes interpretation of these findings and determination of their clinical significance difficult.

3.1.2. Contraceptive Patch and Contraceptive Vaginal Ring. The only study that has investigated the contraceptive patch in women taking ARV is the AIDS Clinical Trial Group (ACTG) Protocol A5188 study, first discussed above and which evaluated the pharmacokinetic interactions between lopinavir/ritonavir and the transdermal contraceptive patch (EE/norelgestromin) in HIV-positive women [15]. Compared to women not taking protease inhibitors, serum of women taking lopinavir/ritonavir demonstrated a 45% decrease in the AUC of EE ($P = 0.064$). There was also an 83% increase in AUC of norelgestromin in the treatment (lopinavir/ritonavir) arm compared to controls. This decrease in EE was similar to that seen when a single dose of oral COC was given, suggesting that the PI interaction with the hormonal contraception is mediated thorough the liver rather than enzymes within the gut. Only eight women on lopinavir/ritonavir were evaluated in this study, and no data are available regarding adverse events or contraceptive failure. Progesterone levels were decreased in both treatment and control arms, suggesting continued ovulation suppression despite changes in hormone levels.

No studies evaluating the pharmacokinetics of the contraceptive intravaginal ring in the setting of ARV use were identified. The package label for NuvaRing (which releases 15 mcg EE/120 mcg etonogestrel (ENG) daily) refers to interactions identified between COCs and protease inhibitors that may affect contraceptive efficacy [49]. There is no discussion of how the pharmacokinetics of a vaginally administered hormone might differ from one that is orally administered, and there are no data specific to etonogestrel. As the influence of ARVs on contraceptive steroids seems to be related to their metabolism rather than absorption, there may be no reason to expect different results between vaginal and oral administration. In other words, while the effects of first-pass metabolism are avoided by nonoral administration, the hepatic clearance of the drug from the serum may be the more important site of drug interaction.

As noted above, the CDC MEC recommendations for combined hormonal methods include COCs, patch, and ring, as there are few studies that offer data for the nonoral combined methods [35]. All combined methods are considered Category 1 for women with HIV or AIDS, Category 2 for women taking NNRTIs, and Category 3 for women taking ritonavir-boosted PIs.

3.2. Progestin-Only Methods

3.2.1. Progestin-Only Pills (POPs). The effectiveness of progestin-only pills is known to be reduced by hepatic enzyme-inducing drugs [50]. POPs are used by only a minority of women, and there are no published studies on the interaction between POPs and ARVs. Since POPs available in the US contain NET, and those available elsewhere contain LNG or desogestrel (DSG), one could potentially extrapolate data from studies with COCs containing these hormones. The CDC assigns the same recommendation categories to POPs as to COCs; that is, concomitant use of POP with NRTIs is Category 1, with NNRTIs is Category 2, and with ritonavir-boosted PIs is Category 3 [35].

3.2.2. Depot Medroxyprogesterone Acetate (DMPA). The most recent labeling for depot medroxyprogesterone acetate (DMPA, Depo-Provera) does not mention any interaction with protease inhibitors or other antiretroviral drugs [51]. The ACTG Protocol A5093 evaluated the pharmacodynamics and safety profile of DMPA in 70 HIV-positive women on stable ARV regimens [52]. All women in the study were taking at least two NRTIs in addition to an NNRTI (efavirenz or nevirapine) or a PI (nelfinavir). Pharmacokinetic parameters of DMPA were not assessed, but no participants ovulated nor became pregnant over the 12-week study period.

An open-label steady-state pharmacokinetic study evaluated the interactions between DMPA and selected ARVs [25]. Study participants were HIV-positive women on one of four ARV regimens: group A—NRTIs only or no ARVs (no NNRTI or PI); group B—nelfinavir and NRTIs; group C—efavirenz and NRTIs; and group D–nevirapine and NRTIs. Serum samples for medroxyprogesterone acetate (MPA) were measured immediately prior to DMPA injection and 4 weeks after the injection, while serum progesterone concentrations were measured immediately prior to DMPA injection and every 2 weeks throughout the 12-week study period. There were no alterations in the pharmacokinetic profile of DMPA noted in any of the treatment groups. There were no pregnancies during the study, and all participants had low (<5 ng/mL) serum progesterone levels, consistent with ovulation suppression [25].

Another prospective study compared the pharmacokinetics of DMPA among 15 HIV-positive women on HAART (zidovudine, lamivudine, and efavirenz) with 15 HIV-positive women on no ARVs [26]. Serum DMPA and progesterone levels were drawn every 2 weeks throughout the 12-week study. In both groups, the MPA C_{max} was reached within 14 days of the DMPA injection, and there were no differences in MPA AUC, C_{min}, half-life, or bleeding patterns between the two groups. The authors concluded that there is no need to shorten the interval between DMPA injections in women taking ARVs, as there is no evidence of decreased serum levels of MPA in women on HAART.

For women with HIV or AIDS, on any ARV regimen, the CDC MEC considers DMPA use to be Category 1 (no restriction for use of contraceptive method) [35].

3.2.3. Contraceptive Implant. There are several case reports that describe contraceptive failure of Implanon, a 3-year etonogestrel implant that releases 20–30 mcg ENG per day, among HIV-positive women using ARVs. A young woman was diagnosed with HIV 13 months after placement of the implant, at which time she started a HAART regimen of zidovudine, lamivudine, and efavirenz [27]. Sixteen months later she was diagnosed with a ruptured ectopic pregnancy. The implant was palpable in her arm at the time of her pregnancy, suggesting that insertion difficulty was not to blame for its contraceptive failure. No evaluation of serum ENG levels was performed. In a letter to the editor, two additional HIV-positive patients who became pregnant while using Implanon and taking HAART are described [28]. Both became amenorrheic due to the implant, were later changed to ARV regimens that included efavirenz, and were subsequently diagnosed with intrauterine pregnancies. One patient chose to continue the pregnancy and delivered a healthy infant at term, while the other opted for a second-trimester abortion. Again, no serum levels of ENG or the ARVs are reported for either patient.

In another case report, a 34-year-old HIV-positive woman on a HAART regimen of zidovudine, lamivudine, and efavirenz was treated for a ruptured ectopic pregnancy 28 months after insertion of an etonogestrel contraceptive implant [29]. Interestingly, this patient did not have her Implanon removed and was treated for a subsequent ectopic pregnancy on the contralateral side nine months later (i.e., more than 3 years after initial placement of the implant). A fourth case report describes two different HIV-positive women who conceived intrauterine pregnancies while the etonogestrel implant was in place [30]. One was a 31-year-old HIV-positive women treated with efavirenz, zidovudine and lamivudine. The other was a 32-year-old HIV-positive woman on tenofovir, emtricitabine, and efavirenz. There are no pharmacokinetic data available regarding interactions between etonogestrel and any ARVs, but efavirenz is known to induce hepatic P450 activity, making it a plausible cause of the implant's contraceptive failure [27].

At this time, the CDC MEC lists Implanon as Category 1 for women with HIV or AIDS, Category 1 for women taking NRTIs, and Category 2 for women taking NNRTIs or ritonavir-boosted PIs [35]. A consistent theme of the above case reports seems to be that pregnancies conceived during ARV use with Implanon in place occur after 24 months of use. Data are currently lacking, but it seems reasonable to consider early replacement of the implant.

3.2.4. Levonorgestrel Intrauterine System (LNG-IUS). As for most nonoral hormonal contraceptives, the labeling for the LNG-IUS (Mirena) cautions against its concomitant use with drugs that induce hepatic P450 activity [53]. The label specifically mentions concern for PIs and NNRTIs potentially altering the serum concentration of progestins.

A 2006 study evaluated serum levels of LNG before and up to twelve months after LNG-IUS placement in a series of twelve HIV-positive women [31]. Ten of the women enrolled (83%) were on HAART during the study period. Serum levels of LNG were similar between women with and without HAART and were in the same range as had been reported in HIV-negative women, suggesting no effect of HAART on the absorption or metabolism of LNG when used for intrauterine contraception.

Two studies provide follow-up data on the LNG-IUS in HIV-infected women [32, 33]. Both concluded that it is a safe option for HIV-positive women desiring long-term contraception and those looking for treatment of heavy menstrual bleeding. In the 2011 study, there was no difference in CD4 counts, HIV viral loads, use of ARVs, or pregnancies between the intervention (15 women who received LNG-IUS) and control (25 women using other methods of contraception) groups [33]. No pharmacokinetic evaluation was done as part of these studies.

It should be noted that the primary mechanism of action of the LNG-IUS is unrelated to serum LNG levels. Rather, it is primarily due to a foreign body reaction and direct effects from the locally released progestin. Further, serum LNG levels can vary widely in users of the LNG-IUS, without apparent correlation to contraceptive effect. Therefore, the clinical contraceptive impact of altered serum LNG levels in women using the LNG-IUS may not be significant. The CDC MEC assigns Category 2 (benefits outweigh risks) to the use of any intrauterine contraception (including the LNG-IUS) for women with HIV who are stable on ARV therapy of any kind [35]. Of note, for women with AIDS, whether on ARVs or not, insertion of an IUD is considered to be Category 3 [35].

3.2.5. Emergency Contraception (EC). Two types of dedicated emergency contraceptive (EC) pills exist: progestin-only pills containing levonorgestrel, and antiprogestins (either mifepristone or ulipristal acetate). The Plan B (two oral doses of LNG 0.75 mg taken 12 hours apart within 72 hours of unprotected intercourse) package labeling raises theoretical concerns regarding coadministration with drugs that induce hepatic enzymes, but provides no data to support or refute these concerns [54]. Only one study was identified that evaluated the interaction between LNG EC and efavirenz [34]. In this single-arm, open-label study, 21 HIV-negative women were given a single course of Plan B. Serial pharmacokinetic blood samples were drawn immediately before and for 12 hours after the first LNG dose. Participants then took 14 days of EFV (600 mg daily), followed by a second course of Plan B and blood sampling after the first LNG dose. Compared to baseline, LNG coadministrated with EFV resulted in a 58% decrease in AUC ($P < 0.0001$) and statistically significant decreases in $C_{\min}$, $C_{\max}$, and half-life [34]. While the authors acknowledge that the minimum effective concentration of LNG for emergency contraception is unknown, they suggest that women taking EFV may require higher doses of LNG to prevent pregnancy, such as the one-time dose of LNG 1.5 mg. A recent review of EC similarly suggests that an increased progestin dose may be considered if an ARV with known

effects on contraceptive hormones is used concomitantly [55]. This recommendation is based on an older study and may not apply to all current ARVs. No data exist regarding the use of antiprogestins during ARV therapy.

COCs may also be used in higher doses to provide EC, referred to as the Yuzpe regimen [56]. There are no data specifically assessing interactions between ARVs and COCs in these doses, but one could expect analogous pharmacokinetic effects to those seen after single-dose COC administration. Whether these effects alter the efficacy of the Yuzpe regimen is not known. In general, the Yuzpe method is less effective than progestin or antiprogestin EC. Regardless of type chosen, theoretical concern for decreased effectiveness should not deter providers from offering EC to women with HIV.

4. Discussion

Assessing the effects of antiretroviral drugs on the efficacy of hormonal contraceptives is a challenging undertaking for many reasons. Most drug-drug interaction studies aim to investigate only two drugs at a time so as to facilitate interpretation of any changes in pharmacokinetic parameters. Studying antiretroviral drugs individually does not reflect their real-world application as part of multiagent HAART regimens, when there may be multiple layers of enzyme induction or inhibition as well as other physiologic effects that may alter drug absorption or excretion. There are also potential disadvantages to conducting these studies in healthy HIV-negative volunteers, who may be better able to adhere to a particular contraceptive method than HIV-positive women who have to contend with managing their illness as well as following a study protocol.

The concept of "pill burden" may be an additional factor to consider when helping an HIV-positive woman on ARVs to choose the best contraceptive method for her. High pill burden is a barrier to adherence to HAART [57, 58]. In this context, a nondaily, nonoral method of contraception may be preferred for some women using ARVs. However, for methods such as the contraceptive patch and vaginal ring there are limited or no data to guide the clinician or the HIV-positive woman.

Of the information that is available about interactions of hormonal contraception and ARVs, much is based on a limited number of PK studies with small sample sizes and short durations of hormone and ARV exposure. Pharmacokinetic measurements are often affected by the hepatic P450 system, but AUC and C_{max}, among other measurements, are dependent on many other factors including age, weight, length of exposure to hormones and ARVs, absorption factors, and even pharmacogenetics. An increase in hormone levels could possibly affect side effects and potential complications (e.g., thromboembolism). A large enough decrease in hormone levels could potentially decrease contraceptive efficacy. Interestingly, among ARVs which lead to decreased hormone levels, the decrease seems to be greatest for EE levels, but it is the progestin component of combined hormonal contraception which is more important to contraceptive efficacy. In addition, therapeutic levels of contraceptive hormones are not actually known. Therefore, the clinical relevance of a percentage decrease in a serum contraceptive hormone level is unclear. A more useful measurement of contraceptive efficacy would be assessments of ovulation via serum hormone levels (e.g., progesterone, LH, FSH) and serial pelvic ultrasounds. With the exception of the Schöller-Gyüre study [22], no markers of ovulation have been included in studies on the interaction of ARVs and hormonal contraception. Therefore, recommendations based on small studies relying only on pharmacokinetic measurements should be treated cautiously.

The development of transdermal and transvaginal dosing regimens avoids the first-pass metabolism that occurs in the gastrointestinal system, thereby reducing the effect of CYP metabolism of contraceptive hormones. Because of this avoidance, nonoral routes of administration would be expected to differ from COCs regarding their metabolism and therefore drug interactions. However, the only study available which looks at a nonoral administration of hormonal contraception with ARVs shows similar changes in hormone pharmacokinetics as studies investigating COCs [22].

From the available evidence, the efficacy of DMPA and LNG-IUS should not be affected by ARV use. Other hormonal methods may be affected by ARV coadministration. Use of condoms in addition to hormonal contraception is recommended. Of course, this recommendation is warranted for all heterosexually active HIV-positive women in order to decrease HIV transmission and acquisition of other sexually transmitted diseases.

The particular case of the ENG implant is intriguing. All reports of contraceptive implant failure reviewed here occurred in HIV-positive women taking efavirenz as a component of their HAART regimen. Based on available information, it appears that all pregnancies that occurred during coadministration of Implanon and efavirenz were conceived in the latter half of the three years for which Implanon is licensed. This raises the question of whether the implant is wholly ineffective when used by women taking efavirenz, or whether its contraceptive activity is depleted more quickly than in women not taking efavirenz. Avoiding unintended pregnancy in women treated with efavirenz is highly important given the potential for teratogenicity with efavirenz exposure, and the implant typically provides excellent, long-acting reversible birth control. Studies that address the mechanism by which efavirenz affects subdermally-implanted etonogestrel are sorely needed.

The issue of whether hormonal contraceptives are safe for women with HIV has been hotly debated in the literature. The WHO recently published a technical statement regarding hormonal contraceptive use by women with HIV, after performing extensive reviews of the literature regarding effects of hormonal contraception on HIV acquisition, transmission, and disease progression [59]. Despite a recent study that found an increase in both HIV acquisition by uninfected women and HIV transmission by HIV-positive women using DMPA [60], the overall body of evidence does not support a definite association. Consequently, the CDC and WHO continue to list DMPA and other hormonal

contraceptives as Category 1 for women infected with HIV [35, 61].

There are some significant pitfalls in relying on individual drugs' package labeling for guidance regarding drug interactions, real, or theoretical. Clinical trials performed during drug development typically involve small numbers of patients, so certain interactions may not come to light until a licensed drug is used in hundreds or thousands of patients. Postmarketing data is an important source of additional information about a drug once it has been used in the general population, but most drugs do not have active surveillance systems and instead rely on patient and provider self-report. Data collected by manufacturers in pursuit of drug approval may not be published in the peer-reviewed literature, and thus may not be readily accessible. However, when there are no published data to guide health care providers, the drug manufacturers' recommendations can provide some basis for clinical decision-making.

5. Conclusions

Although there is no concrete data demonstrating reduced efficacy of the ENG implant when coadministrated with HAART, the numerous case reports of contraceptive failure in women taking efavirenz are concerning. It would be prudent for health care providers to counsel HIV-positive women requesting Implanon regarding the importance of dual contraception, particularly if their HAART regimen includes efavirenz. Until there is a better understanding of whether these medications truly interact, Implanon should continue to be made available to women living with HIV who desire LARC.

While there are demonstrable changes in the serum concentrations of EE and various progestins used in hormonal contraception, it remains unclear how clinically relevant these changes are and whether they can be interpreted as altered contraceptive efficacy. Studies that evaluate clinical markers of ovulation or actual pregnancy rates are necessary to clarify which hormonal contraceptives are most effective for women taking antiretroviral drugs. The data are mixed regarding interactions with combined oral contraceptives, and there is a dearth of information regarding the contraceptive patch, vaginal ring, and implant. However, the data are reassuring that DMPA and the LNG-IUS remain highly effective contraceptives even when used in conjunction with antiretroviral drugs. The Medical Eligibility Criteria published by the CDC and WHO each designate hormonal contraceptives as safe and appropriate (i.e., Category 1) for women with HIV or AIDS, with caution advised for women treated with NNRTIs or ritonavir-boosted PIs [35, 61].

References

[1] UNAIDS/WHO, "AIDS Epidemic Update," 2009.

[2] H. W. Reynolds, B. Janowitz, R. Homan, and L. Johnson, "The value of contraception to prevent perinatal HIV transmission," *Sexually Transmitted Diseases*, vol. 33, no. 6, pp. 350–356, 2006.

[3] M. Zieman, R. A. Hatcher, C. Cwiak, P. D. Darney, M. D. Creinin, and H. R. Stosur, *A Pocket Guide to Managing Contraception*, Bridging the Gap Foundation, Tiger, Ga, USA, 2007.

[4] FFPHRC Guidance, "Drug interactions with hormonal contraception," *Journal of Family Planning and Reproductive Health Care*, vol. 31, no. 2, pp. 139–150, 2005.

[5] M. W. Van Den Heuvel, A. J. M. Van Bragt, A. K. M. Alnabawy, and M. C. J. Kaptein, "Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: The vaginal ring, the transdermal patch and an oral contraceptive," *Contraception*, vol. 72, no. 3, pp. 168–174, 2005.

[6] V. B. Mahesh, "The dynamic interaction between steroids and gonadotropins in the mammalian ovulatory cycle," *Neuroscience and Biobehavioral Reviews*, vol. 9, no. 2, pp. 245–260, 1985.

[7] D. J. Hemrika, E. H. Slaats, J. C. Kennedy, T. J. M. De Vries Robles-Korsen, and J. Schoemaker, "Pulsatile luteinizing hormone secretion during the first and the fourth cycle on two different oral contraceptives containing gestodene," *Acta Endocrinologica*, vol. 129, no. 3, pp. 229–236, 1993.

[8] L. Speroff and M. Fritz, *Clinical Gynecologic Endocrinology and Infertility*, Lippincott Williams & Wilkins, Baltimore, Md, USA, 7th edition, 2005.

[9] F. P. Guengerich, "Metabolism of 17α-ethynylestradiol in humans," *Life Sciences*, vol. 47, no. 22, pp. 1981–1988, 1990.

[10] A. B. Edelman, G. Cherala, and F. Z. Stanczyk, "Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review," *Contraception*, vol. 82, no. 4, pp. 314–323, 2010.

[11] Panel on Antiretroviral Guidelines for Adults and Adolescents, "Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents," Department of Health and Human Services, 2009, http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

[12] Bristol-Meyers Squibb, Reyataz (atazanavir) Package Label, 2010.

[13] Agouron Pharmaceuticals, Viracept (nelfinavir) Package Label, 2009.

[14] Abbott Laboratories, Kaletra (lopinavir/ritonavir) Package Label, 2010.

[15] M. A. Vogler, K. Patterson, L. Kamemoto et al., "Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: Pharmacokinetic results of ACTG trial A5188," *Journal of Acquired Immune Deficiency Syndromes*, vol. 55, no. 4, pp. 473–482, 2010.

[16] D. Ouellet, A. Hsu, J. Qian et al., "Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers," *British Journal of Clinical Pharmacology*, vol. 46, no. 2, pp. 111–116, 1998.

[17] Boehringer Ingelheim Pharmaceuticals, Viramune (nevirapine) Package Label, 2010.

[18] D. Mildvan, R. Yarrish, A. Marshak et al., "Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women," *Journal of Acquired Immune Deficiency Syndromes*, vol. 29, no. 5, pp. 471–477, 2002.

[19] Bristol-Meyers Squibb, Sustiva (efavirenz) Package Label, 2010.

[20] H. Sevinsky, T. Eley, A. Persson et al., "The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing

ethinyl estradiol and norgestimate in healthy HIV-negative women," *Antiviral Therapy*, vol. 16, no. 2, pp. 149–156, 2011.

[21] Janssen Pharmaceuticals, Intelence (etravirine) Package Label, 2008.

[22] M. Schöller-Gyüre, T. N. Kakuda, B. Woodfall et al., "Effect of steady-state etravirine on the pharmacokinetics and pharmacodynamics of ethinylestradiol and norethindrone," *Contraception*, vol. 80, no. 1, pp. 44–52, 2009.

[23] M. S. Anderson, W. D. Hanley, A. R. Moreau et al., "Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women," *British Journal of Clinical Pharmacology*, vol. 71, no. 4, pp. 616–620, 2011.

[24] P. German, M. Wang, D. Warren, and B. P. Kearney, "Pharmacokinetic interaction between Norgestimate/Ethinyl Estradiol and EVG/COBI/FTC/TDF single tablet regimen," in *Proceedings of the 12th International Workshop on Clinical Pharmacology of HIV Therapy*, Miami, Fla, USA, April 2011.

[25] S. E. Cohn, J. G. Park, D. H. Watts et al., "Depo-medroxyprogesterone in women on antiretroviral therapy: Effective contraception and lack of clinically significant interactions," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 2, pp. 222–227, 2007.

[26] K. Nanda, E. Amaral, M. Hays, M. A. M. Viscola, N. Mehta, and L. Bahamondes, "Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy," *Fertility and Sterility*, vol. 90, no. 4, pp. 965–971, 2008.

[27] A. A. Matiluko, L. Soundararjan, and P. Hogston, "Early contraceptive failure of Implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz," *Journal of Family Planning and Reproductive Health Care*, vol. 33, no. 4, pp. 277–278, 2007.

[28] N. Lakhi and A. Govind, "Implanon failure in patients on antiretroviral medication: the importance of disclosure," *Journal of Family Planning and Reproductive Health Care*, vol. 36, no. 3, pp. 181–182, 2010.

[29] E. J. McCarty, H. Keane, K. Quinn, and S. Quah, "Implanonw failure in an HIV-positive woman on antiretroviral therapy resulting in two ectopic pregnancies," *International Journal of STD and AIDS*, vol. 22, no. 7, pp. 413–414, 2011.

[30] N. Leticee, J.-P. Viard, A. Yamgnane, M. Karmochkine, and A. Benachi, "Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz," *Contraception*, vol. 85, no. 4, pp. 425–427, 2012.

[31] O. Heikinheimo, P. Lehtovirta, J. Suni, and J. Paavonen, "The levonorgestrel-releasing intrauterine system (LNG-IUS) in HIV-infected women—effects on bleeding patterns, ovarian function and genital shedding of HIV," *Human Reproduction*, vol. 21, no. 11, pp. 2857–2861, 2006.

[32] P. Lehtovirta, J. Paavonen, and O. Heikinheimo, "Experience with the levonorgestrel-releasing intrauterine system among HIV-infected women," *Contraception*, vol. 75, no. 1, pp. 37–39, 2007.

[33] O. Heikinheimo, P. Lehtovirta, I. Aho, M. Ristola, and J. Paavonen, "The levonorgestrel-releasing intrauterine system in human immunodeficiency virusinfected women: Z 5-year follow-up study," *American Journal of Obstetrics and Gynecology*, vol. 204, no. 2, pp. 126.e1–126.e4, 2011.

[34] M. L. Carten, J. Kiser, A. Kwara, S. MaWhinney, and S. Cu-Uvin, "Pharmacokinetic (PK) interactions between the hormonal emergency contraception Plan B (levonorgestrel) and efavirenz (EFV)," in *Proceedings of the 17th Conference on Retroviruses and Opportunistic Infections*, San Francisco, Calif, USA, February 2010.

[35] Department of Health and Human Services Centers for Disease Control and Prevention, "US medical eligibility criteria for contraceptive use," *Morbidity and Mortality Weekly Report*, vol. 59, no. 4, pp. 1–86, 2010.

[36] Wyeth Laboratories. LoOvral (ethinyl estradiol/norgestrel) Package label, 2007.

[37] Wyeth Pharmaceuticals, Alesse (ethinyl estradiol/levonorgestrel) Package Label, 2008.

[38] Ortho-McNeil-Janssen Pharmaceuticals, Ortho TriCyclen (ethinyl estradiol/norgestimate) Package Label, 2009.

[39] Bayer HealthCare Pharmaceuticals, Yaz (ethinyl estradiol/drospirenone) Package Label, 2010.

[40] Duramed, Mircette (ethinyl estradiol/desogestrel) Package Label, 2009.

[41] GlaxoSmithKline, Agenerase (amprenavir) Package Label, 2002.

[42] Abbott Laboratories, Norvir (ritonavir) Package Label, 2010.

[43] Janssen Therapeuics, Prezista (darunavir) Package Label, 2008.

[44] Boehringer Ingelheim Pharmaceuticals, Aptivus (tipranavir) Package Label, 2011.

[45] Roche Laboratories, Invirase/Fortovase (saquinavir) Package Label, 2010.

[46] M. Fröhlich, J. Burhenne, M. Martin-Facklam et al., "Oral contraception does not alter single dose saquinavir pharmacokinetics in women," *British Journal of Clinical Pharmacology*, vol. 57, no. 3, pp. 244–252, 2004.

[47] S. Abel, D. Russell, L. A. Whitlock, C. E. Ridgway, and G. J. Muirhead, "Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers," *British Journal of Clinical Pharmacology*, vol. 65, no. 1, pp. 19–26, 2008.

[48] Merck and Company, Isentress (raltegravir) Package Label, 2011.

[49] Organon, NuvaRing Package Label, 2010.

[50] Janssen-Ortho, Micronor (norethindrone) Package Label, 2010.

[51] Pfizer, Depo-Provera (depot medroxyprogesterone acetate) Package Label, 2006.

[52] D. H. Watts, J. G. Park, S. E. Cohn et al., "Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093," *Contraception*, vol. 77, no. 2, pp. 84–90, 2008.

[53] Bayer HealthCare Pharmaceuticals, Mirena (levonorgestrel-releasing intrauterine system) Package Label, 2009.

[54] Barr Pharmaceuticals, Plan B (levonorgestrel emergency contraceptive tablet) Product Labeling, 2006.

[55] J. Trussell and E. G. Raymond, "Emergency Contraception: a last chance to prevent unintended pregnancy," 2012, http://ec.princeton.edu/questions/ec-review.pdf.

[56] F. H. Stewart, J. Trussell, and P. F. A. Van Look, "Chapter 6: emergency contraception," in *Contraceptive Technology*, R. A. Hatcher, J. Trussell, A. L. Nelson, W. Cates Jr., F. H. Stewart, and D. Kowal, Eds., pp. 87–116, Ardent Media, New York, NY, USA, 19th edition, 2008.

[57] T. Juday, S. Gupta, K. Grimm, S. Wagner, and E. Kim, "Factors associated with complete adherence to HIV combination antiretroviral therapy," *HIV Clinical Trials*, vol. 12, no. 2, pp. 71–78, 2011.

[58] M. J. Atkinson and J. J. Petrozzino, "An evidence-based review of treatment-related determinants of patients' nonadherence to HIV medications," *AIDS Patient Care and STDs*, vol. 23, no. 11, pp. 903–914, 2009.

[59] World Health Organization, Department of Reproductive Health and Research, "Hormonal contraception and HIV," Technical statement, Geneva, Switzerland, 2012.

[60] R. Heffron, D. Donnell, H. Rees et al., "Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study," *The Lancet Infectious Diseases*, vol. 12, no. 1, pp. 19–26, 2012.

[61] World Health Organization, *Medical Eligibility Criteria for Contraceptive Use*, World Health Organization, Geneva, Switzerland, 2010.

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Review Article

Evaluating Safer Conception Options for HIV-Serodiscordant Couples (HIV-Infected Female/HIV-Uninfected Male): A Closer Look at Vaginal Insemination

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HIV serodiscordant couples represent at least half of all HIV-affected couples worldwide. Many of these couples have childbearing desires. Safer methods of conception may allow for pregnancy while minimizing the risk of sexual transmission of HIV. In serodiscordant partnerships with an HIV-infected female and HIV-uninfected male, vaginal insemination of a partner's semen during the fertile period coupled with 100% condom use may be the safest method of conception.

1. Introduction

It is estimated that there are 34 million HIV-infected people living worldwide with 68% residing in sub-Saharan Africa and 50% of cases occurring among women [1]. Serodiscordance, in which one person in a couple is HIV-infected and the other person is HIV-uninfected, is a common phenomenon. In a multisite collaborative study across East and Southern Africa, 49% of the enrolled heterosexual couples were HIV serodiscordant. HIV transmission within stable serodiscordant partnerships is thought to contribute substantially to the HIV epidemic in sub-Saharan Africa [2]. In the United States, it is estimated that there are more than 140,000 HIV serodiscordant heterosexual couples [3]. In HIV serodiscordant partnerships where conception occurs, the HIV-uninfected partner has a 1.8 (95% confidence interval (CI) 1.01–3.26; $P < 0.05$) increased risk of HIV acquisition in comparison to partnerships where conception did not occur. The majority of HIV-uninfected men and women in serodiscordant partnerships where conception occurs acquire HIV within the six months prior to conception and during the first six months of pregnancy indicating that couples engage in risky practices in order to conceive [4]. The per coital risk of HIV transmission from female-to-male is estimated at 0.0010 (95% CI 0.00060–0.0017) in HIV serodiscordant couples [5].

In the United States, 52% of HIV-infected women in a national probability study reported being in a serodiscordant partnership while 47% of HIV-infected women in sub-Saharan Africa are in stable serodiscordant relationships [6, 7]. Evidence suggests that 20–50% of HIV-infected individuals desire children and this desire for childbearing may lead to unprotected sex and/or nondisclosure of HIV status, which in turn results in an increased risk of sexual HIV transmission [4, 6, 8, 9]. In order to adequately curb HIV incidence, the reproductive desires and intentions of HIV serodiscordant couples must guide prevention interventions. Care for HIV-infected adults should include assessing reproductive goals in the context of the HIV status of one's sexual partners. Through the delivery of comprehensive reproductive healthcare, serodiscordant couples may fulfill their personal reproductive goals while decreasing the risk of sexual HIV transmission.

To date, there is sparse information in the literature describing low-cost assisted reproductive methods, such as vaginal insemination, for HIV-infected females and HIV-uninfected males (HIF/HUM) serodiscordant couples. In the following discussion, we will emphasize the use of vaginal insemination during the fertile period coupled with consistent condom use as a safer method of conception for HIF/HUM serodiscordant couples. The evaluation of safer methods of conception has been limited to the use of timed unprotected intercourse as well as sperm washing coupled with assisted reproductive procedures for HIV-infected males/HIV-uninfected female serodiscordant couples [10, 11].

2. Ethical Implications

It is time for society to normalize the lives of HIV-infected people including the basic human right to conceive and raise children [12, 13]. All couples and individuals have the basic reproductive right "to decide freely and responsibly the number, spacing and timing of their children and to have the information and means to do so" [14]. Childbearing is important to many HIV-affected couples and healthcare providers have the responsibility of providing resources to help couples safely conceive while minimizing the risk of sexual and perinatal HIV transmission. In the current era where HIV-infected individuals are living longer, simply encouraging HIV-affected couples to abstain from procreation is no longer a realistic strategy, particularly in cultures where having children is stressed [15, 16]. Inherent in this discussion is the conflict between the desire to have children and preventing HIV transmission [17]. Existing evidence suggests that HIV serodiscordant couples desiring conception seldom know of practices to reduce periconception sexual transmission and several knowingly risk HIV transmission to their partner in order to conceive [18].

3. Childbearing Desires among HIV Serodiscordant Couples

HIV serodiscordant couples may engage in risky sexual behaviors to conceive [4]. Various factors drive childbearing intentions amongst HIV serodiscordant couples, particularly, women wish to regain their self-status and pursue pregnancy as proof of recovery and evidence of regained self-control [9]. Societal and cultural expectations along with personal reproductive intentions may also drive HIV-infected women in serodiscordant relationships to conceive.

4. Methods of Safer Conception

Options for safer conception in HIF/HUM serodiscordant couples include antiretroviral therapy (ART), male circumcision, timed unprotected intercourse, preexposure prophylaxis (PrEP) for the uninfected male partner, assisted reproductive technology, and vaginal insemination of semen during the fertile period. The use of ART, timed unprotected intercourse, and assisted reproductive technology as safer methods of conception has been evaluated in HIF/HUM. The European studies evaluating the use of assisted reproductive technology in HIF/HUM serodiscordant couples illustrate that HIF may have underlying infertility or decreased response to ovarian stimulation as a result of HIV infection, ART, or tubal factor infertility [19, 20]. Despite evidence supporting the protective effects of timed unprotected intercourse, PrEP for the uninfected partner, and assisted reproductive technology as safer methods of conception there are limited studies evaluating the acceptability and feasibility of these methods amongst HIV serodiscordant couples.

4.1. Antiretroviral Therapy (ART). Prior to initiation of conception attempts, other risk reduction interventions should be considered to reduce HIV transmission to the HUM. Ideally, the HIF should be on ART and attain an undetectable plasma viral load. While fully suppressive ART use by the HIV-infected individual dramatically reduces the chance of sexual transmission, sexual HIV transmission may still occur [21]. A systematic review evaluating the rate of HIV transmission through unprotected intercourse in serodiscordant couples with the HIV-infected partner on ART noted an overall transmission rate of 0.46 (95% CI 0.19–1.09) per 100 person years [22]. Early initiation of ART is associated with a 96% (95% CI 0.01–0.27) relative reduction of HIV transmission to the HIV-negative partner [23]. In the United States, ART is recommended for all HIV-infected individuals [24]. However, initiation of ART with an undetectable serum HIV RNA viral load does not ensure an undetectable viral load in the genital tract. Therefore, couples should be counseled that suppressed plasma viremia does not guarantee that an individual is sexually noninfectious [25–28].

4.2. Male Circumcision. Reduction of HIV transmission to the male partner can also be assisted with male circumcision. Male circumcision, the surgical removal of all or part of the foreskin of the penis, is thought to remove a potential site of entry for HIV infection [29]. Circumcision can reduce the risk of HIV transmission to the index HIV-uninfected male partner by 38–66% over 24 months, assuming an adequate duration of healing prior to reinitiation of sexual activity [30–32]. Circumcision coupled with other safer methods of conception may decrease the risk of sexual HIV transmission.

4.3. Timed Unprotected Intercourse. Natural conception for HIV serodiscordant couples desiring conception involves timing unprotected sexual intercourse during the fertile period. Women are taught to monitor their menstrual cycle to determine the day of ovulation using the basal body temperature, calendar calculation, ovulation prediction kits assessing urinary hormones, and/or monitoring of their cervical mucus. Couples are encouraged to minimize their sexual encounters to the fertile period to decrease the number of unprotected sexual encounters while optimizing their chance of conception. In Spain, there was a cohort of 62 HIV serodiscordant couples with 22 HIF/HUM where timed unprotected intercourse occurred and the female was

receiving suppressive ART; there were no cases of sexual HIV transmission [33]. On the other hand, in France, Mandelbrot et al. found a 4% risk of male-to-female HIV transmission among 92 HIV serodiscordant couples counseled on the use of timed unprotected intercourse. All of the cases of HIV transmission occurred during unprotected sex outside the fertile period and only 21 of the HIV-infected men were receiving ART [11]. Nonetheless, these cases highlight that couples may not adhere to unprotected intercourse only during the fertile period.

4.4. Periconception Preexposure Prophylaxis (PrEP) or "PrEPception". PrEP for the HIV-negative partner prior to attempted conception, "PrEPception," combined with timed unprotected intercourse is another risk reduction technique that may minimize the risk of sexual HIV transmission among serodiscordant couples [3]. In Switzerland, a cohort of 53 HIV serodiscordant couples (male positive, female negative) desiring conception, 46 couples opted for PrEP 12 and 36 hours prior to timed unprotected intercourse and there were no cases of HIV transmission. After the first attempt with timed unprotected intercourse, the pregnancy rate was 26% which increased to 66% after five attempts and reached a plateau of 75% after 12 attempts. PrEP coupled with time unprotected intercourse may help at risk individuals reduce their risk of HIV acquisition during conception [34].

The efficacy of preexposure prophylaxis (PrEP) in HIV serodiscordant couples has been demonstrated, yet its widespread use may be restricted because of issues related to adherence, adequate regimens, cost effectiveness, and use in resource-limited environments [35–41]. PrEP should be available for serodiscordant couples as a risk reduction strategy to prevent sexual HIV transmission. Clinical trials to date have not tested the use of PrEP on an other than daily basis with the exception of the evaluation of tenofovir gel, which is not commercially available, and oral PrEP in HIV serodiscordant couples desiring conception in Switzerland [34, 36, 37]. The data on PrEP from these trials is mixed. The United States Food and Drug Administration has endorsed tenofovir/emtricitabine (Truvada) for use as once daily PrEP in men and women at high risk of sexually acquired HIV infection.

4.5. Assisted Reproductive Technology. Comprehensive reproductive counseling and assisted reproductive technology services are limited for HIV-infected women in serodiscordant relationships desiring pregnancy in resource-limited environments. In developed countries, assisted reproductive technology is not readily available and may be cost prohibitive to couples. In the United States, it has been reported that less than 5% of at least 400 assisted reproductive clinics provide services to HIV-infected individuals [42]. In HIF/HUM serodiscordant couples laborious and expensive reproductive techniques may not be necessary to reduce the risk of HIV transmission during attempted conception, unless there is a documented history of infertility [43]. HIV-infected women may have decreased reproductive potential in terms of ovarian response to stimulation, fertilization, and implantation [44]. In-vitro fertilization with intracytoplasmic intrauterine insemination may improve the rates of fertilization in HIV-infected females with known infertility.

4.6. Vaginal Insemination. Vaginal insemination along with consistent male condom use in a heterosexual HIF/HUM serodiscordant partnership during the fertile period may be the easiest and safest reproductive option to further reduce the risk of sexual HIV transmission compared to timed unprotected sexual intercourse. Vaginal insemination can be performed at home by the HIF/HUM serodiscordant couple during the fertile period of the menstrual cycle after collection of semen from a water-based lubricated condom or clean container.

5. Vaginal Insemination as the Safer Conception Option for HIF/HUM Serodiscordant Couples

The use of vaginal insemination as a safer method of conception may help combat the sexual transmission of HIV [45]. Nonetheless, there are no data in the literature reporting on vaginal insemination despite anecdotal reports supporting its use. To date, the only study registered with ClinicalTrials.gov evaluating the acceptability, feasibility, and efficacy of vaginal insemination amongst HIV serodiscordant couples (HIF/HUM) desiring conception will be conducted in Kisumu, Kenya (ClinicalTrials.gov identifier: NCT01468753).

Vaginal insemination involves the woman monitoring her menstrual cycle to estimate her most fertile days. Semen is collected either during sex with a nonspermicidal (water-based lubricated) condom or via ejaculation into a clean container (Figure 1). The semen is then aspirated shortly after ejaculation into a needless syringe or a bulb pipette. The woman lies on her back with her hips elevated while the semen is slowly deposited into the vagina by herself or her partner.

Despite the theoretical ease of the vaginal insemination procedures, there are potential challenges that may impede its acceptability and efficacy. Determination of the fertile days in the menstrual cycle without advance technologies in a resource-limited setting may prove difficult. Without accurate determination of the fertile days in an ovulating woman, the vaginal insemination procedures may be ineffective, unless couples correctly time vaginal insemination for use during the fertile period. There are five established methods of predicting ovulation: serial ultrasound, calendar calculation, basal body temperature, consistency of cervical mucus, and urine hormones. Ultrasound detection of the day of ovulation is a direct method and most accurate but is unavailable outside of a clinical facility. Calendar calculation and basal body temperature are considered to be unreliable, however, thin, clear, stretchy cervical mucus (spinnbarkeit) and urine luteinizing hormone are the two methods that correlate best with ultrasound detection of ovulation [46, 47]. In addition to the challenge of determining the fertile period of the cycle,

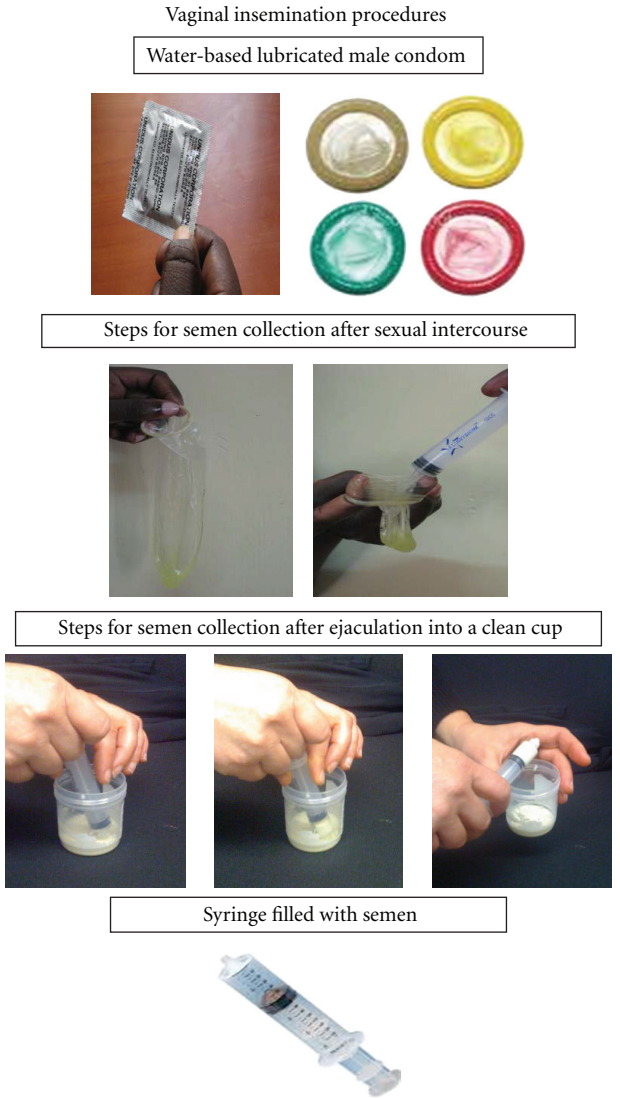

Figure 1: Steps for vaginal insemination of semen: (1) on a fertile day of the menstrual cycle, engage in sex using nonspermicidal condom (water-based lubricated or nonlubricated condom) or semen can be collected from a clean cup after ejaculation. (2) Collect the semen with a plastic needle-less syringe from a condom or clean cup. (3) The female or male partner will insert the syringe with the semen as high as possible into the vagina, ideally immediately after ejaculation. (4) The female partner may lie down for at least thirty minutes after insertion. (5) Steps (1–4) may be repeated every other day during the fertile period.

couples may also encounter cultural and technical challenges with performing the vaginal insemination. Couples may be uncomfortable with the insemination process, use of the devices, or touching their genitalia to perform the vaginal insemination procedures. The incorporation of continued counseling and education may help couples overcome these potential challenges as they prepare for safer conception with vaginal insemination [48]. The interest and motivation amongst HIV serodiscordant couples may also contribute to overcoming the perceived cultural and technical barriers [49].

6. Guidelines for Healthcare Providers

In HIF/HUM serodiscordant couples, there are three unique clinical challenges: maintaining the woman's health before, during, and after the pregnancy; preventing perinatal transmission; preventing sexual transmission to the HIV negative partner [16]. In order to facilitate conception and a safe pregnancy, the health of both members of the couple should be optimized. The HIV-infected woman should have a thorough clinical assessment (CD4 count, viral load, and genotype if available), evaluation of antiretroviral regimen, identification and management of comorbidities such as tuberculosis, diabetes, or hypertension in addition to other transmissible infections or cofactors that may increase the risk of HIV transmission or acquisition [10, 12]. Similarly, an HIV-infected person should be counselled on the risks of conception with a detectable HIV-1 RNA viral load, documented infertility or presence of conditions affecting fertility in either partner, nondisclosure of HIV status, or medical contraindications to pregnancy [12]. In couples with documented infertility, they may be referred to a fertility clinic for preconception counseling and discussion of available options, if available. If either partner has conditions affecting fertility the couple can be allowed to continue their attempts at conception; however, they should be encouraged to seek assisted reproductive technology services after six unsuccessful attempts at vaginal insemination or timed unprotected intercourse over six cycles [12, 34]. Couples should also have a clinical assessment to screen and treat for sexually transmitted infections prior to attempts at conception [12]. In eligible HIV-infected women, antiretroviral therapy (ART) should be initiated and optimized to improve their health status and reduce the risk of HIV transmission [23]. The use of combination antiretroviral regimens in HIV-infected women is associated with a near elimination of perinatal HIV transmission [50].

Male circumcision, ART, timed unprotected intercourse, PrEP for the uninfected male partner, and vaginal insemination of semen during the fertile period can be used in concert for HIF/HUM desiring conception. For example, an HIF on ART may attempt timed unprotected intercourse or vaginal insemination with her HUM partner that has been circumcised. Together, these low-cost interventions may allow HIF/HUM serodiscordant couples to safely conceive while decreasing the risk of sexual HIV transmission.

Preventing sexual transmission of HIV to the uninfected partner involves counseling on the consistent use of condoms with all sexual encounters while attempting to conceive with timed unprotected intercourse, PrEP, assisted reproductive technology, or vaginal insemination. Despite these recommendations, the barriers to consistent condom use should not be overlooked. Difficulties that have been reported with consistent condom use include loss of spontaneity, reduced libido, and decreased frequency of sexual intercourse [17]. However, healthcare providers can help HIV serodiscordant couples overcome these challenges with an emphasis on their motivation to safely conceive and minimize sexual HIV transmission. It has been argued that couples and medical providers accepting the risk of transmitting a disease to their

offspring do not act unethically if all reasonable precautions to prevent transmission are taken [33, 51].

As the paradigm shifts to assisting HIV-affected couples fulfill their reproductive goals of procreating, healthcare providers must also begin to expand their understanding of the family planning concept beyond contraception to include methods of safer conception. This more comprehensive concept of reproductive healthcare also includes safer methods of conception. The integration of comprehensive reproductive healthcare services into HIV care and treatment programs will strengthen the repertoire of medical services available to HIV-affected couples desiring children.

7. Future Directions

The armamentarium of safer methods of conception for HIV serodiscordant couples desiring conception is expanding. Existing evidence supports the use of ART, male circumcision, timed unprotected intercourse, PrEP, and assisted reproductive technology as safer methods of conception for serodiscordant couples. Although the existing evidence may have some limitations, they can be used alone or in combination to decrease the risk of sexual HIV transmission while attempting conception. Anecdotal evidence supports the use of vaginal insemination as a low-cost and feasible method of safer conception by HIF/HUM serodiscordant couples. However, the paucity of existing data supporting the use of vaginal insemination calls for studies to address the feasibility and efficacy of this method. We anticipate that the current study evaluating vaginal insemination in a low resource environment will address the perceived cultural and technical challenges with performing the vaginal insemination procedures in a monogamous HIF/HUM serodiscordant partnership. The findings of this study will assist in establishing guidelines for its use as a component of comprehensive reproductive healthcare for HIV-affected couples. In the future, we expect that periovulatory vaginal insemination coupled with consistent condom use will be widely supported and endorsed by healthcare providers for HIF/HUM serodiscordant partnerships.

8. Conclusion

Improvements in HIV care and treatment allow HIV-infected individuals around the world to live longer and consider their reproductive goals. In an effort to help HIV-infected individuals meet these goals, HIV serodiscordant couples need access to methods of safer conception. Although there have been great gains with the advent of reproductive technologies to assist with conception, unfortunately these technologies are not readily available for most people affected by HIV and fortunately, not necessary for a large majority of HIV serodiscordant couples with preserved fertility. Periovulatory vaginal insemination coupled with consistent condom use may allow HIF/HUM serodiscordant couples to fulfill their desire of having children without risking sexual HIV transmission.

References

[1] UNAIDS World AIDS Day Report, 2011, http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2216_WorldAIDSday_report_2011_en.pdf.

[2] J. R. Lingappa, B. Lambdin, E. A. Bukusi et al., "Regional differences in prevalence of HIV-1 discordance in Africa and enrollment of HIV-1 discordant couples into an HIV-1 prevention trial," *PLoS ONE*, vol. 3, no. 1, Article ID e1411, 2008.

[3] M. A. Lampe, D. K. Smith, G. J. E. Anderson, A. E. Edwards, and S. R. Nesheim, "Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States," *American Journal of Obstetrics and Gynecology*, vol. 204, no. 6, pp. 488.e1–488.e8, 2011.

[4] S. G. Brubaker, E. A. Bukusi, J. Odoyo, J. Achando, A. Okumu, and C. R. Cohen, "Pregnancy and HIV transmission among HIV-discordant couples in a clinical trial in Kisumu, Kenya," *HIV Medicine*, vol. 12, no. 5, pp. 316–321, 2011.

[5] J. P. Hughes, J. M. Baeten, J. R. Lingappa et al., "Determinants of per-coital act HIV-1 infectivity among African HIV-1 serodiscordant couples," *Journal of Infectious Disease*, vol. 205, no. 3, pp. 358–365, 2012.

[6] J. L. Chen, K. A. Phillips, D. E. Kanouse, R. L. Collins, and A. Miu, "Fertility desires and intentions of HIV-positive men and women," *Family Planning Perspectives*, vol. 33, no. 4, pp. 144–152, 2001.

[7] O. Eyawo, D. de Walque, N. Ford, G. Gakii, R. T. Lester, and E. J. Mills, "HIV status in discordant couples in sub-Saharan Africa: a systematic review and meta-analysis," *The Lancet Infectious Diseases*, vol. 10, no. 11, pp. 770–777, 2010.

[8] L. T. Matthews, J. M. Baeten, C. Celum, and D. R. Bangsberg, "Periconception pre-exposure prophylaxis to prevent HIV transmission: benefits, risks, and challenges to implementation," *AIDS*, vol. 24, no. 13, pp. 1975–1982, 2010.

[9] O. Awiti Ujiji, A. M. Ekström, F. Ilako, D. Indalo, and B. Rubenson, "'I will not let my HIV status stand in the way'. Decisions on motherhood among women on ART in a slum in Kenya—a qualitative study," *BMC Women's Health*, vol. 10, article 13, 2010.

[10] P. Barreiro, J. del Romero, M. Leal et al., "Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy," *Journal of Acquired Immune Deficiency Syndromes*, vol. 43, no. 3, pp. 324–326, 2006.

[11] L. Mandelbrot, I. Heard, E. Henrion-Géant, and R. Henrion, "Natural conception in HIV-negative women with HIV-infected partners," *The Lancet*, vol. 349, no. 9055, pp. 850–851, 1997.

[12] L. G. Bekker, V. Black, L. Myer et al., "Guideline on safer conception in fertile HIV-infected individuals and couples," *Southern African Journal of HIV Medicine*, vol. 12, no. 3, pp. 31–44, 2011.

[13] S. Gruskin, R. Firestone, S. MacCarthy, and L. Ferguson, "HIV and pregnancy intentions: do services adequately respond to women's needs?" *American Journal of Public Health*, vol. 98, no. 10, pp. 1746–1750, 2008.

[14] WHO Definition of Reproductive Rights and United Nations, "Programme of action," in *International Conference on Population Development*, Cairo, September 1994, Paragraph 7.12.

[15] A. van Sighem, L. Gras, P. Reiss, K. Brinkman, and F. de Wolf, "Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals," *AIDS*, vol. 24, no. 10, pp. 1527–1535, 2010.

[16] L. T. Matthews and J. S. Mukherjee, "Strategies for harm reduction among HIV-affected couples who want to conceive," *AIDS and Behavior*, vol. 13, supplement 1, pp. S5–S11, 2009.

[17] L. C. Rispel, C. A. Metcalf, K. Moody, A. Cloete, and G. Caswell, "Sexual relations and childbearing decisions of HIV-discordant couples: an exploratory study in South Africa and Tanzania," *Reproductive Health Matters*, vol. 19, no. 37, pp. 184–193, 2011.

[18] L. T. Matthews, T. Crankshaw, J. Giddy et al., "Reproductive decision-making and periconception practices among HIV-positive men and women accessing HIV care in Durban," in *Proceedings of the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*, Rome, Italy, 2011, Poster Exhibition TUPE325.

[19] O. Coll, A. Suy, F. Figueras et al., "Decreased pregnancy rate after in-vitro fertilization in HIV-infected women receiving HAART," *AIDS*, vol. 20, no. 1, pp. 121–123, 2006.

[20] P. Terriou, P. Auquier, V. Chabert-Orsini et al., "Outcome of ICSI in HIV-1-infected women," *Human Reproduction*, vol. 20, no. 10, pp. 2838–2843, 2005.

[21] M. Stürmer, H. W. Doerr, A. Berger, and P. Gute, "Is transmission of HIV-1 in non-viraemic serodiscordant couples possible?" *Antiviral Therapy*, vol. 13, no. 5, pp. 729–732, 2008.

[22] S. Attia, M. Egger, M. Müller, M. Zwahlen, and N. Low, "Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis," *AIDS*, vol. 23, no. 11, pp. 1397–1404, 2009.

[23] M. S. Cohen, Y. Q. Chen, M. McCauley et al., "Prevention of HIV-1 infection with early antiretroviral therapy," *The New England Journal of Medicine*, vol. 365, no. 6, pp. 493–505, 2011.

[24] Adult ART Guidelines, June 2012, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services, Initiating Antiretroviral Therapy in Treatment-Naïve Patients, http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

[25] G. Lorello, C. la Porte, R. Pilon, G. Zhang, T. Karnauchow, and P. MacPherson, "Discordance in HIV-1 viral loads and antiretroviral drug concentrations comparing semen and blood plasma," *HIV Medicine*, vol. 10, no. 9, pp. 548–554, 2009.

[26] J. D. Homans, S. Christensen, C. H. Wang et al., "Permissive and protective factors associated with presence, level and longitudinal pattern of cervicovaginal HIV shedding," *Journal of Acquired Deficiency Syndrome*, vol. 60, no. 1, pp. 99–110, 2012.

[27] G. Liuzzi, A. Chirianni, M. Clementi et al., "Analysis of HIV-1 load in blood, semen and saliva: evidence for different viral compartments in a cross-sectional and longitudinal study," *AIDS*, vol. 10, no. 14, pp. F51–F56, 1996.

[28] P. L. Vernazza, L. Troiani, M. J. Flepp et al., "Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV," *AIDS*, vol. 14, no. 2, pp. 117–121, 2000.

[29] N. Siegfried, M. Muller, J. J. Deeks, and J. Volmink, "Male circumcision for prevention of heterosexual acquisition of HIV in men," *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD003362, 2009.

[30] B. Auvert, D. Taljaard, E. Lagarde, J. Sobngwi-Tambekou, R. Sitta, and A. Puren, "Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial," *PLoS Medicine*, vol. 2, no. 11, article e298, 2005.

[31] R. C. Bailey, S. Moses, C. B. Parker et al., "Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial," *The Lancet*, vol. 369, no. 9562, pp. 643–656, 2007.

[32] R. H. Gray, G. Kigozi, D. Serwadda et al., "Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial," *The Lancet*, vol. 369, no. 9562, pp. 657–666, 2007.

[33] P. Barreiro, A. Duerr, K. Beckerman, and V. Soriano, "Reproductive options for HIV-serodiscordant couples," *AIDS Reviews*, vol. 8, no. 3, pp. 158–170, 2006.

[34] P. L. Vernazza, I. Graf, U. Sonnenberg-Schwan, M. Geit, and A. Meurer, "Pre-exposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child," *AIDS*, vol. 25, no. 16, pp. 2005–2008, 2011.

[35] *Pivotal Study Finds That HIV Medications are Highly Effective as Prophylaxis against HIV Infection in Men and Women in Africa*, University of Washington International Clinical Research Center, Washington, DC, USA, 2012.

[36] R. M. Grant, J. R. Lama, P. L. Anderdson et al., "Preexposure chemoprophylaxis for HIV prevention in men who have sex with men," *The New England Journal of Medicine*, vol. 363, no. 27, pp. 2587–2599, 2010.

[37] Q. A. Karim, S. S. A. Karim, J. A. Frohlich et al., "Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women," *Science*, vol. 329, no. 5996, pp. 1168–1174, 2010.

[38] T. Kelesidis and R. J. Landovitz, "Preexposure prophylaxis for HIV prevention," *Current HIV/AIDS Reports*, vol. 8, no. 2, pp. 94–103, 2011.

[39] M. S. Cohen, K. E. Muessig, M. K. Smith et al., "Antiviral agents and HIV prevention: controversies, conflicts and consensus ," *AIDS*. In press.

[40] R. P. Walensky, J. E. Park, R. Wood et al., "The cost-effectiveness of pre-exposure prophylaxis for HIV infection in South African women," *Clinical Infectious Disease*, vol. 54, no. 10, pp. 1504–1513, 2012.

[41] T. R. Koppenhaver, W. S. Sorenson, W. Stephen et al., "The cost-effectiveness of pre-exposure prophylaxis in men who have sex with men in the United States: an epidemic model," *Journal of Acquired Immune Deficiency Syndromes*, vol. 58, no. 2, pp. e51–e52, 2011.

[42] E. S. Daar and J. F. Daar, "Human immunodeficiency virus and fertility care: embarking on a path of knowledge and access," *Fertility and Sterility*, vol. 85, no. 2, pp. 298–300, 2006.

[43] J. Ohl, M. Partisani, C. Wittemer et al., "Assisted reproduction techniques for HIV serodiscordant couples: 18 months of experience," *Human Reproduction*, vol. 18, no. 6, pp. 1244–1249, 2003.

[44] A. E. Semprini, L. H. Hollander, A. Vucetich, and C. Gilling-Smith, "Infertility treatment for HIV-positive women," *Women's Health*, vol. 4, no. 4, pp. 369–382, 2008.

[45] Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Section: Reproductive Options for HIV Concordant and Serodiscordant Couples, http://www.aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/153/reproductive-options-for-hiv-concordant-and-serodiscordant-couples, 2011.

[46] R. Ecochard, H. Boehringer, M. Rabilloud, and H. Marret, "Chronological aspects of ultrasonic, hormonal, and other indirect indices of ovulation," *British Journal of Obstetrics and Gynaecology*, vol. 108, no. 8, pp. 822–829, 2001.

[47] A. C. Thornton, F. Romanelli, and J. D. Collins, "Reproduction decision making for couples affected by HIV: a review of the literature," *Topics in HIV Medicine*, vol. 12, no. 2, pp. 61–67, 2004.

[48] O. Mmeje, M. Workneh, B. Njoroge et al., "Perspectives on vaginal insemination as a safer method of conception among HIV serodiscordant couples and their healthcare providers in Kisumu, Kenya," *AIDS Research and Treatment*. In press.

[49] S. G. Brubaker, L. Darbes, E. A. Bukusi et al., "Risk perception and the desire for children among HIV discordant couples in Kisumu, Kenya," in *Proceedings of the 6th IAS Conference on HIV Pathogenesis and Treatment*, International AIDS Society, 2010, TUPE 332.

[50] R. Tubiana, S. Matheron, J. LeChenadec et al., "Extremely low risk of HIV in women starting HAART before pregnancy: french perinatal cohort, ANRS EPF CO1/11," in *Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections*, 2011, 735.

[51] The Ethics Committee of the American Society for Reproductive Medicine, "Human immunodeficiency virus and infertility treatment," *Fertility and Sterility*, vol. 82, supplement 1, pp. S228–S231, 2004.

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Research Article

Fertility Intentions and Interest in Integrated Family Planning Services among Women Living with HIV in Nyanza Province, Kenya: A Qualitative Study

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Despite increasing efforts to address the reproductive health needs of people living with HIV, a high unmet need for contraception exists among HIV+ women in sub-Saharan Africa. This study explores the fertility intentions and family planning (FP) preferences of Kenyan women accessing HIV treatment. We conducted 30 semistructured interviews and qualitatively analyzed the data with a grounded theory approach. Fears of premature death, financial hardship, and perinatal HIV transmission emerged as reasons for participants' desire to delay/cease childbearing. Participants strongly identified FP needs, yet two-thirds were using male condoms alone or no modern method of contraception. Women preferred the HIV clinic as the site of FP access for reasons of convenience, provider expertise, and a sense of belonging, though some had privacy concerns. Our findings support the acceptability of integrated FP and HIV services. Efforts to empower women living with HIV to prevent unintended pregnancies must expand access to contraceptive methods, provide confidential services, and take into account women's varied reproductive intentions.

1. Introduction

In the last decade, it has been increasingly recognized that global HIV/AIDS efforts often fail to address the reproductive health—and specifically family planning (FP)—needs of people living with HIV [1]. The need for an integrated approach to reproductive health and HIV was formally acknowledged as early as the 1994 International Conference on Population and Development [2] and has since generated substantial policy support and academic interest [3–5]. Yet disconnected and "vertically oriented" HIV programs persist [6], largely the product of separate funding streams and what has been described more recently as the "PEPFAR effect," which refers to the consequences of restrictions on the US President's Emergency Plan for AIDS Relief-(PEPFAR-) supported programs against using funding for family planning [7].

In sub-Saharan Africa (SSA), a region where reproductive-aged women account for the majority of people living with HIV [8], there also exists a high unmet need for contraception. Unintended pregnancies (unwanted or mistimed) are estimated to account for 14–58% of all pregnancies in SSA [9]. Recent evidence suggests an even higher burden of unintended pregnancy among women living with HIV. In a cohort of Ugandan women started on antiretroviral therapy (ART), 17% became pregnant over the 2-year followup period, despite 93% not wanting or planning pregnancy. Additionally, among the women who did not desire children, only 14% were using a modern contraceptive method other than condoms [10]. Another study of South African pregnant women attending a prevention of parent-to-child transmission (PPCT) clinic found that 84% of clients' pregnancies were unintended [11].

From both reproductive rights-based and public health perspectives, the prevention of unintended pregnancy among women living with HIV has significant implications for maternal and child health. The World Health Organization/United Nations Population Fund Glion Call to Action emphasized family planning as one of four critical elements of a comprehensive PPCT strategy [12], reflecting the evidence on the cost savings and demonstrated effectiveness of contraception in averting HIV-positive births [13, 14]. Improved access to contraception among this population is also expected to facilitate efforts to decrease maternal morbidity and mortality, as well as poor neonatal outcomes [15, 16].

The Kenyan government, consistent with international policy recommendations, has demonstrated a strong commitment to the need to improve systems linkages between reproductive health and national HIV programs, reflected in its recently developed national policy strategy for reproductive health and HIV/AIDS integration [17]. However, little research has yet evaluated the clinical effectiveness of integration. This qualitative study was conducted as part of formative research for a cluster-randomized controlled trial (RCT) comparing integrated family planning and HIV services with the existing referral-based model in Nyanza Province, Kenya with respect to contraceptive prevalence. Located in western Kenya bordering Lake Victoria, Nyanza Province has the highest HIV prevalence in Kenya, at 16% among women and 11% among men [18]. According to the 2009 Demographic and Health Survey, 76% of reproductive-age women in Kenya wanted to delay pregnancy at least 2 years or have no more children, while only 33% were using a modern contraceptive method [18].

Despite the growing body of literature on the complex reproductive desires of people living with HIV/AIDS [19], there exist few in-depth studies set in Kenya and even fewer on people's attitudes towards integrated FP-HIV services [20]. This study sought to explore reproductive intentions, contraceptive experience, and family planning preferences among women accessing HIV care and treatment in Nyanza Province. Our aim was to gain a better understanding of HIV-positive women's experience and needs in order to guide efforts to reduce unmet need for contraception within this population, in part through designing the FP-HIV integrated service model for use in the cluster RCT.

2. Methods

2.1. Sites. This qualitative study was conducted between July and September 2009 in parallel with the baseline data-collection phase of the cluster RCT described above, that is, before integration took place. Participants were recruited from 11 public sector HIV clinics taking part in the cluster RCT in Kisumu East, Migori, Nyatike, Rongo, and Suba Districts of Nyanza Province; 1 dispensary, 8 health centers, 1 subdistrict hospital, and 1 district hospital were included in rural and periurban areas. Qualitative interviews were conducted at each site in conjunction with a knowledge, attitudes, practices, and behavior (KAPB) survey. All sites were supported by Family AIDS Care and Education Services (FACES), a collaboration between the University of California, San Francisco (UCSF), and the Kenyan Medical Research Institute (KEMRI). This study was approved by the ethical review boards of KEMRI and UCSF.

2.2. Eligibility. Eligible participants were nonpregnant and nonsterilized, HIV-positive women aged 18–45 who were accessing care at FACES-supported HIV clinics. A convenience sample of KAPB survey respondents was invited to participate in an interview immediately after survey completion; each participant provided voluntary written informed consent and received a reimbursement of approximately USD $2.50 for their time and travel.

2.3. Open-Ended Interviews. Thirty open-ended interviews were conducted to explore female clients' fertility intentions and family planning preferences in the context of integration of FP services into HIV care and treatment. Interviews were conducted in participants' first language (DhoLuo or Kiswahili) by a trained female interviewer. Each interview lasted approximately 60 minutes and was based on a semistructured interview guide. All interviews were audio recorded.

2.4. Data Analysis. Interviews were transcribed and translated into English. Data were managed in Atlas-ti 5.2 (Scientific Software Development, Berlin, Germany), and transcripts were coded and analyzed with a grounded theory approach [21], though unlike classic grounded theory the data were collected and analyzed sequentially. Three investigators independently conducted initial coding of the transcripts according to a codebook constructed from the interview guide content and a preliminary content analysis of the raw data; inductive codes based on the data were developed as concepts emerged. Each coded transcript was checked by a second investigator, and discrepancies were resolved through discussion and consensus. In the final analysis, codes and quotations were grouped to identify thematic trends and variant views. Quotes presented here are identified by the age of the participant, the number of living children she has, and her current contraceptive method, if any; multiple quotes from the same participant are identified as such. Nonnumerical quantifiers such as "the majority," "a minority," "almost all," and "a few," are used to frame various themes; where proportions of participants are quantified, it is for the purpose of highlighting specific points and is intended to be descriptive only.

3. Results

The mean participant age was 30 years, with a median of 29.5 years (Table 1). The majority (70%) were married or living with a man, and 8 (27%) were in polygynous marriages. Among the 28 (93%) women who had given birth, the mean number of live births was 4.6, with an average of 3.2 living children. One-third had begun an antiretroviral regimen. Eight (27%) women were using a method of contraception

Table 1: Participant sociodemographic characteristics and current contraceptive use among 30 study participants in Nyanza Province, Kenya.

	N (%)	Mean	Range
Age		30	18–42
18–24	6 (20%)		
25–34	18 (60%)		
35–42	6 (20%)		
Marital status			
Married or living with a man	21 (70%)		
Polygynous marriage	8 (27%)		
Widowed/inherited	7 (23%)/4 (14%)		
Unmarried, not living with a man	2 (7%)		
Education			
Primary school or less	25 (84%)		
Secondary school	5 (17%)		
Literacy			
Reads with difficulty or not at all	17 (57%)		
Reads easily	13 (43%)		
Number of live births, $N = 28$		4.6	1–11
Number of living children, $N = 28$		3.2	1–7
Time since HIV diagnosis (years)		1.5	<1–4
Currently on ART	10 (33%)		
Current contraceptive use			
No modern method	10 (33%)		
Injectable	7 (23%)		
Combined oral contraceptives	1 (3%)		
Condoms only	12 (40%)		
Dual method use	2 (7%)		

other than condoms, while 12 (40%) were using condoms only, and 10 (33%) were not using a modern contraceptive method.

3.1. Desire to Delay or Cease Childbearing. All but two participants wanted to delay pregnancy for at least two years or have no more children; of note, the women who desired a child within the next two years were both nulliparous. Of the 16 women who desired a future pregnancy, over half wanted to delay the pregnancy for 4–10 years. Several main themes emerged around participants' desire to delay or cease childbearing.

The perceived detrimental effects of pregnancy and childbirth on HIV-related poor health and immune status were frequently expressed concerns. One participant had been counseled that her CD4 count was too low to have a child; another woman who had recently given birth explained,

> "*I don't want to give birth soon because I am sick. The virus is … destroying my blood so if I give birth very soon then my immunity goes down …*" (P1: 29 years, 2 children, no modern method)

Related to concerns about deteriorating health, several women feared dying prematurely and spoke of uncertainty around the length of one's life in the context of caring for existing or future children as a reason to stop having children. Single relationship status, often synonymous with widowhood, was also a factor for several participants. Inherited by a brother-in-law according to some Luo people's custom after her husband died, one widow said,

> "*Before I tested HIV positive, I was at liberty, I knew that even if one day I die it would just come as my days were numbered by God, but with HIV I felt that I would die prematurely and since their [my children's] father was not there and I was solely taking care of them it worried me. Before then I was happy …*" (P7: 39 years, 6 children, injectable contraception)

The majority of participants considered the risk of transmitting HIV to a child in their fertility intentions, although a wide spectrum of knowledge existed around the likelihood of perinatal transmission. Many women had sophisticated understandings of prevention strategies, while others believed transmission inevitable: "*because I am giving birth to them when I am sick, and they would also be born sick….*" Some women described previous experiences of losing children to AIDS. A participant who had known her status for less than a year and already had five children said:

> "*I have been worried about the child that I have now because of being HIV positive, whether the child is infected or not … I don't have the desire to have another child … because I fear … I am sick and I don't know my baby's future.*" (P26: 31 years, 5 children, male condom)

Financial hardship, often related to poor health and subsequent inability to do strenuous labor or lack of support from a male partner, was also a common theme related to preventing future pregnancies. Many participants prioritized providing for existing children in the context of diminishing resources. One woman said, "*nowadays when I go to the farm I can't work longer because I am weak and … I have no steady source of livelihood.*" Another woman who was concerned about providing for her children's education, despite her family's need for labor, reasoned,

> "*The family members do not like women to go for family planning. They ask … "why is a woman going for family planning, yet there is a huge parcel of land?" ….*" (P22: 23 years, 3 children, injectable contraception)

3.2. Influences on Fertility Intentions. Participants cited health care providers as influences on their reproductive intentions more often than they mentioned family or other community members. Provider counseling contributed to a range of understandings of the risks associated with

pregnancy and/or HIV transmission, which might have depended on the woman's health.

> "*Following the kind of counseling we get here at the clinic, one can just decide not to have another pregnancy if you are already infected. This is because the pregnancy lowers your immune system thereby making you vulnerable to other infections* ….." (P9: 33 years, 4 children, male condom)

> "*… If you give birth, the health care providers try so hard to protect the child such that if you follow the counseling the children will just be okay. So even if you got HIV having only one child, you can go ahead and have more children.*" (P8: 23 years, 3 children, no modern method)

Although many participants spoke of joint decision making around fertility with partners, others had never spoken of their specific plans to delay or stop childbearing with partners. Albeit obliquely, some women discussed the complexity of their communication with men around reproductive issues, dually focusing on the woman as the final decision maker and the need to cement couple relationships by having a child:

> "*If you don't have any child then you might be forced to have because you know it is the child that allows a woman to stay in a man's house. You will be forced to give birth even to two so that they can say that so-and-so gives birth, then after that you stop.*" (P12: 28 years, 2 children, male condom)

Family members and in-laws significantly influenced several women's reproductive intentions in both directions. A few women stated that their HIV status was the reason they had been advised against pregnancy. For example,

> "*We had discussed it with [my sisters], and they felt I shouldn't get another pregnancy … They were saying that having another child would just give lots of problems to the child because the child will also have HIV.*" (P11: 32 years, 5 children, male condom/pill)

Another participant noted that her mother-in-law, who expected her to die of AIDS, "*told me that I should not give birth because there is no one who will raise the children, because your husband is dead.*" Other participants felt a social imperative towards fertility. Feeling pressure by extended family to get pregnant again, a woman whose child had recently died said,

> "*You may tell [the relatives] that now you don't feel like having another child … They don't like it … they tell you 'just continue to give birth you are still young'.*" (P1: 29 years, 2 children, no modern method)

Another woman put it like this: "You know, it's good to have a child so that people don't look down on you."

3.3. Unintended Pregnancy. When discussing their most recent pregnancies, roughly half of women said their pregnancies had been desired or planned, and half were undesired, for reasons very similar to those discussed above. Narratives of unintended pregnancy centered on poor health and consequences to one's child(ren) rather than positive HIV status itself.

> "*During my last pregnancy I became very sick, and when I eventually gave birth the baby also had very poor health, [and] after one month the baby died. That is when I learned of my HIV status … Since my child died as a result of that I don't see the need of getting another child* …." (P20: 42 years, 2 children, no modern method)

Most participants expressed profoundly negative feelings when asked how they would react to a pregnancy now. Women also spoke of a sense of powerlessness around unintended pregnancy, which was linked to the belief that pregnancy occurs according to "God's plan." Almost a quarter spontaneously volunteered that they would try to procure an abortion if they learned they were pregnant, despite financial and potentially lethal consequences:

> "*I would contemplate abortion, but I also fear that I would lose my life in the process of abortion; however, I would seriously consider terminating the pregnancy.*" (P7: 39 years, 6 children, injectable contraception)

3.4. Contraceptive Experience. The vast majority of participants expressed a need for FP (27/30), though over two-thirds were currently using male condoms only, or no modern method of contraception (Table 1). When women were asked which FP method they would prefer to use, injectable and implantable, followed by oral, methods were most frequently desired, and over half indicated that they would prefer tubal ligation then or in the future. Some women discussed the benefits of condoms as an FP method, either alone or in combination with another method to prevent sexually transmitted infections, while others focused on the pitfalls associated with negotiating condom use.

> "*You know at times you may want to use it [condom], but then your partner will think maybe you don't trust him, and you may end up infecting him.*" (P8: 23 years, 3 children, no modern method)

Women's choice to use or not use a particular contraceptive was strongly influenced by perceptions of method side effects, regardless of whether the side effects had been experienced personally or heard about from others. Most personally experienced side effects were associated with injectables and involved excessive or irregular vaginal bleeding. However, participants had heard about various methods causing infertility, drug reactions with ART, wasting, weakness and inability to work, as well as pain, other physical complications, and even death. One participant,

who was using injectable contraception without her partner's knowledge since learning of her HIV status, spoke of his reasons for opposing FP use:

> "*They [pills and injectables] may hinder you from giving birth later or you might even have another problem which may lead to you going for an operation ….*" (P2: 26 years, 2 children, injectable contraception)

3.5. Unmet Need. Though the majority of participants denied encountering any difficulties in accessing FP, many expressed an unmet need for contraception. Several access-related obstacles emerged in addition to health concerns, among which were unreliable stock of contraceptive methods and provider availability, inability of some providers to speak the local language, and distance to the clinic. Partner resistance to FP was another barrier to access participants mentioned, although many emphasized their own decision-making autonomy as "*the one who will bear the burden.*" Several women spoke of using FP secretly, some risking separation or abandonment by their partners.

> "*The problem [regarding family planning] is at home. But once you turn your back there is no problem … it is the person you are living with that causes the problem by saying that 'I don't want that'.*" (P1: 29 years, 2 children, no modern method)

3.6. Preference for Integrated Services. When asked where participants would prefer to access FP services, the majority stated a preference for the HIV clinic, and all but a few women preferred integrated FP-HIV services when this option was specifically proposed. Convenience and a sense of belonging at the HIV clinic were the most commonly mentioned advantages to integrated services. Many were already making trips to the HIV clinic for drugs and felt like an established "*regular*" there.

> "*[The HIV clinic] is the place where I come and I get all the services without announcing my problem elsewhere. I meet my need and I leave for home.*" (P1: 29 years, 2 living children, no modern method)

Other women preferred the HIV clinic as the site of FP access for reasons of provider expertise; the "*good doctors who are educated*" were able to avoid prescribing FP methods that may react with antiretroviral drugs and to provide more family-oriented counseling and services, thereby helping to protect children from HIV. Women mistrusted volunteers and community health workers (CHWs), who they perceived as lacking the necessary knowledge and training to provide FP. Participants preferred FP to be provided by trained clinicians.

Women's individual experiences accessing care at the various HIV clinic sites appeared to inform their perspectives on how integrated services might affect privacy concerns. One participant remarked on the potential for increased privacy around FP at the HIV clinic, as one was able to speak to a nurse one-on-one in this setting, whereas at the FP clinic several women may be counseled at the same time. The only woman to say she would refuse FP at the HIV clinic spoke of the need for clandestine FP services:

> "*Family planning is something secret … I would like to get it from a different, private place.*" (P29: 30 years, 3 children, male condom)

Of note, this participant reported that her partner said he would leave her if he found out she was using an FP method other than condoms.

Similarly, the idea of accessing FP in a "mixed up" setting, that is, one that also served men, was simultaneously viewed as an advantage and disadvantage to integrated services. One woman wanted to access FP where there were only women, while another preferred the HIV clinic "*because while we are waiting to go in men and women are counseled together.*" Two women admitted using injectable contraception without their partners' knowledge, and both preferred integrated services.

4. Discussion

This study provides insights into the fertility desires and family planning needs of a sample of Kenyan women accessing HIV care. It is among the first to specifically explore women's perspectives on FP-HIV integration, as increasing priority is placed on strengthening health systems globally. This contribution is particularly relevant, both in the context of the related cluster RCT as well as the wider efforts on FP-HIV integration, given the imperative to design integration interventions that take into account women's lived experiences. Our findings corroborate other studies' portrayal of the diversity and complexity of reproductive intentions among people living with HIV in sub-Saharan Africa, which are influenced by overlapping health-related, sociocultural, and socioeconomic factors [22–24]. Yet the value of qualitative, geographically-specific perspectives such as those generated in this study lies in their capacity to uncover nuances that are essential in informing both interventions and further research.

We observed a strong desire on the part of most participants to delay or cease childbearing, the reasons for which were often HIV-related. However, consistent with prior studies and the larger KAPB survey sample [25, 26], contraceptive prevalence was low. Though many women spoke of various barriers to FP access as presented above, a good number of participants did not provide a rationale for their "unmet need," that is, why they were not taking action to prevent pregnancy. This disconnect is salient given the substantial minority of participants who were ready to face significant costs to terminate a pregnancy. Abortion is legally restricted in Kenya, and unsafe abortion accounts for approximately 17% of maternal mortality in Eastern Africa [27, 28].

Many participants were not as forthcoming about systems-related sources of unmet need for contraception as expected based on formative research in the region [29].

For example, reports from the field as the cluster RCT continues suggest that user fees are a barrier to FP use [30], while only one participant in this study mentioned cost as an obstacle to access. Rather, fears of method safety and partner influence were more dominant themes. The significant role of men in reproductive decision making has been recognized in the literature for years [31, 32], leading many to call for interventions to increase male involvement in family planning programs. Yet, gendered power dynamics around contraception are, without question, complex. Our participants' narratives included mention of women's preference for injectables as a more easily concealed method; whether or not covert contraceptive use is being used as a "practical strategy to subvert male authority," [33] 16% of married women in Nyanza Province use contraception without their partners' knowledge, and nearly half of all modern contraceptive users in Kenya are using injectable methods [18]. Though this study necessarily concentrated on women living with HIV, our findings suggest that the factors associated with unmet need for FP among HIV+ women may reflect the social, economic, and cultural circumstances of the women of Nyanza Province in general. Clearly, from a rights-based perspective, it is essential to work toward meeting all women's needs for contraception.

Though most women stated a strong preference for integrated FP-HIV services, concerns about privacy emerged. One could interpret these concerns in the context of covert contraceptive use, or the widespread belief among men in Kenya that contraception use leads to female promiscuity [18]. In contrast, a pilot study of integrated FP, ART, and Voluntary Counseling and Testing (VCT) services in Uganda revealed a preference for integration in part because women felt that attending sessions with male partners would help them change their partners' negative views on FP [20]. More research is needed to better understand how relationship and gender dynamics influence reproductive and contraceptive choice among women in sub-Saharan Africa.

In contrast with other research [22, 34], study participants made no mention of health care provider disapproval or stigma as a potential deterrent to accessing reproductive health services at the HIV care and treatment clinics or referral clinics. This reflects the results of recent interviews with providers at these same clinics, who strongly supported the reproductive rights of women living with HIV and their desire to have children when they want [35]. However, it should be noted that the majority of women had not accessed formal FP services since learning of their HIV status. Provider counseling, on the other hand—particularly around the risk of perinatal HIV transmission and the effects of pregnancy on HIV disease—emerged as an influential factor on women's reproductive intentions in both directions. Additionally, women's lack of confidence in the ability of CHWs and volunteers to provide FP methods was notable, particularly in the setting of decades of research demonstrating the acceptability of programs such as community-based distribution of contraception in the region [36]. Our study's participants tended to associate CHWs with practitioners of traditional, or herbal, medicine. Women also placed a high value on obtaining care from those they viewed as legitimate medical professionals, as reflected in the finding that provider expertise at the HIV clinic was a major factor in participants' preference for accessing FP there. It is possible that this sample of women, who were already established in the medical system, were more concerned with credentials than other women in the community.

Fears of method side effects and other untoward effects, many of which would be considered misperceptions, significantly shaped women's reproductive choices among our participants. Such concerns are the leading reason for contraceptive nonuse in Kenya more broadly [18]. Furthermore, the desire for permanent or long-acting contraception surfaced frequently in our interviews, often among women who were currently using less effective methods or no modern FP method and expressed considerable fears regarding contraceptive methods. These findings suggest that addressing women's FP needs, including permanent and LARC methods, must incorporate balanced reproductive health and FP counseling for people living with HIV, as well as community-based education on method safety [37, 38]. Partially in response to these findings, the cluster RCT included a training focus on counseling about and provision of long-acting reversible contraception (LARC), as well as referral for surgical sterilization.

This exploratory study has several limitations. As with most qualitative studies, its sample size is small, and the study was not designed to produce findings that would be generalizable to other women living with HIV in Kenya or elsewhere in SSA. Instead, the aim was to provide deeper insights that could inform results from larger samples. The quantitative data describing our study participants is not intended to be representative of a broader population. In addition, study participants were already accessing HIV care; we did not include women living with HIV from the community who were not accessing HIV care or women of unknown HIV status, who may have had different perspectives. Given that these women were recruited from clinic sites and might have associated interviewers with care providers, there is also a risk of social desirability bias. Though theoretical saturation was reached around all main themes, some concepts, such as the desire for fertility within two years and the influence of cultural practices such as wife inheritance and polygyny on fertility intentions, could not be fully developed due to the small sample size. Finally, nuances of language and nonverbal communication strategies may have been lost or misinterpreted during the process of data transcription and translation.

Women living with HIV, like all women, should have access to highly effective methods to avoid unintended pregnancy. The integration of FP services into HIV care has been identified as a promising strategy to reduce unmet need for contraception among women living with HIV, and this study supports its acceptability. However, our findings emphasize that increasing access from the health systems perspective will not necessarily address other important determinants of access and choice, such as the balance of power in intimate relationships and fears regarding method safety. Despite these challenges, efforts to empower women

living with HIV to prevent unintended pregnancies must expand access to all contraceptive methods, particularly long-acting and permanent methods. These efforts must also provide confidential, informed services that take into account women's varied reproductive intentions and needs.

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References

[1] S. Gruskin, L. Ferguson, and J. O'Malley, "Ensuring sexual and reproductive health for people living with HIV: an overview of key human rights, policy and health systems issues," *Reproductive Health Matters*, vol. 15, no. 29, pp. 4–26, 2007.

[2] United Nations Population Fund (UNFPA), International Conference on Population and Development (ICPD) Programme of Action, United Nations Population Fund, Cairo, Egypt, 1995.

[3] J. Fleishman, *Integrating Reproductive Health and HIV/AIDS Programs: Strategic Opportunities for PEPFAR*, Center for Strategic and International Studies, Washington, DC, USA, 2006.

[4] R. Wilcher, W. Cates Jr., and S. Gregson, "Family planning and HIV," *AIDS*, vol. 23, supplement 1, pp. S1–S130, 2009.

[5] K. Angela, D. R. Bangsberg, G. Gray, R. S. Hogg, R. King, and C. L. Miller, "HIV, HAART, and Fertility in sub-Saharan Africa," *AIDS and Behavior*, vol. 13, supplement 1, pp. S1–S112, 2009.

[6] C. Dickinson, K. Attawell, and N. Druce, "Progress on scaling up integrated services for sexual and reproductive health and HIV," *Bulletin of the World Health Organization*, vol. 87, no. 11, pp. 846–851, 2009.

[7] R. Wilcher, W. Cates Jr., and S. Gregson, "Family planning and HIV: strange bedfellows no longer," *AIDS*, vol. 23, supplement 1, pp. S1–S6, 2009.

[8] UNAIDS, "UNAIDS Report on the Global AIDS Epidemic," 2010, http://www.unaids.org:80/globalreport/Global_report.htm.

[9] H. W. Reynolds, B. Janowitz, R. Wilcher, and W. Cates, "Contraception to prevent HIV-positive births: current contribution and potential cost savings in PEPFAR countries," *Sexually Transmitted Infections*, vol. 84, supplement 2, pp. ii49–ii53, 2008.

[10] J. Homsy, R. Bunnell, D. Moore et al., "Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study," *PLoS One*, vol. 4, no. 1, Article ID e4149, 2009.

[11] T. J. Rochat, L. M. Richter, H. A. Doll, N. P. Buthelezi, A. Tomkins, and A. Stein, "Depression among pregnant rural South African women undergoing HIV testing," *Journal of the American Medical Association*, vol. 295, no. 12, pp. 1376–1378, 2006.

[12] United Nations Population Fund (UNFPA), "The Glion Call to Action on Family Planning and HIV/AIDS in Women and Children," 2004, http://www.unfpa.org/public/publications/pid/1435.

[13] H. W. Reynolds, B. Janowitz, R. Homan, and L. Johnson, "The value of contraception to prevent perinatal HIV transmission," *Sexually Transmitted Diseases*, vol. 33, no. 6, pp. 350–356, 2006.

[14] M. D. Sweat, K. R. O'Reilly, G. P. Schmid, J. Denison, and I. de Zoysa, "Cost-effectiveness of nevirapine to prevent mother-to-child HIV transmission in eight African countries," *AIDS*, vol. 18, no. 12, pp. 1661–1671, 2004.

[15] A. Duerr, S. Hurst, A. P. Kourtis, N. Rutenberg, and D. J. Jamieson, "Integrating family planning and prevention of mother-to-child HIV transmission in resource-limited settings," *The Lancet*, vol. 366, no. 9481, pp. 261–263, 2005.

[16] P. Brocklehurst and R. French, "The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis," *British Journal of Obstetrics and Gynaecology*, vol. 105, no. 8, pp. 836–848, 1998.

[17] Republic of Kenya, *National Reproductive Health and HIV/AIDS Integration Strategy*, National AIDS and STI Control Program (NASCOP) and the Division of Reproductive Health (DRH), Nairobi, Kenya, 2009.

[18] Kenya National Bureau of Statistics (KNBS) and USAID, *Kenya Demographic and Health Survey 2008-09*, 2010, http://www.measuredhs.com/pubs/pdf/FR229/FR229.pdf.

[19] B. Nattabi, J. Li, S. C. Thompson, C. G. Orach, and J. Earnest, "A systematic review of factors influencing fertility desires and intentions among people living with HIV/AIDS: implications for policy and service delivery," *AIDS and Behavior*, vol. 13, no. 5, pp. 949–968, 2009.

[20] D. Asiimwe, R. Kibombo, J. Matsiko, and K. Harden, *Study of the Integration of Family Planning and VCT/PMTCT/ART Programs in Uganda*, Makerere Institute for Social Research and POLICY for USAID, 2005.

[21] K. Charmaz, *Constructing Grounded Theory: A Practical Guide Through Qualitative Analysis*, Sage, Thousand Oaks, Calif, USA, 2006.

[22] D. Cooper, J. Harries, L. Myer, P. Orner, and H. Bracken, "'Life is still going on': reproductive intentions among HIV-positive women and men in South Africa," *Social Science & Medicine*, vol. 65, no. 2, pp. 274–283, 2007.

[23] F. Laher, C. S. Todd, M. A. Stibich et al., "A qalitative assessment of decisions affecting contraceptive utilization and fertility intentions among HIV-positive women in Soweto, South Africa," *AIDS and Behavior*, vol. 13, supplement 1, pp. S47–S54, 2009.

[24] D. Cooper, J. Moodley, V. Zweigenthal, L. G. Bekker, I. Shah, and L. Myer, "Fertility intentions and reproductive health care needs of people living with HIV in Cape Town, South Africa: implications for integrating reproductive health and HIV Care services," *AIDS and Behavior*, vol. 13, supplement 1, pp. S38–S46, 2009.

[25] A. Anand, R. W. Shiraishi, R. E. Bunnell et al., "Knowledge of HIV status, sexual risk behaviors and contraceptive need among people living with HIV in Kenya and Malawi," *AIDS*, vol. 23, no. 12, pp. 1565–1573, 2009.

[26] S. Newmann, D. Grossman, C. Blat et al., "Contraceptive use and receptivity to integration of family planning services into

HIV care among HIV-infected men and women in Nyanza province, Kenya," in *Proceedings of the Reproductive Health*, Atlanta, Ga, USA, September 2010.

[27] World Health Organization (WHO), *Unsafe Abortion: Global and Regional Estimates of the Incidence of Unsafe Abortion and Associated Mortality in 2008*, World Health Organization, Geneva, Switzerland, 6th edition, 2011, http://www.who.int/reproductivehealth/publications/unsafe_abortion/9789241501118/en/index.html.

[28] United Nations Population Division, *World Abortion Policies 2007*, 2007, http://www.un.org/esa/population/publications/2007_Abortion_Policies_Chart/2007AbortionPolicies_wallchart.htm.

[29] K. Koh, "Suggestions for improving reproductive health care at FACES Clinics," Personal communication, 2006.

[30] G. A. Ong'udi, "Personal communication," 2011.

[31] B. Wolff, A. K. Blanc, and J. Ssekamatte-Ssebuliba, "The role of couple negotiation in unmet need for contraception and the decision to stop childbearing in Uganda," *Studies in Family Planning*, vol. 31, no. 2, pp. 124–137, 2000.

[32] N. Dodoo, "Men matter: additive and interactive gendered preferences and reproductive behavior in Kenya," *Demography*, vol. 35, no. 2, pp. 229–242, 1998.

[33] A. E. Biddlecom and B. M. Fapohunda, "Covert contraceptive use: prevalence, motivations, and consequences," *Studies in Family Planning*, vol. 29, no. 4, pp. 360–372, 1998.

[34] S. Bharat and V. S. Mahendra, "Meeting the sexual and reproductive health needs of people living with HIV: challenges for health care providers," *Reproductive Health Matters*, vol. 15, supplement 29, pp. 93–112, 2007.

[35] S. Newmann, K. Mishra, E. A. Bukusi et al., "Integration of family planning into HIV care in Nyanza Province, Kenya: what do providers think?,". In press.

[36] J. F. Phillips, W. L. Greene, and E. F. Jackson, *Lessons from Community-Based Distribution of Family Planning in Africa*, Population Council, New York, NY, USA, 1999, http://www.popcouncil.org/pdfs/wp/121.pdf.

[37] J. Harries, D. Cooper, L. Myer, H. Bracken, V. Zweigenthal, and P. Orner, "Policy maker and health care provider perspectives on reproductive decision-making amongst HIV-infected individuals in South Africa," *BMC Public Health*, vol. 7, article 282, 2007.

[38] N. Rutenberg and C. Baek, "Field experiences integrating family planning into programs to prevent mother-to-child transmission of HIV," *Studies in Family Planning*, vol. 36, no. 3, pp. 235–245, 2005.

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Clinical Study

Awareness and Interest in Intrauterine Contraceptive Device Use among HIV-Positive Women in Cape Town, South Africa

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Objective. To assess awareness of and interest in intrauterine contraceptive device (IUCD) use among HIV-positive women in Cape Town, South Africa. *Design*. Cross-sectional survey. *Methods*. HIV-positive women aged 18 through 45 years presenting for care at a primary health care clinic in Cape Town, South Africa participated in this study. Consented participants completed a staff-administered questionnaire in a private setting. Descriptive statistics were generated. Comparisons between demographic and reproductive health-related variables and IUCD awareness and interest were performed with multiple logistic regression. Analyses for IUCD interest excluded women with prior surgical sterilization. *Results*. Of 277 HIV-positive women, 37% were aware of the IUCD; awareness was independently associated with greater age (adjusted odds ratio (AOR) = 1.15, 95%; confidence interval (CI): 1.10–1.20) and not switching contraceptive methods in the last year (AOR = 2.45, 95% CI: 1.03–5.83). Following an IUCD information session, 86% of women (n = 206/240) were interested in IUCD use. IUCD interest was inversely associated with age (AOR = 0.91, 95% CI: 0.86–0.97) and marginally positively associated with current menstrual bleeding pattern complaints (AOR = 2.14, 95% CI: 0.98–4.68). *Conclusions*. Despite low levels of method awareness, HIV-positive women in this setting are frequently interested in IUCD use, indicating need for programming to expand method access.

1. Introduction

Contraceptive use to prevent unplanned pregnancy is the most cost-effective means of preventing maternal-to-child transmission of HIV [1–4]. Systemic hormonal contraceptives and male condoms are among the most popular contraceptive methods in Sub-Saharan Africa, the global region with the greatest proportion of HIV-infected women [5–7]. Some studies have suggested that systemic hormonal contraceptive method use by HIV-positive women may increase HIV transmission to male partners and progression of HIV disease among users, particularly for depot medroxyprogesterone acetate (DMPA), though findings are mixed [8–14]. These findings, coupled with high unmet need for contraception in Sub-Saharan Africa, have spurred calls for safe, long-acting reversible contraceptive methods for HIV-positive women [4, 15].

The intrauterine contraceptive device (IUCD) is a highly effective, long-acting contraceptive method and is not widely used in Sub-Saharan Africa, including South Africa [16]. Two studies among reproductive aged women in South Africa indicate low (26–41%) awareness of the IUCD as a contraceptive method, despite its inclusion in contraceptive method mix and availability at no cost through the public sector [17, 18]. Both studies found that a majority (69–74%) of women were interested in IUCD use after receipt of basic information about the method [17, 18]. However, these studies did not differentiate women by HIV

status, although other studies indicate that HIV infection often impacts contraceptive method choice, potentially resulting in differences in IUCD receptivity [5, 19].

Among HIV-positive women, the safety of the copper IUCD has been established in terms of both disease progression and pelvic inflammatory disease incidence [20–23]. A small European case-control trial suggests the levonorgestrel IUCD is also safe for HIV-positive women [24]. Despite the potential role of IUCDs in the method mix for HIV-positive women, levels of awareness of and interest in the IUCD among HIV-positive women are not well understood. Qualitative assessments among HIV-positive women in South Africa and Kenya indicate that prior IUCD use is uncommon [25, 26]. Awareness of the IUCD is largely based on peer-communicated knowledge of negative effects but does not reflect potential interest in method use with receipt of correct information [25, 26]. Recent data from 271 HIV-positive Malawian women meeting IUCD eligibility criteria reflect that 79% were willing to accept the copper IUCD, even if it was not their first choice for a method but did not explore reasons impacting decision to use [27]. We conducted a study to assess awareness level and potential interest in the IUCD as a contraceptive method as well as characteristics associated with awareness of and receptivity to the IUCD among HIV-positive women in Cape Town, South Africa.

2. Methods

2.1. Setting and Participants. This cross-sectional survey was conducted at a single clinic in Cape Town, South Africa between February and June 2011. This facility offers a range of primary care services, including HIV care and family planning, to approximately 17,000 individuals [28]. The local community is predominantly low socioeconomic status, and the HIV prevalence in this setting among individuals >15 years of age is estimated to be greater than 20% [28].

Eligible participants were women aged between 18 and 45 years who had documented HIV infection, were seeking family planning or HIV services, and were able to provide written informed consent.

2.2. Measures. A pretested questionnaire was administered to all participants in either English or isiXhosa, per participant preference. The study instrument assessed demographics, reproductive and HIV health history, partnership status, and awareness of the IUCD. The question about IUCD awareness was asked twice, once during an assessment of awareness of a list of contraceptive methods and once asking solely about the IUCD. The proportion reporting IUCD awareness differed by 7% between the two questions. The lower value is retained in analyses as the second query was performed in conjunction with other queries about the device. For women unaware of the IUCD, a brief description of the method, inclusive of appearance, efficacy, duration, and potential side-effects, was developed and provided at a midpoint in the interview. The script content was as follows.

> "The IUD is small and looks like a T made of plastic, and contains copper or a hormone. The IUD is inserted into the womb to prevent pregnancy for a period of five years and longer. It can be removed when someone wants to have a baby, and then the person can fall pregnant immediately. The IUD is inserted and is removed easily at the clinic. The most common change associated with the IUD may be the change in the woman's menstrual cycle."

Actual copper and levonorgestrel IUCDs were also shown to participants at the end of the information session, and potential interest in IUCD use was assessed through the query, "Do you think the loop/IUCD sounds like an option you can consider for contraception?", followed by the most important reasons for either positive or negative interest. Open-ended questions on receptivity and positive and negative perceptions of potential IUCD use were analyzed for common themes and coded into close-ended categories; these data are clearly marked in Results.

2.3. Procedures. Participants were selected consecutively upon completion of clinic visits during periods when trained study staff were available. Study staff approached eligible potential participants within the clinic and asked for interest in survey participation. Interested women were brought to a private room to discuss the study and provide written informed consent.

Following consent, the questionnaire was administered in the participant's preferred language by trained interviewers. Participants desiring contraception and not using a method or those interested in switching methods were referred to the family planning services within the clinic site; participants received a food gift certificate (value US$10) for participation.

The protocol was reviewed and approved by the institutional review boards of the University of Cape Town and Columbia University Medical Center.

2.4. Analysis. Descriptive statistics and measures of IUCD awareness and interest were generated using counts, means, and proportions. Correlates of IUCD awareness and interest in use were assessed with logistic regression analysis; strength of association was assessed in multivariable models to produce adjusted odds ratios (AORs). All analysis was performed with STATA Version 10 and Version 11.1 (StataCorp, College Station, TX, USA).

3. Results

Between February and June, 2011, 277 women participated in this study (data on refusal rates were not collected). Sociodemographic characteristics and a summary of reproductive and HIV health history are displayed in Table 1. Participants had a mean age of 32.0 (standard deviation (SD) ± 6.4) years with most being unemployed (71%) and having completed at least some secondary school (89%).

Table 1: Sociodemographic and health characteristics of HIV-positive women participating in a contraceptive preference assessment in Cape Town, South Africa ($N = 277$).

Variable	Number	Percentage
Age group		
19–25	51	18%
26–30	71	26%
31–35	63	23%
36–40	61	22%
41–45	31	11%
Currently unemployed	196	71%
Educational level		
None/primary	30	11%
Secondary	247	89%
Native language		
IsiXhosa	270	97%
IsiZulu	2	1%
Afrikaans	3	1%
Sotho	2	1%
Number of persons living in household		
Just respondent (1)	24	9%
2–5 people	217	79%
6–9 people	31	11%
12–16 people	4	1%
Home type		
Informal dwelling/hokkie	243	88%
Home ownership	4	1%
Flat/municipal house	30	11%
Time from HIV diagnosis		
<=1 year	57	21%
>1–3 years	53	19%
>3–5 years	56	20%
>5–7 years	46	17%
>7 years	65	23%
Sexually active in last year	239	86%
Of those sexually active ($N = 239$) in the last year, number of sexual partners in that time period		
One partner	211	88%
Two partners	21	9%
Three to five partners	7	3%
Currently in relationship	227	82%
Relationship status		
Married, living together	29	13%
Married, not living together	6	3%
Not married, living together	92	41%
Not married not living together	98	43%
Taking antiretrovirals (ARVs)	177	64%
Duration on ARVs		
<=1 year	48	27%
>1–3 years	45	25%
>3–5 years	42	23%
>5 years	42	23%
Ever pregnant	254	92%

Table 1: Continued.

Variable	Number	Percentage
Number of prior pregnancies ($N = 254$)		
One	65	23%
Two	72	26%
Three	70	25%
Four or greater	47	17%
Number of abortions/terminations ($N = 253$)		
None	209	82%
One	40	16%
Two	4	2%
Number of live births ($N = 254$)		
None	9	4%
One	73	29%
Two	87	34%
Three to Five	85	33%
Number of living children ($N = 254$)		
None	12	5%
One	75	30%
Two	91	36%
Three to Five	76	31%

N = number.

Table 2: Contraceptive method awareness and current and prior contraceptive use among HIV-positive women in Cape Town, South Africa ($N = 277$).

Method	Awareness		Prior use		Current use	
	N	%	N	%	N	%
Pill/oral contraceptive	264	95%	97	35%	9	3%
Injectables	277	100%	269	97%	145	52%
IUCD	103	37%	6	2%	0	0%
Diaphragm	28	10%	4	1%	3	1%*
Male condom	274	99%	261	94%	57	21%*
Female condom	264	95%	60	22%	4	1%*
Tubal ligation	258	93%	34	12%	37	13%
Male sterilization	77	28%	2	1%	0	0%

*Overall, many (83%, $N = 230$) participants reported male condom use; statistic reported reflects those using male condoms alone rather than double coverage. Similarly, 6/10 women using the diaphragm and 33/37 of those reporting female condom use were using other methods concomitantly.
N = number.
IUCD = intrauterine contraceptive device.

Most participants (82%) were in a relationship, with the majority describing their status as unmarried and either living with (41%) or without a partner (43%). The mean time since HIV diagnosis was 4.6 years (SD ± 3.6), and 64% were using antiretroviral therapy (ART) at the time of interview. Most participants (92%) had been pregnant previously with a mean of 2.0 (SD ± 1.1) living children currently.

All participants reported awareness of at least one contraceptive method, and nearly all ($n = 276$, 99%) had previously used a method. Most women (93%, $n = 258$) reported current contraceptive use; the most common reason stated for not using a method was lack of a current sexual partner. Current method mix, history of prior methods used, and awareness of specific contraceptive methods are displayed in Table 2. Of those currently using contraception ($n = 258$), most women (89%) reported satisfaction with and intent to continue use of their current method, while 4% planned to discontinue their method due to desire for pregnancy ($n = 7$), or dissatisfaction with method ($n = 2$). Another 3% were not satisfied with the method yet planned to continue use. A majority (78%, $n = 202$ of 258 currently using contraception) of women reported using male condoms in conjunction with another method.

Women were queried regarding the most attractive features of an ideal contraceptive method, with multiple answers permitted. The most advantageous features of a contraceptive method were (of 516 responses) efficacy to prevent

Table 3: Correlates of intrauterine contraceptive device (IUCD) awareness and interest in IUCD use among HIV-positive women in Cape Town, South Africa by univariable logistic regression analysis.

Variable (mean, SD)	IUCD aware ($n = 103$)	Not aware ($n = 174$)	OR, 95% CI	IUCD interest ($n = 206$)	Not interested ($n = 34$)	OR, 95% CI
Age (years)	35.2 ± 5.9	30.1 ± 5.9	1.15, 1.10–1.21	30.7 + 5.8	34.0 ± 7.4	0.92, 0.86–0.97
Years education	8.9 ± 2.7	9.6 ± 2.0	0.88, 0.80–0.98	9.5 ± 2.1	9.3 ± 2.6	1.04, 0.89–1.22
Years since HIV diagnosis	5.1 ± 3.6	4.4 ± 3.5	1.06, 0.99–1.13	4.4 ± 3.4	4.0 ± 3.8	1.03, 0.93–1.16
Total prior pregnancies	2.8 ± 1.3	1.9 ± 1.2	1.68, 1.37–2.06	2.1 ± 1.3	2.4 ± 1.6	0.83, 0.64–1.09
Total living children	2.3 ± 1.2	1.6 ± 1.1	1.70, 1.35–2.14	1.7 + 1.1	1.9 ± 1.3	0.84, 0.62–1.15
(%, Number)						
Employed	29%, 30	29%, 51	0.99, 0.58–1.69	26%, 53	41%, 14	0.49, 0.23–1.05
Using antiretrovirals	71%, 73	62%, 108	1.49, 0.88–2.51	65%, 133	65%, 22	0.99, 0.47–2.12
Not changing contraceptive method in last 12 months	92%, 91	81%, 140	2.86, 1.28–6.67	18%, 38	9%, 3	2.34, 0.68–8.05
More than 1 sexual partner in last year	9%, 9	11%, 19	0.78, 0.34–1.80	13%, 26	0%, 0	N/A
Currently in relationship	78%, 80	85%, 147	0.64, 0.34–1.19	84%, 172	74%, 25	1.82, 0.78–4.24
Sexually active in last year	82%, 84	90%, 156	0.51, 0.25–1.02	89%, 184	77%, 26	2.57, 1.04–6.38
Current menstrual complaints	45%, 103	53%, 92	0.72, 0.44–1.17	50%, 102	32%, 11	2.05, 0.95–4.42
Regular menstrual cycle ($n = 166$)	75%, 53	68%, 87	1.39, 0.72–2.66	69%, 100	50%, 11	2.27, 0.92–5.63

*Excludes women previously sterilized.
CI = confidence interval.
n = number.
OR = odds ratio.
SD = standard deviation.

pregnancy (32%), preventing sexually transmitted infections and/or HIV transmission/reinfection (26%), lasting for long duration without necessitating a clinic visit for readministration (11%), causing no menstrual changes (7%), having no associated weight changes (4%), no associated mood or other side effects (3%), and having no interaction with ARVs (3%).

Method change in the last year was reported by 42 (15%) women, with the key reasons for changing methods being desired pregnancy (29%), heavy menstrual bleeding (12%), irregular menses (10%), and other side effects (10%). Method change rarely occurred in response to HIV diagnosis (9%) or ARV initiation (3%). Stated reasons for method change at the time of HIV diagnosis by 24 women included concern for how the method would interact with HIV disease (30%), planned sexual abstinence or cessation of current relationship (18%), side effects excluding menstrual and weight changes (17%), desire for pregnancy (13%), or heavy menstrual bleeding (9%).

Awareness of the IUCD was reported by 37%, with only the diaphragm and male surgical sterilization having lower levels of general awareness. Very few (8%) participants reported having been informed about the IUCD previously by a medical provider, and fewer were specifically aware of the copper (4%) or levonorgestrel (3%) IUCD. IUCD awareness was significantly associated with greater age, greater numbers of prior pregnancies and living children, lower education, and lower likelihood of sexual activity or not switching contraceptive methods in the last year (Table 3). In multivariable logistic regression analysis, only increasing age (AOR = 1.15, 95%, confidence intervals, CI: 1.10–1.20) and not switching contraceptive methods in the last year (AOR = 2.45, 95% CI: 1.03–5.83) were independently associated with IUCD awareness.

Following a brief information session on IUCDs, 86% ($n = 206$ of 240 women not having been sterilized) were potentially interested in future IUCD use. Interest in IUCD use was associated with younger age and being sexually active in the last year; marginal associations were noted with being unemployed, having a regular menstrual cycle, or having perceived menstrual irregularities in bivariate logistic regression. Of note, all women with more than one sexual partner in the last year reported interest in the IUCD (Table 3). In multivariable logistic regression, interest in IUCD use was independently inversely associated with age

(AOR = 0.91, 95% CI: 0.86–0.97) and marginally with having menstrual bleeding pattern complaints (AOR = 2.14, 95% 0.98–4.68). Those interested in the IUCD were queried about the positive features of the IUCD as an open-ended question, and the common features ranking highest (of 408 total responses, multiple responses were allowed) were duration of action (42%), reversible method/rapid restoration of fertility (33%), efficacy at preventing pregnancy (12%), and ease of insertion/removal (10%). Based on potential menstrual changes, particularly with the levonorgestrel IUCD, willingness to use the IUCD with accompanying menstrual changes was queried. Nearly all interested participants ($n = 204$) desired the IUCD if oligo/amenorrhea resulted, while only 8 were willing to use an IUCD if menstrual bleeding increased. Many (60%, $n = 143$) believed their partner would be receptive to the IUCD.

4. Discussion

This study demonstrates low IUCD awareness relative to other methods, particularly injectable contraceptives, and high prevalence of IUCD interest among HIV-positive women. These results are quite similar to those among general clinical populations in South Africa and suggest that there is significant potential to promote the IUCD in this setting [17, 18].

We found that older women were more likely to be aware of the IUCD before the study, possibly based on exposure to information about a variety of contraceptive methods over time. We speculate that the association between awareness and not changing contraceptive methods in the last year may reflect quality of counseling provided by medical staff, inclusive of a comprehensive presentation of available options. Alternately, women may be more likely to continue methods with which they have a degree of comfort provided by peer experience or reinforcement. Further investigation is needed to determine factors associated with method continuation among this patient population. The very low rate of prior personal IUCD use or reported mention of the IUCD by medical providers likely contributes to lower overall awareness or prior interest in use; peers may be the predominant information source. IUCD information relayed by HIV-positive women from peer sources has been noted to be of questionable accuracy; inaccurate information in this group and among South African women have negatively predisposed some women toward the IUCD [17, 25, 26].

Despite low levels of awareness, many women were receptive to IUCD use after receiving an explanation of the method, similar to levels recorded in other South African studies [17, 18]. Younger age was associated with interest in the IUCD, possibly due to reduced potential exposure to negative information from peers or due to the appeal of IUCD longevity and reversibility without need for return clinic visits. Sexual activity was also associated with interest in IUCD use, with those more sexually active being more receptive to its use, indicating self-awareness of pregnancy risk. Though reported IUCD interest was high, it is important to note that interest is not always correlated with actual method uptake [29]. In a similar vein, stated preferred methods may not be the only method a woman is willing to accept. This is particularly important with regard to the IUCD due to low levels of awareness. For example, in Malawi, HIV-positive women stating preference for other contraceptive methods were willing to accept the IUCD, potentially indicating the role for well-informed counseling [27].

Participants perceived many advantages to the IUCD, with duration of action and reversibility being the most important features in an environment where contraceptive-induced menstrual bleeding disturbances are common as the predominant method is the hormonal injectable. Overall, the IUCD appears to be a useful option for this patient population as the most desirable qualities of a contraceptive method were efficacy in preventing pregnancy, prevention of sexually transmitted infections or HIV reinfection, and long duration of action. The IUCD possesses two of these qualities, and dual method use with male condoms is a reportedly normative behavior among this patient group. Of note, changing methods in response to HIV diagnosis or disease progression was uncommon, and considerations relative to impact on HIV disease, with the exception of reinfection or transmission to partners, were relatively less important than considerations surrounding contraceptive efficacy and duration when mentioning desirable method attributes.

However, bleeding changes were a common reason reported for method discontinuation, second only to desiring pregnancy, and this sensitivity deserves introspection when considering the IUCD for HIV-positive women [30]. Though there was a marginal positive association between women with reported abnormal menstrual bleeding and IUCD interest, the association may reflect dissatisfaction with the current method and desire to change rather than a considered preference for the IUCD. The most common reason for discontinuation of the copper IUCD is increased menstrual bleeding [31], a side effect which the current study participants reported would prevent use of the IUCD. However, participants were willing to use an IUCD that may cause oligo/amenorrhea, a side effect profile similar to that of the hormonal injectable, the most common nonbarrier method used by participants. Though the levonorgestrel IUCD is not currently available in the public sector system and the high cost of the device is likely prohibitive for many participants, this population is likely to benefit from such a method. Advocacy and further research on the safety and acceptability of the levonorgestrel IUCD for HIV-positive women are indicated to improve method choice for this population.

These data should be viewed in light of several limitations. First, participants were enrolled through convenience sampling at one clinic in urban Cape Town, and the generalizability of the findings is unclear. This study was performed in Western Cape, the province with the second highest contraceptive prevalence rate in South Africa, [32] and reported contraceptive use rates and interest in the IUCD may be somewhat higher than elsewhere in South or sub-Saharan Africa. We did not collect data on reasons for attending the clinic and do not have data

on number and reasons for refusals to participate. In addition, the questionnaire was interviewer administered, potentially resulting in socially desirable responses such as overreporting of contraceptive and condom use. However, reported contraceptive prevalence was similar to results in South Africa reported by Gutin et al. [17]. Prospective studies are needed to evaluate use acceptability of the IUCD for HIV-positive women, particularly in comparison with other methods. Last, provider awareness, knowledge, and perceptions regarding IUCD safety for HIV-positive women were not assessed and potentially presents an opportune route to improve IUCD use, as noted by van Zijl et al. [18]. Future studies should also include both HIV and reproductive health care provider perspectives for greater insight into the contraceptive decision-making process.

5. Conclusions

In summary, these data suggest that HIV-positive women may be receptive to IUCD use despite low levels of method awareness. Our data support efforts to expand contraceptive method mix for this population through programming to promote IUCD use directed at providers and patients.

Disclosure

Partial results are presented at the International Family Planning Conference, Abstract no. 685, Dakar, Senegal, November 30, 2011.

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References

[1] M. D. Sweat, K. R. O'Reilly, G. P. Schmid, J. Denison, and I. de Zoysa, "Cost-effectiveness of nevirapine to prevent mother-to-child HIV transmission in eight African countries," *AIDS*, vol. 18, no. 12, pp. 1661–1671, 2004.

[2] H. W. Reynolds, B. Janowitz, R. Homan, and L. Johnson, "The value of contraception to prevent perinatal HIV transmission," *Sexually Transmitted Diseases*, vol. 33, no. 6, pp. 350–356, 2006.

[3] W. Hladik, J. Stover, G. Esiru, M. Harper, and J. Tappero, "The contribution of family planning towards the prevention of vertical HIV transmission in Uganda," *PLoS ONE*, vol. 4, no. 11, Article ID e7691, 2009.

[4] R. Wilcher, T. Petruney, H. W. Reynolds, and W. Cates, "From effectiveness to impact: contraception as an HIV prevention intervention," *Sexually Transmitted Infections*, vol. 84, supplement 2, pp. ii54–ii60, 2008.

[5] A. Kaida, F. Laher, S. A. Strathdee et al., "Contraceptive use and method preference among women in Soweto, South Africa: the influence of expanding access to HIV care and treatment services," *PLoS ONE*, vol. 5, no. 11, Article ID e13868, 2010.

[6] D. Hubacher, I. Mavranezouli, and E. McGinn, "Unintended pregnancy in sub-Saharan Africa: magnitude of the problem and potential role of contraceptive implants to alleviate it," *Contraception*, vol. 78, no. 1, pp. 73–78, 2008.

[7] UNAIDS, "Report on the global AIDS epidemic," Tech. Rep., UNAIDS, Geneva, Switzerland, 2008.

[8] R. Heffron, D. Donnell, H. Rees et al., "Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study," *The Lancet Infectious Diseases*, vol. 12, no. 1, pp. 19–26, 2012.

[9] C. S. Morrison, S. Skoler-Karpoff, C. Kwok et al., "Hormonal contraception and the risk of HIV acquisition among women in South Africa," *AIDS*, vol. 26, no. 4, pp. 497–504, 2012.

[10] B. A. Richardson, P. A. Otieno, D. Mbori-Ngacha, J. Overbaugh, C. Farquhar, and G. C. John-Stewart, "Hormonal contraception and HIV-1 disease progression among postpartum Kenyan women," *AIDS*, vol. 21, no. 6, pp. 749–753, 2007.

[11] E. M. Stringer, J. Levy, M. Sinkala et al., "HIV disease progression by hormonal contraceptive method: secondary analysis of a randomized trial," *AIDS*, vol. 23, no. 11, pp. 1377–1382, 2009.

[12] C. B. Polis, M. J. Wawer, N. Kiwanuka et al., "Effect of hormonal contraceptive use on HIV progression in female HIV seroconverters in Rakai, Uganda," *AIDS*, vol. 24, no. 12, pp. 1937–1944, 2010.

[13] E. M. Stringer, M. Giganti, R. J. Carter, W. El-Sadr, E. J. Abrams, and J. S. A. Stringer, "Hormonal contraception and HIV disease progression: a multicountry cohort analysis of the MTCT-plus initiative," *AIDS*, vol. 23, supplement 1, pp. S69–S77, 2009.

[14] C. S. Morrison, P. L. Chen, I. Nankya et al., "Hormonal contraceptive use and HIV disease progression among women in Uganda and Zimbabwe," *Journal of Acquired Immune Deficiency Syndromes*, vol. 57, no. 2, pp. 157–164, 2011.

[15] C. S. Morrison and K. Nanda, "Hormonal contraception and HIV: an unanswered question," *The Lancet Infectious Diseases*, vol. 12, no. 1, pp. 2–3, 2012.

[16] D. Clifton, T. Kaneda, and L. Ashford, *Family Planning Worldwide: 2008 Data Sheet*, Population Reference Bureau, Washington, DC, USA, 2008.

[17] S. A. Gutin, R. Mlobeli, M. Moss, G. Buga, and C. Morroni, "Survey of knowledge, attitudes and practices surrounding the intrauterine device in South Africa," *Contraception*, vol. 83, no. 2, pp. 145–150, 2011.

[18] S. van Zijl, C. Morroni, and Z. M. van der Spuy, "A survey to assess knowledge and acceptability of the intrauterine device in the family planning services in Cape town, South Africa," *Journal of Family Planning and Reproductive Health Care*, vol. 36, no. 2, pp. 73–78, 2010.

[19] C. S. Todd, M. A. Stibich, F. Laher et al., "Influence of culture on contraceptive utilization among HIV-positive women in Brazil, Kenya, and South Africa," *AIDS and Behavior*, vol. 15, no. 2, pp. 454–468, 2011.

[20] C. S. Morrison, C. Sekadde-Kigondu, S. K. Sinei, D. H. Weiner, C. Kwok, and D. Kokonya, "Is the intrauterine device appropriate contraception for HIV-1-infected women?" *British Journal of Obstetrics and Gynaecology*, vol. 108, no. 8, pp. 784–790, 2001.

[21] E. M. Stringer, C. Kaseba, J. Levy et al., "A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human

immunodeficiency virus," *American Journal of Obstetrics and Gynecology*, vol. 197, no. 2, pp. 144.e1–144.e8, 2007.

[22] World Health Organization, *Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use*, World Health Organization, Geneva, Switzerland, 3rd edition, 2004.

[23] O. Heikinheimo, P. Lehtovirta, I. Aho, M. Ristola, and J. Paavonen, "The levonorgestrel-releasing intrauterine system in human immunodeficiency virusinfected women: a 5-year follow-up study," *American Journal of Obstetrics and Gynecology*, vol. 204, no. 2, pp. 126.e1–126.e4, 2011.

[24] B. A. Richardson, C. S. Morrison, C. Sekadde-Kigondu et al., "Effect of intrauterine device use on cervical shedding of HIV-1 DNA," *AIDS*, vol. 13, no. 15, pp. 2091–2097, 1999.

[25] F. Laher, C. S. Todd, M. A. Stibich et al., "A qalitative assessment of decisions affecting contraceptive utilization and fertility intentions among HIV-positive women in Soweto, South Africa," *AIDS and Behavior*, vol. 13, supplement 1, pp. S47–S54, 2009.

[26] K. E. Imbuki, C. S. Todd, M. A. Stibich, D. N. Shaffer, and S. K. Sinei, "Factors influencing contraceptive choice and discontinuation among HIV-positive women in Kericho, Kenya," *African Journal of Reproductive Health*, vol. 14, no. 4, pp. 98–109, 2010.

[27] L. Haddad, M. Nyirenda, C. Cwiak et al., "Contraceptive eligibility, choice and acceptance of the copper intrauterine device (IUD) among HIV+ clients at an ART clinic in Lilongwe, Malawi," in *Proceedings of the 6th International AIDS Society*, Rome, Italy, July 2011, Oral abstract WEAX0205.

[28] K. Middelkoop, L. G. Bekker, L. Myer et al., "Antiretroviral program associated with reduction in untreated prevalent tuberculosis in a South African township," *American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 8, pp. 1080–1085, 2010.

[29] D. Hubacher, E. R. Raymond, M. Beksinska et al., "Hormonal contraception and the risks of STI acquisition: results of a feasibility study to plan a future randomized trial," *Contraception*, vol. 77, no. 5, pp. 366–370, 2008.

[30] F. Laher, C. S. Todd, M. A. Stibich et al., "Role of menstruation in contraceptive choice among HIV-infected women in Soweto, South Africa," *Contraception*, vol. 81, no. 6, pp. 547–551, 2010.

[31] P. A. O'Brien, R. Kulier, F. M. Helmerhorst, M. Usher-Patel, and C. D'Arcangues, "Copper-containing, framed intrauterine devices for contraception: a systematic review of randomized controlled trials," *Contraception*, vol. 77, no. 5, pp. 318–327, 2008.

[32] Health Systems Trust, 2012, http://www.hst.org.za/recently-updated-indicators.

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Research Article

Small-for-Gestational-Age Births in Pregnant Women with HIV, due to Severity of HIV Disease, Not Antiretroviral Therapy

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Objectives. To determine rate and factors associated with small-for-gestational-age (SGA) births to women with HIV. *Methods*. Prospective data were collected from 183 pregnant women with HIV in an urban HIV prenatal clinic, 2000–2011. An SGA birth was defined as less than the 10th or 3rd percentile of birth weight distribution based upon cut points developed using national vital record data. Bivariate analysis utilized chi-squared and *t*-tests, and multiple logistic regression analyses were used. *Results*. The prevalence of SGA was 31.2% at the 10th and 12.6% at the 3rd percentile. SGA at the 10th (OR 2.77; 95% CI, 1.28–5.97) and 3rd (OR 3.64; 95% CI, 1.12–11.76) percentiles was associated with cigarette smoking. Women with CD4 count >200 cells/mm^3 at the first prenatal visit were less likely to have an SGA birth at the 3rd percentile (OR 0.29; 95% CI, 0.10–0.86). Women taking NNRTI were less likely to have an SGA infant at the 10th (OR 0.28; 95% CI, 0.10–0.75) and 3rd (OR 0.16; 95% CI, 0.03–0.91) percentiles compared to those women on PIs. *Conclusions*. In this cohort with high rates of SGA, severity of HIV disease, not ART, was associated with SGA births after adjusting for sociodemographic, medication, and disease severity.

1. Introduction

It is estimated that 8,700 women with HIV give birth annually in the United States [1]. Through improvements in early prenatal care initiation and the use of antiretroviral therapy (ART) during pregnancy, the rates of perinatal HIV transmission have decreased to as low as 1% to 2% in the developed world [2]. However, women with HIV are still at risk for adverse birth outcomes [3, 4]. Research investigating birth outcomes of infants born to women with HIV has mainly concentrated on preterm birth (PTB; birth prior to 37 completed weeks of gestation) and low birth weight (LBW; birth at less than 2500 grams). Results from these studies are mixed with some studies showing an increased risk and others not showing this risk: PTB between 5% and 20% and LBW between 10% and 20% [4]. It is unclear whether the increased risk is related to HIV infection and its consequences or to elevated prevalence rates of other risk factors for PTB and LBW among women with HIV [5].

We have chosen to focus on a measure combining both gestational age and birth weight: small for gestational age (SGA). Using cut points developed by Elo and Culhane, derived from national vital records data, each infant's status with regard to SGA was determined at both the 3rd and the 10th percentiles of gestational-age specific birth weight distributions. Infants born SGA experience higher rates of mortality and morbidity compared to infants born at appropriate weight for their GA [6]. Sequelae associated with SGA include both short- and long-term adverse outcomes, such as respiratory complications, hypotension, hypoglycemia, neurological impairment, type 2 diabetes mellitus, and cardiovascular complications, among others

[6]. This definition of SGA is increasingly being used with most current studies investigating the risk factors for SGA, having used population centiles to define SGA [7]; however, few studies investigating outcomes in infants born to women with HIV have used the definition of SGA.

Published data conflict as to whether receipt of ART during pregnancy is associated with adverse pregnancy outcomes. This information is needed to inform healthcare providers for best practices and to improve the quality of life and health of women with HIV and their infants. The aim of this study was to determine the rate of SGA infants delivered to women with HIV and to assess contributing factors, with specific emphasis on the possible contribution of ART that may influence the likelihood that a woman with HIV will deliver an SGA infant.

2. Methods

A prospective cohort study was conducted among 183 pregnant women with HIV from January 2000 through January 2011 at Drexel University College of Medicine's Partnership Plus Clinic, an urban medical clinic in Philadelphia, PA specializing in prenatal HIV care. The study was approved by the Drexel University College of Medicine Institutional Review Board and conducted with the understanding and the consent of the participants. The study was designed to assess overall maternal health (biological and psychosocial) and infant health outcomes among pregnant women with HIV seeking care at this specialized comprehensive prenatal care clinic. Clinical care is delivered by an interdisciplinary team consisting of members of the Department of Infectious Diseases and the Department of Obstetrics and Gynecology. All women with HIV who were seen in this clinic over the identified period were approached at the time of their first prenatal visit. After informed consent was obtained from the women, data were collected through patient interviews and from medical chart review. Subjects were included in this study if they were HIV-infected, pregnant, and more than 17 years of age. Women who had an abortion or miscarriage, switched prenatal providers, or were incarcerated during the index pregnancy were excluded. Repeat pregnancies were not included, and only the first infant delivered in twin gestations (twin A) was included in these analyses.

2.1. Measures. Data were obtained through questionnaire-guided interviews and medical chart abstraction. Interviews were conducted by one trained HIV clinician who saw all participants in this cohort; chart abstraction was completed by trained research assistants.

2.1.1. Demographic Data. Demographic data included age, race/ethnicity, education level (categorized as 8th grade; some high school; high school/GED; some college; 4-year college; master's degree or more), employment status, and marital status.

2.1.2. Health Behaviors. Health behaviors included smoking history and substance use history. Measures for smoking included ever smoking a cigarette as well as the prevalence of smoking at the time of the study. Crack cocaine, heroin, and marijuana use in lifetime as well as the prevalence at time of the study was used to create variables for illicit drug use.

2.1.3. Medical Data. Medical information pertaining to HIV that was abstracted from charts included HIV transmission route (categorized as unprotected sex with a man; intravenous drug use; blood transfusion; or other), date of ART initiation and regimen, CD4 T lymphocyte counts and HIV viral load measures at each medical visit, and year of HIV diagnosis. ART initiation was categorized as prepregnancy, first, second and at third trimester. Viral load and CD4 counts were used as continuous measures to evaluate trajectory over time. Viral load at the first and last visits were dichotomized at 1000 copies, and CD4 count at the first visit was dichotomized at 200 cells for final analysis.

Hospital obstetrical records were reviewed to collect data on birth outcomes. Variables included date of delivery, gestational age at delivery, gender, infant birth weight and length, and any neonatal or postpartum complications. Owing to the critical nature of gestational age in determining SGA status, we highlight this variable below. In addition, we discuss the construction of the main dependent variable SGA.

2.1.4. Gestational Age at Birth. Gestational age at birth was determined by the following criteria: patients who were dated by a sure LMP in first trimester were subsequently confirmed by the second trimester anatomy ultrasound. In those with unsure last menstrual period due to either history of irregular menstruation, the patient being a poor historian, or the pregnancy being conceived on hormonal contraception, the first trimester ultrasound was used as the dating tool. Those who presented to prenatal care after the first trimester with unsure last menstrual period were dated by a second or third trimester ultrasound depending on the gestational age at presentation to prenatal care.

2.2. SGA Birth. An SGA birth was defined as a newborn weighing less than the 10th percentile of gestational age-specific birth weight distribution based on the infant's sex and the mother's parity [8]. Specifically, to identify births as SGA we used reference curves developed based on vital statistics birth record data for singleton births born to US resident mothers in the 50 states and the District of Columbia in 1998, 1999, and 2000. Sex-specific reference curves for SGA cut points indicating the 10th percentile in the birth weight distribution for gestational ages 20–44 weeks were developed for first births and second or higher order births. In constructing the SGA cut points, births with extreme deviation from the mean birth weight for a given gestational week were excluded so that the established cut points were not influenced by extreme outliers in the data. We identified outliers by using standard procedures developed by Tukey whereby outliers were defined as births that fell outside the interquartile range of the birth weight distribution for a given gestational week. Based on these procedures approximately

1.5% of births were excluded in the construction of the standard. These reference curves (available from the authors upon request) update previously published standards [8]. In addition to the 10th percentile cut point, another SGA variable was created by dichotomizing at the 3rd percentile gestational age-specific birth weight distribution for a more stringent definition of SGA [9].

2.3. Statistical Analysis. For descriptive analysis, frequencies, percentages, prevalence rates, means, and standard deviations were calculated. Bivariate analyses were conducted to evaluate the association between SGA and the demographic, behavioral, and medical characteristics. Chi-square tests were used for comparing categorical variables. Fisher's exact test was utilized if the expected values in the cells were less than five. For comparison of maternal age, Student's t-test was used. Multiple logistic regression was then used to analyze the risk of SGA, adjusting for covariates and potential confounders. Variables that were significant at the 0.25 level in the bivariate analyses were included in the logistic regression model. Using a 0.25 level of significance as an inclusion criterion for the regression model allows us to consider a wider pool of potentially important covariates, some of which may eventually be significant in the multivariate model. It has been noted that traditional significance levels of 0.05 can fail to identify variables known to be important in models [10–12]. Since the use of nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) medications is correlated, separate models were run to evaluate the associations on SGA with the same covariates. A generalized linear model was fitted to the CD4 count data to evaluate differences in rate of change of CD4 over time between the SGA groups. The generalized linear model used a gamma distribution and log link function along with robust standard errors and adjusted for the clustering of the data by participant. The Gamma distribution was used due to the skewed nature of the CD4 data. Time in months since entry into care was used as the time variable, and an interaction term of time with the SGA group was used to assess differences in rate of change of CD4 over time. A similar model was used to evaluate differences in rate of change of viral load over time.

All data were coded and entered in SPSS version 18 (IBM, Armonk, NY); Stata 11.2 (StataCorp, College Station, TX) was used for all analyses.

3. Results

Baseline characteristics of the sample are presented in Table 1. Out of 221 pregnancies the number of discreet women included in this analysis was 183. Our final sample of 183 women was reached because of the following exclusions: 20 repeat deliveries; 2 twins; 5 births with incomplete delivery information; 4 abortions or miscarriages; 3 changed prenatal providers; and 4 incarcerations during the index pregnancy. The cohort was mostly African American (74.7%, $n = 136$) and single (86.7%, $n = 157$) with a mean age of 28.0 years (SD = 6.2). Educational attainment was low (high school or less; 63.4%, $n = 116$). A total of 69.1% ($n = 123$) of the women reported at least one birth prior to this pregnancy; 38.3% ($n = 70$) reported smoking during this pregnancy; 44.3% ($n = 81$) reported a history of ever using illicit drugs (majority of illicit drug use in this cohort was cocaine), and 18.0% ($n = 33$) reported using illicit drugs during the current pregnancy. The mean GA of the infant at the time the mother entered care was 14.6 weeks (SD = 7.5); the mean GA at outcome was 38 weeks (SD = 2.1). There were no significant differences of the GA at entry into prenatal care by SGA at the 10th percentile (14.8 weeks; SD = 7.4, $P = 0.7029$) or SGA at the 3rd percentile (13.2 weeks; SD = 3.7, $P = 0.9630$; Table 2). The average duration of time since HIV diagnosis for the cohort was 4.3 years (SD = 4.3). The incidence of preeclampsia was 13.6% ($n = 21/150$).

Table 1: Sociodemographic, behavioral, and medical characteristics of sample.

Variable	*N* (%)
Age—mean (SD)	28.0 (*6.2*)
Race—African American	136 (74.7)
Race—all other	46 (25.3)
Married	24 (13.3)
Single	157 (86.7)
Education—less than high school	36 (19.7)
Education—high school/some high school	80 (43.7)
Education—college/some college	19 (10.4)
Education—unknown	48 (26.2)
Parity—no children	55 (30.9)
Parity—1 or more children	123 (69.1)
Ever smoked	93 (50.8)
Currently smoking	70 (38.3)
Ever used illicit drugs	81 (44.3)
Currently using illicit drugs	33 (18.0)
First viral load > 1000	101 (55.2)
Last viral load > 1000	27 (14.8)
First CD4 > 200	134 (73.2)
Started medications in pregnancy	137 (74.9)
ART started: prepregnancy	46 (25.1)
ART started: first trimester	26 (14.2)
ART started: second trimester	90 (49.2)
ART started: third trimester	21 (11.5)
NNRTI	39 (21.3)
PI	117 (63.9)
SGA, 10th percentile	57 (31.2)
SGA, 3rd percentile	23 (12.6)
Gestational age at care entry—mean (SD)	14.6 (7.5)
Gestational age at delivery—mean (SD)	38.0 (2.1)
Infant birth weight (grams) —mean (SD)	2900.0 (523.4)
Low birth weight	31 (16.9)
Preterm birth	34 (18.6)

ART, antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; SGA, small for gestational age.

Table 2: Socio-demographic, behavioral, and medical characteristics, by SGA at 10th percentile and SGA at 3rd percentile.

Variable	10th percentile			3rd percentile		
	SGA: no $n = 126$ (%)	SGA: yes $n = 57$ (%)	P value	SGA: no $n = 160$ (%)	SGA: yes $n = 23$ (%)	P value
Age—mean (SD)	27.7 (5.8)	28.7 (7.0)	0.411	27.9 (6.1)	29 (6.7)	0.337
Race—African American	89 (71.2)	47 (82.5)	0.105	119 (74.8)	17 (73.9)	0.924
Race— all other	36 (28.8)	10 (17.5)		40 (25.2)	6 (26.1)	
Married	17 (13.6)	7 (12.5)	0.840	21 (13.2)	3 (13.6)	0.956
Single	108 (87.5)	49 (87.5)		138 (86.8)	19 (86.4)	
Education—less than high school	24 (19.1)	12 (21.1)		27 (16.9)	9 (39.1)	
Education—high school/some high school	58 (46.0)	22 (38.6)	0.650	73 (45.6)	7 (30.4)	0.028
Education—college/some college	11 (8.7)	8 (14.0)		15 (9.4)	4 (17.4)	
Education—unknown	33 (26.2)	15 (26.3)		45 (28.1)	3 (13.0)	
Parity—no children	37 (30.6)	18 (31.6)	0.893	47 (30.3)	8 (34.8)	0.666
Parity—1 or more children	84 (69.4)	49 (68.4)		108 (69.7)	15 (65.2)	
Never smoked	62 (49.2)	18 (31.6)		74 (46.3)	6 (26.1)	
Ever smoked	59 (46.8)	34 (59.7)	0.057	77 (48.1)	16 (69.6)	0.153
Ever smoked—unknown	5 (4.0)	5 (8.8)		9 (5.6)	1 (4.4)	
Not currently smoking	75 (59.5)	27 (47.4)		93 (58.1)	9 (39.1)	
Currently smoking	45 (35.7)	27 (43.9)	0.250	57 (35.6)	13 (56.5)	0.056
Current smoking—unknown	6 (4.8)	5 (8.8)		10 (6.3)	1 (4.4)	
Never used illicit drugs	71 (56.4)	26 (45.6)		85 (53.1)	12 (52.2)	
Ever used illicit drugs	52 (41.3)	29 (50.9)	0.396	70 (43.8)	11 (47.8)	0.671
Ever used illicit drugs—unknown	3 (2.4)	2 (3.5)		5 (3.1)	0 (0)	
Not currently using illicit drugs	97 (76.9)	44 (77.2)		122 (77.3)	19 (82.6)	
Currently using illicit drugs	23 (18.3)	10 (17.5)	0.984	29 (18.1)	4 (17.4)	0.495
Currently using illicit drugs—unknown	6 (4.8)	3 (5.3)		9 (5.6)	0 (0)	
First viral load >1000	63 (50.0)	38 (66.7)	0.036	87 (54.4)	14 (60.9)	0.558
Last viral load >1000	17 (13.5)	10 (17.5)	0.474	22 (13.8)	5 (21.8)	0.312
First CD4 >200	94 (74.6)	40 (70.2)	0.531	122 (76.3)	12 (52.2)	0.015
Started medications in pregnancy	91 (72.2)	46 (80.7)	0.221	116 (72.5)	21 (91.3)	0.052
ART started: prepregnancy	35 (27.8)	11 (19.3)		44 (27.5)	2 (8.7)	
ART started: first trimester	19 (15.1)	7 (12.3)	0.532	23 (14.4)	3 (13.0)	0.069
ART started: second trimester	58 (46.0)	32 (56.1)		73 (45.6)	17 (73.9)	
ART started: third trimester	14 (11.1)	7 (12.3)		20 (12.5)	1 (4.4)	
NNRTI	32 (25.4)	7 (12.3)	0.045	37 (23.1)	2 (8.7)	0.114
PI	78 (61.9)	39 (68.4)	0.395	100 (62.5)	17 (73.9)	0.287
Gestational age at care entry—mean (SD)	14.6 (7.6)	14.9 (7.4)	0.7029	14.8 (7.9)	13.2 (3.6)	0.9630
Gestational age at delivery—mean (SD)	38.2 (1.9)	37.6 (2.6)	0.3071	38.1 (2.0)	37.9 (3.0)	0.7364
Infant birth weight (grams) —mean (SD)	3111.1 (392.2)	2434.2 (475.1)	<0.001	2980.2 (479.9)	2344.1 (481.6)	<0.001
Low birth weight	5 (4.0)	26 (45.6)	<0.001	17 (10.6)	14 (60.9)	<0.001
Preterm birth	19 (15.1)	15 (26.3)	0.070	31 (19.4)	3 (13.0)	0.465

ART, antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; SGA, small for gestational age.

Two perinatal transmissions occurred in this cohort; neither were SGA. The first infant was 37 weeks gestation, 2952 grams. Maternal factors included ART of NRTI and NNRTI (nevirapine); CD4 count of 20; and viral load at the time of delivery, 98,500. The second infant was 42.2 week-gestation, 3430.3 grams. Maternal factors included ART of NRTI and PI combination (lopinavir/ritonavir); CD4 count of 626, viral load at time of delivery , 1000. It was suspected that transmission occurred during breastfeeding immediately following delivery.

CD4 T lymphocyte counts and HIV viral loads were recorded throughout pregnancy and at the time of delivery. The majority of women had CD4 counts greater than 200 copies/mm^3 ($n = 134$, 73.2%); 55.2% ($n = 101$) had viral loads greater than 1000 copies/mL at entry into prenatal care and 72.1% ($n = 132$) were diagnosed with HIV prior to the index pregnancy. Disease severity as measured by CD4 at entry into care, and length of time of HIV diagnosis did not vary significantly between the women taking NNRTIs and those taking PIs. The number of women with CD4 counts greater than 200 and taking PIs (146) was 105 (71.9%) whereas the number of those taking NNRTIs (43) was 30 (60.8%), $P = 0.78$. Average duration of time since HIV diagnosis for those taking PIs was 5.08 years (SD = 4.7) compared with 4.72 years (SD = 4.3; $P = 0.884$) for those taking NNRTIs.

All women were taking ART during the pregnancy; 100% ($n = 183$) had nucleoside reverse transcriptase inhibitors (NRTIs) as part of their background regimen, with 14.8% ($n = 27$) taking NRTIs alone; 21.3% ($n = 39$) were taking nonnucleoside reverse transcriptase inhibitors (NNRTIs), and 63.9% ($n = 117$) were taking protease inhibitors (PIs). There were 11 (40.7%) women who were taking NRTI only and whose infants were SGA at the 10th percentile, as compared to all other women (on either a PI and NNRTI) whose infants were SGA at the 10th percentile (46, 29.5% $P = 0.244$). Four (14.8%) women were taking NRTI only whose infants were SGA at the 3rd percentile as compared to all others who were SGA at the 3rd percentile (19, 12.2% $P = 0.703$). Therefore, those women taking NRTI only did not have a higher rate of SGA at the 10th or 3rd percentiles.

Of the women taking NNRTIs, 1.1% ($n = 2$) were taking efavirenz, 16.9% ($n = 31$) were taking nevirapine, and 3.3% ($n = 6$) were taking etravirine. The following PIs were used in this cohort: amprenavir (2.7%, $n = 5$); atazanavir (15.8%, $n = 29$); darunavir (1.1%, $n = 2$); lopinavir/ritonavir (20.8%, $n = 38$); fosamprenavir (1.1%, $n = 2$); nelfinavir (23%, $n = 42$); and ritonavir (15.8%, $n = 29$). No participants were taking indinavir, raltegravir, or saquinavir. The majority of this sample ($n = 137$; 74.9%) was not taking ART prior to the index pregnancy and started the HIV medication regimen during the prenatal period.

We found that ritonavir did not have the adverse outcome of an SGA infant as others have reported [13, 14]. There were 67 women on ritonavir-boosted regimens compared to 116 who were not exposed to ritonavir. A total of 22 (32.8%) women were taking ritonavir who also had SGA infants at the 10th versus 35 (30.2%) women not taking ritonavir who had SGA infants at the 10th ($P = 0.708$). A total of 8 (11.9%) women taking ritonavir also had SGA at the 3rd versus 15 (12.9%) women not taking ritonavir with SGA infants at the 3rd percentile ($P = 0.846$). The overall prevalence of SGA was high with 31.2% at the 10th percentile and 12.6% at the 3rd percentile. In bivariate analyses at the 10th percentile, newborns were less likely to be SGA if their mother was taking NNRTI medication compared to those newborns whose mothers were not taking NNRTI medication (12.3% versus 25.4%; $P = 0.045$). Newborns were more likely to be SGA if their mother's first viral load was >1000 copies/mL (50.0% versus 66.7%; $P = 0.036$. There were no significant differences in the rates of SGA in bivariate analyses for the following factors: the first available CD4 value dichotomized at 200 cells/mm^3; the rate of change of CD4 and viral load during the prenatal period; starting ART during pregnancy compared to starting ART prior to pregnancy or even starting ART later in pregnancy; taking a PI; length of time with HIV diagnosis; and viral load measurements at entry into the prenatal period and every trimester thereafter. There were no significant differences in those infants delivered preterm who were at the 10th percentile ($n = 15$, 26.3%) compared to the non-SGA infants ($n = 19$, 15.1%; $P = 0.070$). As expected, the birth weight for those with SGA at the 10th percentile was significantly less than those without SGA ($P < 0.001$). A higher percentage of the women with SGA infants had ever smoked cigarettes ($P = 0.057$), though smoking at the time of the study ($P = 0.250$) was not statistically significant for an SGA infant at the 10th percentile (Table 2).

The same comparisons were reevaluated using SGA at the 3rd percentile where the rate was shown to be 12.6% (Table 2). Education status was significantly associated with SGA at the 3rd percentile with a higher percentage of women with SGA infants having less than a high school education ($P = 0.028$). Current smoking status was close to significant ($P = 0.056$). CD4 counts >200 cells/mm^3 at the first prenatal visit were significantly associated with a decreased risk of SGA at the 3rd percentile ($P = 0.015$). All other factors were not significantly associated with SGA at the 3rd percentile including HIV viral load measurements at entry into the prenatal period and every trimester thereafter, choice of ART (either NNRTI [$P = 0.114$] or PI [$P = 0.287$]), initiation of ART during the index pregnancy compared to those who started ART prior to the index pregnancy ($P = 0.052$), or starting ART in the third trimester. There were no significant differences in those infants delivered preterm at the 3rd percentile ($n = 3$, 13%) as compared to the non-SGA infants ($n = 31$, 19.4%; $P = 0.465$). As expected, the birth weight for those with SGA at the 3rd percentiles was significantly less than those without SGA ($P < 0.001$).

Cesarean delivery was the most prevalent mode of delivery for all infants, regardless of SGA status. Among the women for whom the mode of delivery was known ($n = 193$, 87%), 54% of the deliveries were cesarean births. SGA was not associated with an increased risk of cesarean delivery. The two SGA groups had comparable distribution of vaginal and cesarean deliveries. The modes of delivery of those infants at the 10th percentile were vaginal, 42.1% ($n = 24$); cesarean, 54.4% ($n = 31$); and unknown 3.5% ($n = 2$); for those at

the 3rd percentile, vaginal deliveries were 39.1% ($n = 9$) and cesarean deliveries were 60.9% ($n = 14$).

The results of the logistic regression models are presented in Table 3. In the adjusted model for SGA at the 10th percentile, cigarette smoking was significantly associated with a higher likelihood of an SGA birth (OR 2.77; 95% CI, 1.28–5.97). Interestingly, even after adjustment, women taking NNRTI medications were significantly less likely to have an SGA birth at the 10th percentile (OR 0.28; 95% CI, 0.10–0.75) compared to those treated with other HIV regimens.

In the adjusted model for SGA at the 3rd percentile, current cigarette smoking was associated with a higher likelihood of an SGA birth (OR 3.64; 95% CI, 1.12–11.76). Those who had a CD4 value greater than 200 cells/mm^3 at the first clinic visit were significantly less likely to have an SGA infant (OR 0.29, 95% CI, 0.10–0.86). As at the 10th percentile, after adjustment, women taking NNRTI medications were significantly less likely to have an SGA birth at the 3rd percentile (OR 0.16; 95% CI, 0.03–0.91) compared to those treated with other HIV regimens.

The rates of SGA in this cohort remained exceptionally elevated even when compared to a rate of 16% SGA births defined as less than the 10th percentile observed in a similar group of HIV-negative non-Hispanic black women from Philadelphia, PA. The comparison dataset was from a community-based study examining maternal stress and maternal and infant health and health-related behaviors [15]. The women were recruited from a consortium of eight health centers run by the Philadelphia Department of Public Health. The sample used for comparison is a subsample of 3990 on whom SGA data were available.

When we formally compare the 183 to the 3990, we find the following differences: the HIV-infected cohort is significantly older ($M = 28.0$; SD $= 6.2$) compared to the HIV negative comparison ($M = 24.1$; SD $= 5.7$; $P < .001$). The HIV-infected cohort has a significantly higher percentage of women who were African American (74.7% versus 67.1% $P = 0.03$), and single (86.7%, 75.7% $P = 0.001$), and HIV-infected women are more likely to have greater parity (more than 1 child: 69.1% versus 55.7% $P = 0.001$) and higher rates of ever having smoked (50.8% versus 35.1%, $P = 0.001$). In our sample of HIV-infected women the risk factors associated with SGA are more prevalent; however, when accounted for in the multivariate model, none except smoking was statistically significant.

4. Discussion

The present study sought to determine the rate of SGA deliveries among HIV-infected pregnant women, and to assess contributing factors that may influence the likelihood that an HIV-infected woman will deliver an SGA infant. A high rate of SGA births was observed in this sample: 31.2% of the sample delivered an SGA infant at the 10th percentile and 12.6% of the sample delivered an SGA infant at the 3rd percentile. These rates remain exceptionally elevated even when compared to an SGA rate of 16%, defined using the same cut points at the 10th percentile, and observed in a sociodemographically at-risk cohort of HIV-negative non-Hispanic black women from Philadelphia, PA [8]. Further, the rate of SGA, defined at the 3rd percentile, in this cohort of HIV-positive women was 12.6% as compared to the national average of 3%.

In this prospective observational study, several factors emerged as potential contributors to this increased rate. The severity of HIV disease, but not the ART regimen, was associated with a significantly increased rate of SGA at the 3rd percentile. Infants born to mothers with a CD4 > 200 were 70% less likely to be SGA at the 3rd percentile compared to infants born to mothers with CD4 ≤ 200 (95% CI, 0.10–0.86). However, CD4 was not significantly associated with increased risk of SGA at the 10th percentile. The length of time with a diagnosis of HIV did not affect SGA outcome in this cohort.

Another factor that could explain the high rate of SGA infants is that this cohort has sociodemographic and behavior characteristics that have been noted to contribute to SGA outcomes. We compared this cohort to a dataset of 3990 women who were recruited from a consortium of eight health centers run by the Philadelphia Department of Public Health that targeted vulnerable populations. The HIV group had more of the risk factors associated with SGA infants, but after accounting for these risk factors in the multivariate model, only smoking was significantly associated with SGA outcomes. After adjusting for maternal sociodemographic and behavioral characteristics, women taking NNRTIs were less likely to have SGA infants in both at the 10th percentile (OR 0.28; 95% CI, 0.10–0.75; $P = 0.045$) and at the 3rd percentile (OR 0.16; 95% CI, 0.03–0.91), though the 3rd percentile was not significant ($P = 0.114$). Published data are conflicting as to whether receipt of ART during pregnancy is associated with adverse pregnancy outcomes. A large US single-center study found a 1.8-fold increase in preterm delivery among women who received PIs as compared to those on a non-PI containing regimen. After adjustment for possible confounders including disease severity, only combination therapy with a PI was associated with risk for preterm delivery compared to any other regimen (95% CI, 1.1–3.0) [16]. However, those receiving PIs had more advanced disease in this cohort. The European Collaborative Study and the Swiss Mother and Child HIV Cohort Study [17] report that even with adjustment for CD4 count and injection drug use an odds ratio for prematurity of 2.60 (95% CI, 1.43–4.75) and 1.82 (95% CI, 1.13–2.92) for infants exposed to ART with or without a PI, respectively, was compared to no treatment. In contrast, in a meta-analysis of seven prospective clinical studies comparing women on antenatal ART with those not on ART (1990–1998), no increase in the rate of preterm birth or low birth weight was observed in women taking ART [18]. Other studies also report no significant associations between use of ART by class or category and adverse pregnancy outcome [19–22].

Associations between timing of the initiation of ART and risk of preterm births have been reported. One large cohort study showed women receiving ART initiated before their pregnancy were twice as likely to deliver prematurely as those starting therapy during the third trimester [17]. In

Table 3: Logistic regressions predicting 10th percentile and 3rd percentile.

Variable	10th percentile		3rd percentile	
	Odds ratio	Confidence interval	Odds ratio	Confidence interval
Age ≤ 22 years	1		1	
Age 23–26 years	0.53	(0.20, 1.58)	0.20	(0.03, 1.30)
Age 27–31 years	0.35	(0.12, 1.02)	0.54	(0.13, 2.34)
Age > 31 years	1.08	(0.42, 2.75)	1.01	(0.26, 3.85)
Race—African American	1		1	
Race—all other	0.51	(0.22, 1.21)	1.12	(0.32, 3.95)
Ever smoked	2.77	(1.28, 5.97)		
Ever smoked—unknown	5.11	(1.13, 23.01)		
Currently smoking			3.64	(1.12, 11.76)
Current smoking—unknown			1.01	(0.08, 12.08)
Education—less than high school			1	
Education—high school/some high school			0.36	(0.10, 1.27)
Education—college/some college			1.98	(0.34, 11.46)
Education—unknown			0.27	(0.06, 1.21)
First viral load > 1000	1.57	(0.74, 3.32)	0.92	(0.29, 2.86)
First CD4 > 200	0.67	(0.31, 1.44)	0.29	(0.10, 0.86)
Started medications in pregnancy	1.47	(0.60, 3.58)	4.64	(0.81, 26.42)
NNRTI	0.28	(0.10, 0.75)	0.16	(0.03, 0.91)
PI*	1.68	(0.79, 3.55)	2.73	(0.83, 9.00)

* Run as a separate model with the same covariate.
NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

an updated report from this same cohort, the risk of delivery before 34 weeks of gestation was increased by 2.5-fold for those starting ART during pregnancy and 4.4-fold for those entering pregnancy on ART as compared to those women not on ART [23]. Powis et al. [24] found that PI-based highly active antiretroviral therapy (HAART) initiated in the third trimester of pregnancy was associated with a 2-fold higher odds of a preterm delivery compared with triple NRTI-based HAART begun at the same time. In our study, those who started ART after prenatal care initiation compared to those who were on ART prior to pregnancy had a trend toward SGA at the 3rd percentile ($P = 0.052$), but not at the 10th percentile.

Mode of delivery was not associated with an increased risk of SGA at either the 10th or the 3rd percentile. The effect of cigarette smoking during the index pregnancy at the 10th percentile (OR 2.77; 95% CI, 1.28–5.97) and the 3rd percentile (OR 3.64; 95% CI, 1.12–11.76) was significantly associated with a higher likelihood of an SGA birth. However, other established risk factors for SGA, such as gestational and chronic hypertension, and preeclampsia were not evaluated in this cohort due to inadequate data collection on these variables. Of the 150 women who had available data on preeclampsia, we found higher rates of preeclampsia (13.6%, $n = 21$), compared to the national average of 2-3% of all pregnancies (5–7% in nulliparous women) [25]. This finding may be due to the provision of regular antenatal care in this cohort, including management of HIV status, sexually transmitted infections, hypertension, and diabetes which could contribute to the lack of association with these important potential risks for SGA [7].

In attempting to decipher why this cohort had exceptionally high levels of SGA infants, it is possible that exposure to HIV has an independent association with increased risk of SGA as a result of immune activation. Ongoing immune activation is associated with poor recovery of CD4+ T cells during early and long-term ART and might contribute to the pathogenesis of non-AIDS-related HIV diseases, such as atherosclerotic vascular disease and non-AIDS-related cancers [26–28]. Studies investigating the effect of HIV and pregnancy on the immune system have shown that even with low levels of viremia, HIV-infected women at delivery showed an immunologic profile different from that of both healthy non-HIV-infected women in the puerperium and nonpregnant women, with lower CD4 T lymphocytes and higher CD8 T lymphocytes, high levels of CD38 expression, but low CD56 expression on CD8+ T cells and low natural killer cell numbers [29, 30]. Fiore et al. [31] have proposed ART immunomodulation as a potential mechanism triggering preterm deliveries. This group proposed that immune reconstitution with resultant cytokine shifts may underlie the association. In the current study, the rate of change in CD4 cells between women experiencing SGA deliveries and those experiencing non-SGA deliveries was not significantly different. Further investigation into this potential mechanism is required; possibly a larger sample will be able to demonstrate a more robust association.

Our study had several limitations. Due to the limited number of participants, the study was underpowered to detect an association with less prevalent risk factors. Due to the length of data collection over 10 years, the ART regimens had greater variations than if this study were completed over

a shorter period. Additionally, we did not collect information on body mass index, which is an indicator of poor fetal outcomes. Future studies should include this variable. A strength of this study is the use of the SGA outcome, because it is a more sensitive measure of adverse outcomes than is preterm delivery or low gestational weight. Few studies have explored SGA as an outcome in this population [32]. We were able to use robust data for SGA definition based upon curves developed from vital statistics data for singleton births born to US resident mothers in the 50 states and the District of Columbia in 1998, 1999, and 2000. Additionally, we used a comparison dataset of 3990 women who were recruited from a consortium of eight health centers run by the Philadelphia Department of Public Health for whom SGA data were available. A strength of this study was the ability to use these data sets, which helped to quantify SGA in this small but important population. Additionally, this is a prospective study, thus eliminating the inconsistencies of a retrospective study.

5. Conclusions

In this prospective longitudinal cohort study of women with HIV, we found there was an increase in SGA births compared to a similar HIV negative population: 31.2% as compared to 16%. However, we found no association between increased risk of SGA birth and class and category of ART. Interestingly, NNRTIs had a protective effect for the risk of SGA infants. ART is a critical component in the prevention of perinatal transmission in both the developed and developing world and offers proven benefits to maternal and infant health. Many uncertainties remain regarding potential adverse effects of taking ART during pregnancy. The association of SGA in this study was likely due to severity of HIV disease, not ART. Future research to better understand the pathophysiology of SGA in pregnant women with HIV is warranted to better characterize the risk factors associated with delivering an SGA infant.

References

[1] S. K. Whitmore, X. Zhang, A. W. Taylor, and J. M. Blair, "Estimated number of infants born to HIV-infected women in the United States and five dependent areas, 2006," *Journal of Acquired Immune Deficiency Syndromes*, vol. 57, no. 3, pp. 218–222, 2011.

[2] Centers for Disease Control and Prevention, "Mother-to-Child (Perinatal) HIV Transmission and Prevention," 2007, http://www.cdc.gov/hiv/topics/perinatal/resources/factsheets/perinatal.htm.

[3] J. R. Cocroft, W. W. Hauck, L. Cosler, and B. J. Turner, "The effect of ethnicity and maternal birthplace on small-for-gestational-age deliveries to HIV-infected women," *Journal of Urban Health*, vol. 79, no. 1, pp. 147–160, 2002.

[4] J. Mirpuri and L. Jain, "Issues of prematurity and HIV infection," *Clinics in Perinatology*, vol. 37, no. 4, pp. 887–905, 2010.

[5] P. Traisathit, J. Y. Mary, S. Le Cœur et al., "Risk factors of preterm delivery in HIV-infected pregnant women receiving zidovudine for the prevention of perinatal HIV," *Journal of Obstetrics and Gynaecology Research*, vol. 35, no. 2, pp. 225–233, 2009.

[6] P. Saenger, P. Czernichow, I. Hughes, and E. O. Reiter, "Small for gestational age: short stature and beyond," *Endocrine Reviews*, vol. 28, no. 2, pp. 219–251, 2007.

[7] L. McCowan and R. P. Horgan, "Risk factors for small for gestational age infants," *Best Practice and Research*, vol. 23, no. 6, pp. 779–793, 2009.

[8] I. T. Elo, J. F. Culhane, I. V. Kohler et al., "Neighbourhood deprivation and small-for-gestational-age term births in the United States," *Paediatric and Perinatal Epidemiology*, vol. 23, no. 1, pp. 87–96, 2009.

[9] J. Gardosi, "New definition of small for gestational age based on fetal growth potential," *Hormone Research*, vol. 65, no. 3, pp. 15–18, 2006.

[10] Z. Bursac, C. H. Gauss, D. K. Williams, and D. W. Hosmer, "Purposeful selection of variables in logistic regression," *Source Code for Biology and Medicine*, vol. 3, article 17, 2008.

[11] R. B. Bendel and A. A. Afifi, "Comparison of stopping rules in forward "stepwise" regression," *Journal of the American Statistical Association*, vol. 72, pp. 46–53, 1977.

[12] R. M. Mickey and S. Greenland, "The impact of confounder selection criteria on effect estimation," *American Journal of Epidemiology*, vol. 129, no. 1, pp. 125–137, 1989.

[13] J. Sibiude, J. Warszawski, R. Tubiana et al., "Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost?" *Clinical Infectious Diseases*, vol. 54, no. 9, pp. 1348–1360, 2012.

[14] F. Kakkar, V. Lamarre, H. Soudeyns et al., "Use of boosted protease inhibitor in pregnancy and risk of prematurity among HIV-exposed uninfected infants: Canada," in *Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections*, Poster #1026, Seattle Wash, USA, March 2012.

[15] E. F. Dennis, D. A. Webb, S. A. Lorch, L. Mathew, J. R. Bloch, and J. F. Culhane, "Subjective social status and maternal health in a low income urban population," *Maternal and Child Health Journal*, vol. 16, no. 4, pp. 834–843, 2011.

[16] A. M. Cotter, A. G. Garcia, M. L. Duthely, B. Luke, and M. J. O'Sullivan, "Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth?" *Journal of Infectious Diseases*, vol. 193, no. 9, pp. 1195–1201, 2006.

[17] M.-L. Newell, C. Aebi, M. Battegay et al., "Combination antiretroviral therapy and duration of pregnancy," *AIDS*, vol. 14, no. 18, pp. 2913–2920, 2000.

[18] R. E. Tuomala, D. E. Shapiro, L. M. Mofenson et al., "Antiretroviral therapy during pregnancy and the risk of an adverse outcome," *New England Journal of Medicine*, vol. 346, no. 24, pp. 1863–1870, 2002.

[19] K. Patel, D. E. Shapiro, S. B. Brogly et al., "Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy," *Journal of Infectious Diseases*, vol. 201, no. 7, pp. 1035–1044, 2010.

[20] R. E. Tuomala, H. Watts, D. Li et al., "Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy," *Journal of Acquired Immune Deficiency Syndromes*, vol. 38, no. 4, pp. 449–473, 2005.

[21] E. G. Szyld, E. M. Warley, L. Freimanis et al., "Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth," *AIDS*, vol. 20, no. 18, pp. 2345–2353, 2006.

[22] A. P. Kourtis, C. H. Schmid, D. J. Jamieson, and J. Lau, "Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis," *AIDS*, vol. 21, no. 5, pp. 607–615, 2007.

[23] C. Thorne, D. Patel, and M. L. Newell, "Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe," *AIDS*, vol. 18, no. 17, pp. 2337–2339, 2004.

[24] K. M. Powis, D. Kitch, A. Ogwu et al., "Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy," *Journal of Infectious Diseases*, vol. 204, no. 14, pp. 506–514, 2011.

[25] Royal College of Obstetricians and Gynaecologists, "Pre-eclampsia—study group consensus statement," 2003, http://www.rcog.org.uk/womens-health/clinical-guidance/pre-eclampsia-study-group-consensus-statement.

[26] A. N. Phillips, J. Neaton, and J. D. Lundgren, "The role of HIV in serious diseases other than AIDS," *AIDS*, vol. 22, no. 18, pp. 2409–2418, 2008.

[27] M. A. French, M. S. King, J. M. Tschampa, B. A. Da Silva, and A. L. Landay, "Serum immune activation markers are persistently increased in patients with HIV infection after 6 years of antiretroviral therapy despite suppression of viral replication and reconstitution of CD4+ T Cells," *Journal of Infectious Diseases*, vol. 200, no. 8, pp. 1212–1215, 2009.

[28] P. W. Hunt, J. N. Martin, E. Sinclair et al., "T cell activation is associated with lower CD4+ T cell gains in human immunodeficiency vires-infected patients with sustained viral suppression during antiretroviral therapy," *Journal of Infectious Diseases*, vol. 187, no. 10, pp. 1534–1543, 2003.

[29] J. M. Denney, E. L. Nelson, P. D. Wadhwa et al., "Longitudinal modulation of immune system cytokine profile during pregnancy," *Cytokine*, vol. 53, no. 2, pp. 170–177, 2011.

[30] H. H. M. Truong, M. S. Sim, M. Dillon et al., "Correlation of immune activation during late pregnancy and early postpartum with increases in plasma HIV RNA, CD4/CD8 T cells, and serum activation markers," *Clinical and Vaccine Immunology*, vol. 17, no. 12, pp. 2024–2028, 2010.

[31] S. Fiore, E. Ferrazzi, M. L. Newell, D. Trabattoni, and M. Clerici, "Protease inhibitor-associated increased risk of preterm delivery is an immunological complication of therapy," *Journal of Infectious Diseases*, vol. 195, no. 6, pp. 914–916, 2007.

[32] N. Parekh, H. Ribaudo, S. Souda et al., "Risk factors for very preterm delivery and delivery of very-small-for-gestational-age infants among HIV-exposed and HIV-unexposed infants in Botswana," *International Journal of Gynecology and Obstetrics*, vol. 115, no. 1, pp. 20–25, 2011.

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Research Article

Incidence of Pregnancy after Initiation of Antiretroviral Therapy in South Africa: A Retrospective Clinical Cohort Analysis

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Background. Little is known about rates of incident pregnancy among HIV-positive women initiating highly active antiretroviral therapy (HAART). *Methods*. We conducted a retrospective clinical cohort study among therapy-naïve women ages 18–45 initiating HAART between 1 April 2004 and 30 September 2009 at an adult HAART clinic in Johannesburg, South Africa. We used Poisson regression to characterize rates and rate ratios of pregnancy. *Results*. We evaluated 5,996 women who experienced 727 pregnancies during 14,095 person-years at risk. The overall rate of pregnancy was 5.2 per 100 person-years (95% confidence limits [CL] 4.8, 5.5). By six years, cumulative incidence of first pregnancy was 22.9% (95% CL 20.6%, 25.4%); among women ages 18–25 at HAART initiation, cumulative incidence was 52.2% (95% CL 35.0%, 71.8%). The strongest predictor of incidence of pregnancy was age, with women 18–25 having 13.2 times the rate of pregnancy of women ages 40–45 in adjusted analysis. CD4 counts below 100 and worse adherence to HAART were associated with lower rates of incident pregnancy. *Conclusions*. Women experience high rates of incident pregnancy after HAART initiation. Understanding which women are most likely to experience pregnancy will help planning and future efforts to understand the implications of pregnancy for response to HAART.

1. Introduction

Women of childbearing age bear the largest burden of HIV in sub-Saharan Africa [1, 2]. This is especially true in South Africa, the country with the largest population of HIV-positive individuals in the world [3]. In South Africa, HIV prevalence among young women is three times that among young men [4], and a stabilizing overall prevalence of HIV may actually mask very high HIV incidence rates among rural and urban women in some parts of the country [5].

The overlap between pregnancy and HIV is even more striking, with very high rates of both HIV and pregnancy incidence reported among young women in parts of South Africa [5] and HIV prevalence reaching 40% among pregnant women in some age groups [2–4]. A recent publication reporting on multiple sites across Africa noted high HIV incidence rates among HIV-positive women in many settings, as well as a 70% increased hazard of pregnancy after initiation of highly active antiretroviral therapy (HAART) [6].

With international support to attain universal access to HAART [7] and a growing interest in "treatment-as-prevention" [8], an increasing incidence of pregnancy among women receiving HAART seems inevitable. While there are some limited data from the pre-HAART era about how pregnancy affects rate of HIV disease progression [9], very little is known about how pregnancy affects responses to HAART [10, 11]. Understanding the patterns and risk factors

for incident pregnancy after HAART initiation is therefore of significant concern to planning and management of women in treatment for HIV; this is especially true in South Africa, where there is wide access to HAART and a very large at-risk population of reproductive-age women.

Here, we characterize predictors of incident pregnancy after HAART initiation in the Themba Lethu Clinic, an adult antiretroviral therapy clinic in urban Johannesburg, South Africa.

2. Methods

2.1. Study Population. We analyzed data from the Themba Lethu Clinic (TLC) observational cohort [12], an observational clinical cohort of adults initiating HAART in Johannesburg, South Africa. Since the beginning of the government era of HAART in South Africa on 1 April 2004, the TLC has provided free antiretroviral therapy and (since October 2006) free clinical care to HIV-positive adults. At present, TLC has over 17,000 patients in care and is the largest single clinic providing HAART in South Africa. Here, we studied previously antiretroviral therapy-naïve women from the time of HAART initiation between 1 April 2004 and 30 September 2009 and followed these women until administrative end of followup on 31 March 2010 or the end of care due to dropout, death, or transfer of care to another site. We excluded women with a baseline age over 45 (in whom pregnancy is rare).

First-line HAART in the time period under study was stavudine, lamivudine, and efavirenz. Due to concerns about teratogenicity, women found to be pregnant are typically placed on lopinavir and ritonavir rather than efavirenz or on nevirapine; nonpregnant women with declared pregnancy intention are placed on nevirapine or lopinavir-ritonavir. Adherence was captured from pharmacy records as the cumulative proportion of days in which a woman had access to antiretroviral drugs; this estimate of adherence is an *upper limit* on potential adherence, because drugs can only be taken correctly if they are available.

Additional details of the TLC clinical database, clinic procedures, and outcomes have been described previously [12, 13]; here we note only that clinical data are captured prospectively in the TLC and that accuracy of data entry has been previously validated [12].

2.2. Statistical Analysis. Baseline characteristics of women were described using simple statistics, including chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. We used discrete time hazards models fit with pooled logistic regression to characterize predictors of incident pregnancy.

The main outcome in this study was pregnancy after baseline of HAART initiation, hereafter incident pregnancy. We studied all pregnancies recorded in the database, allowing women to have multiple pregnancies; women became at risk of a new pregnancy at the end of a previous pregnancy (including baseline prevalent pregnancy).

Rates and relative rates of pregnancy were estimated using univariate and multivariate Poisson regression, accounting for repeated outcomes using a robust variance estimator. Multivariate analysis of predictors of pregnancy considered baseline measures of employment, history of smoking, and pregnancy, and time-updated measures of age, HAART regimen, body mass index, hemoglobin, CD4 count, viral load, and adherence. In addition, we investigated the effect of baseline employment status and a baseline history of smoking on incidence of pregnancy, but neither strongly predicted pregnancy and so were omitted from final models. Cumulative incidence curves for first pregnancy (only) were estimated using extended Kaplan-Meier estimators.

3. Results

3.1. Population. The initial study population comprised 5,996 women who contributed a total of 175,795 person-months (14,650 person-years) of followup until death, dropout, or end of followup. Person-time at risk for new incident pregnancy (i.e., subtracting person-time experienced during a pregnancy) was 169,138 person-months (14,095 person-years).

Of the 5,996 women, 586 (10%) were pregnant at baseline. Systematic differences between those women pregnant at baseline and those nonpregnant at baseline have been documented elsewhere; generally women who were pregnant at baseline are younger and healthier than those who are nonpregnant at baseline (and are initiating HAART entirely because they are sick) [11]. We review select baseline characteristics of women by baseline pregnancy status in Table 1.

3.2. Incidence of Pregnancy. There were 727 incident pregnancies experienced in the total population; 612 women experienced one pregnancy, 50 women experienced two pregnancies, and 5 women experienced three pregnancies during followup. Of the 727 incident pregnancies, 85 (12%) were among women pregnant at baseline. Among all women, the overall crude rate of incident pregnancy was 5.2 per 100 person-years (95% confidence limits (CLs) 4.8, 5.5 per 100 person-years). Figure 1 shows cumulative incidence of first pregnancy among all women remaining alive and in care, and at risk, during followup; by six years, estimated cumulative incidence of first pregnancy was 22.9% (95% CL 20.6%, 25.4%). The estimated cumulative incidence of pregnancy among women who were between 18 and 25 years old was 52.2% (95% CL 35.0%, 71.8%) by six years of followup.

The median time from HAART initiation to first pregnancy was 14 months (interquartile range (IQR) 7, 26) among women nonpregnant at baseline and 18 months (IQR 10, 28) among those pregnant at baseline. Median time from end of first incident pregnancy to second incident pregnancy among the 55 second pregnancies was 10 months (IQR 5–16). The five observed third pregnancies happened at 4, 10, 12, 18, and 24 months after the end of the second pregnancy.

Table 1: Characteristics of 5,996 women initiating HAART in Johannesburg, South Africa from 1 April 2004 to 30 September 2009 by pregnancy status at baseline.

Baseline characteristics	Pregnant ($n = 586$)	Not pregnant ($n = 5{,}410$)	P-value
Age (years)	30 (26, 33)	34 (29, 38)	<0.0001
Weight (kg)	68 (60, 77)	57 (49, 65)	<0.0001
Body mass index (kg/m^2)	26.5 (23.3, 29.7)	22.2 (19.5, 25.5)	<0.0001
WHO stage III or IV	100 (18.2)	2372 (43.1)	<0.0001
Hemoglobin, low‡	123 (30.9)	2918 (54.7)	<0.0001
CD4 count (cells/mm^3)	156 (106, 200)	93 (35, 164)	<0.0001
CD4 count ≤ 50 (cells/mm^3)	45 (8.8)	1739 (32.6)	<0.0001

Categorical variables are expressed as number (% total); continuous variables are expressed as median (interquartile range). P-values are two-sided by chi-square test or Wilcoxon rank sum test. ‡After adjustment for altitude, lower limit of normal hemoglobin is 11.35 and 10.35 g/dL for nonpregnant and pregnant women, respectively.

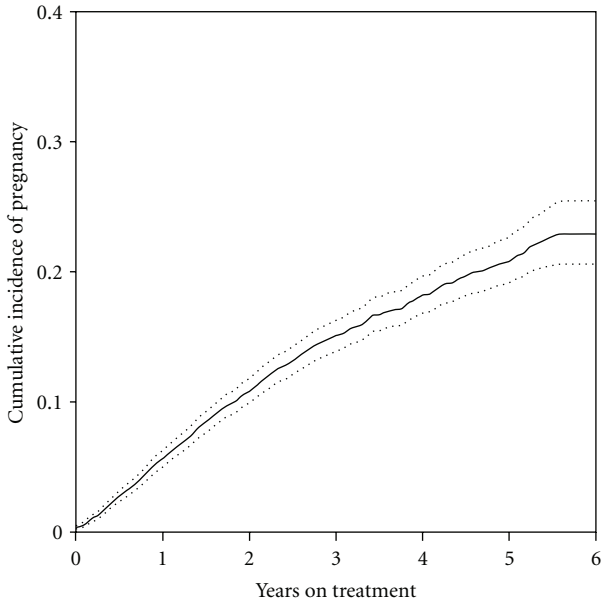

Figure 1: Cumulative incidence of first pregnancy among 5,996 women initiating HAART in Johannesburg, South Africa, from time of HAART initiation, with 95% confidence bounds.

3.3. Characteristics of Incident Pregnancies. Among women who became pregnant, median (interquartile range (IQR)) age at first pregnancy was 31.5 (28.1, 34.7). Age at second pregnancy (among the 55 women who experienced a second pregnancy) was 31.0 (28.2, 35.5). The plurality of pregnancies ($n = 281$) occurred in women ages 30–35, but rate of pregnancy was highest among 18–25-year olds at 10.4 (95% CL 8.2, 13.3) per 100 person-years to 0.9 (95% CL 0.6, 1.3) per 100 person-years among 40–45-year olds in this population (Table 2).

The median CD4 count at first pregnancy was 314 (IQR 193, 448) cells/mm^3, with a mean of 338 cells/mm^3. At second pregnancy, median CD4 count was 377 (IQR 305, 515) cells/mm^3 with a mean of 427 cells/mm^3. The majority of pregnancies ($n = 223$) occurred in women with CD4 200–350 cells/mm^3, while only 18 happened in women with CD4 ≤ 50 cells/mm^3. Rates of pregnancy were highest in women with CD4 counts between 350 and 500 cells/mm^3 (Table 2).

Body mass index (BMI) was similar at time of first and second pregnancy; overall, median BMI was 24.8 (IQR 21.9, 27.7) kg/m^2 at time of any incident pregnancy, with a mean of 25.5 kg/m^2. About half of pregnancies ($n = 348$) occurred in women with BMI 18.5–25.0 kg/m^2. Rates of pregnancy were highest in women with BMI between 25 and 30 kg/m^2 (Table 2).

The majority of incident pregnancy occurred while exposed to efavirenz ($n = 522$, 72% of all pregnancies); of these, about 75% switched away from efavirenz within the term of the pregnancy. Among the remaining pregnancies, approximately equal proportions were exposed to nevirapine and lopinavir-ritonavir. Rates of pregnancy were highest among women receiving nevirapine (Table 2).

3.4. Predictors of Incident Pregnancy. In this population, incident pregnancy was more common among younger, healthier women. Table 2 shows the multivariate incidence rate ratios (IRRs) for associations of various demographic, clinical, and laboratory indicators with incident pregnancy. Of note, accounting for other factors, incidence of pregnancy was much higher in younger than older women, with rate ratios of 13.2 (95% CL 8.4, 20.8) and 10.8 (95% CL 7.3, 16.1) comparing women ages 18–25 and 25–30 both to women ages 40–45.

In both crude and adjusted analysis, incidence of pregnancy was lower with lower CD4 count, especially among women with CD4 counts ≤100 cells/mm^3; surprisingly, there was no reduction in incidence rate of pregnancy associated with CD4 counts in the 101–200 cells/mm^3 range compared to higher CD4 counts. In an additional simplified model, we found only mild and inconsistent interaction between the effect of age and CD4 count (dichotomized at 100 cells/mm^3); what effect there was showed a slightly reduced impact of age on incidence of pregnancy among women with CD4 counts ≤100 cells/mm^3.

Incidence of pregnancy differed somewhat by drug regimen, with higher crude rates of pregnancy among women receiving lopinavir-ritonavir and nevirapine; however, in

Table 2: Incident rate and adjusted incident rate ratio for association of demographic, clinical, and laboratory indicators with incident pregnancy among antiretroviral therapy-naïve 18–45-year-old women initiating HAART in Johannesburg.

Demographics	Incidence rate, crude, per 100 person-years	Rate ratio, adjusted (95% confidence limits)
Current age (years)		
18–24.9	10.4 (8.2, 13.2)	13.21 (8.41, 20.75)
25–29.9	9.1 (8.0, 10.4)	10.81 (7.26, 16.09)
30–34.9	7.0 (6.2, 7.8)	7.93 (5.37, 11.70)
35–39.9	3.6 (3.0, 4.2)	4.01 (2.69, 5.99)
40–45.0	0.9 (0.6, 1.3)	1
Baseline pregnancy		
Pregnant	6.2 (5.1, 7.7)	0.80 (0.63, 1.03)
Not pregnant	5.0 (4.7, 5.5)	1
Clinical (all time-updated)		
HAART regimen		
Includes EFV	4.7 (4.3, 5.2)	1
Includes LPVr	5.6 (4.7, 6.7)	1.01 (0.82, 1.26)
Includes NVP	8.2 (6.7, 9.9)	1.19 (0.94, 1.50)
Body mass index (kg/m^2)		
<18.5	3.7 (2.6, 5.2)	1
18.5–24.9	5.2 (4.7, 5.8)	1.04 (0.71, 1.53)
25.0–29.9	5.5 (4.8, 6.2)	1.16 (0.78, 1.72)
≥30	5.2 (4.3, 6.2)	1.19 (0.79, 1.80)
Laboratory (all time updated)		
Hemoglobin‡		
Normal	5.3 (4.9, 5.8)	1
Low	4.5 (3.7, 5.3)	0.96 (0.76, 1.20)
CD4 count (cells/mm^3)		
≤50	2.1 (1.3, 3.3)	0.33 (0.15, 0.75)
51–100	3.2 (2.2, 4.7)	0.68 (0.42, 1.10)
101–200	5.4 (4.5, 6.3)	0.96 (0.77, 1.20)
201–350	5.5 (4.8, 6.3)	
351–500	6.1 (5.3, 7.1)	1
>500	5.0 (4.2, 5.9)	
Viral load (copies/mL)		
≤400	5.5 (5.0, 5.9)	1
401–10,000	5.1 (3.6, 7.3)	0.86 (0.59, 1.25)
>10,000	4.0 (2.8, 5.7)	0.88 (0.60, 1.29)
Adherence		
0–79%	3.7 (2.7, 5.3)	0.67 (0.45, 1.01)
80%–94%	5.9 (5.2, 6.8)	1.13 (0.95, 1.34)
≥95%	5.0 (4.5, 5.5)	1

‡After adjustment for altitude, lower limit of normal hemoglobin is 11.35 g/dL for non-pregnant women.

a multivariate predictive model controlling for other predictors of pregnancy these differences were not significant. Having a measured adherence under 80% was associated with lower incidence of pregnancy, with IRR = 0.67 (95% CL 0.45, 1.01) compared to adherence ≥95%.

In addition to the time-updated predictors of pregnancy noted above, we also examined baseline predictors of incident pregnancy, especially age and CD4 count. Figures 2(a) and 2(b) show cumulative incidence of first pregnancy by *baseline* age category, stratified by *baseline* CD4 count dichotomized at 100 cells/mm^3, among women alive and in care. Of note, cumulative incidence of pregnancy is extremely high among all women who initiated HAART between the ages of 18 and 25 regardless of baseline CD4 count.

3.5. Sensitivity Analyses for Predictors of Incident Pregnancy. We performed three sensitivity analyses of these data. First, we fit a discrete time proportional hazards model, Cox proportional hazards model, for these same data, finding

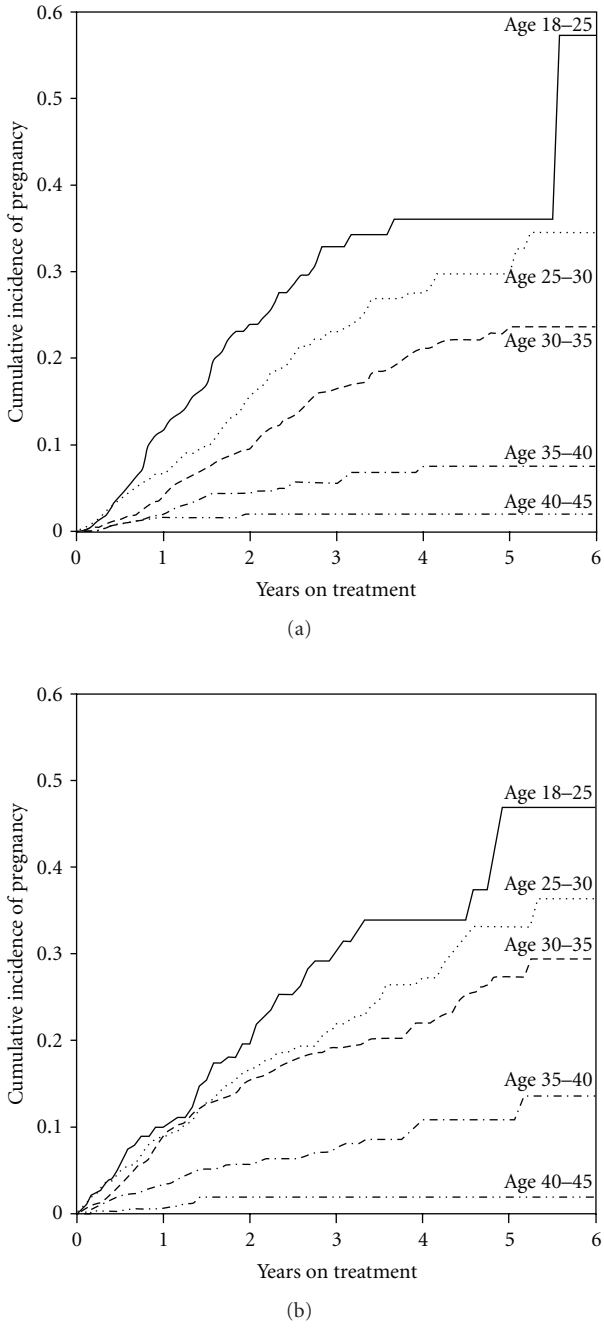

Figure 2: Cumulative incidence of first pregnancy among 5,996 women initiating HAART in Johannesburg, South Africa, from time of HAART initiation, by baseline age and baseline CD4 count: (a) $\leq$100 cells/mm^3; (b) >100 cells/mm^3. Curves are estimated using the extended Kaplan-Meier method.

similar findings to those reported. We looked at results separately by baseline pregnancy status; in this case, rate ratios for incidence of pregnancy among nonpregnant women were similar to overall rate ratios (Table 2); we had insufficient numbers to fit the multivariate model among baseline pregnant women alone or to fit a model including interactions for all variables with prevalent pregnancy status.

Finally, there were substantial missing data in the main analysis: a total of 23,425 of 169,138 person-months, or about 14% of observations. However, 85% ($n = 20,020$) of these missing observations were due to missing viral load data, so we reran the multivariate regression model leaving out viral load measurements—so in this analysis, 98% of the 169,138 possible observations were used. In this last sensitivity analysis, the key differences from Table 2 were (a) a slight rise in rate ratio associated with high body mass index (point estimates moved from 1.04–1.19 in Table 2 to 1.25–1.44, though none reached statistical significance at a P-value of 0.05) and (b) a significant effect of nevirapine on incidence of pregnancy (IRR 1.31, 95% CL 1.06, 1.62).

3.6. Efavirenz Exposure. First-trimester exposure to efavirenz is believed to be associated with an increased risk of congenital abnormalities [14, 15], although one systematic review disagrees [16]. In these data, 522 (72%) of pregnancies were exposed to efavirenz. In separate work, several clinical investigators from the TLC followed up infants exposed to efavirenz *in utero*, investigating 136 and analyzing 41 for congenital abnormalities and for developmental delays with the Denver Developmental Screening Test. No congenital abnormalities were identified. We found 30 infants to be within normal limits, and 11 infants to be suspect for neurodevelopment delay. This work was presented in conference [17] and included in the systematic review noted above [16].

4. Discussion and Conclusion

Planning for the integration of fertility or prenatal care services with clinical HIV services requires a clear understanding of which women will become pregnant and at what rates. In this observational study of HIV-positive women in urban South Africa, we found that pregnancy was relatively common after HAART initiation, reaching an estimated cumulative incidence of 52% among women who were 18–25 when they initiated HAART.

A recent study by Myer et al. reported on the incidence of 589 pregnancies after initiation of HAART among 4,531 women in seven African countries [6]. However, the generalizability of these findings may be somewhat limited by the fact that all these women entered care through prevention of mother-to-child transmission of HIV programs; by virtue of pregnancy, they may have been healthier than women who initiated HAART because they were sick [18] and—for this reason and others—may have been more likely to experience subsequent pregnancy. In addition, the main results reported by Myer et al. were a mix of very high and low pregnancy-incidence settings, with by-country rates ranging from 21.7 per 100 person-years in Rwanda to 3.3 (95% CL 2.6, 4.2) per 100 person-years in three urban sites in South Africa, from both pre- and post-HAART initiation. Our results show an overall higher rate of 5.2 per 100 person-years in only women who have initiated HAART. Our work shows similar incidence rates by age category: Myer et al. reported a rate of 11.5 (95% CL 9.4, 14.0) per 100 person-years among women under age 25 and on antiretroviral therapy; we reported a

rate of 10.4 (8.2, 13.3) per 100 person-years. The relatively high rates of pregnancy seen here, taken in context with recent results suggesting that pregnancy during HAART is associated with increased rates of virologic failure [11, 19], point to the need to better integrate reproductive healthcare services with provision of antiretroviral therapy.

Previous work [11] and theory [20] both suggest that women who are pregnant at baseline may respond to HAART in substantially different ways compared with nonpregnant women, in part because their initiation onto HAART may have more to do with their pregnancy status rather than their immune status. Here, we had insufficient data to evaluate whether predictors of incident pregnancy differ substantially by baseline pregnancy status. We saw a higher crude rate of incident pregnancy in women who were pregnant at baseline (6.2 versus 5.0 pregnancies per 100 person-years), but a slight reduction in relative rate (IRR 0.80, 95% CL 0.62, 1.03) in multivariate analysis. The lowered relative rate in multivariate analysis may be the result of a desire to space out births and/or a period of lowered risk of new pregnancy immediately postpartum (e.g., due to lactational amenorrhea). However, prevalent pregnant women are about twice as likely to be lost to followup as non-prevalent pregnant women; this finding should, therefore, not be overinterpreted.

There are several limitations of this work. Chief among these is our lack of data on use of contraception. However, it is likely that contraceptive use in this setting is likely to be lower than in the South African sites evaluated by Myer et al., as that work examined women who were accessing prevention of mother-to-child transmission services [6]. The present work deals with a general adult population, in which access to contraceptives may be more typical of the experience of an average South African woman presenting for general HIV care [21]; further, contraceptives are not offered at the pharmacy where TLC patients receive their antiretroviral medications, which is likely to further depress usage. Future studies will assess the impact and efficacy of contraception in this setting as well as assess unmet needs for contraception in the adult female population of this clinic. In addition, we analyzed observational data from a clinical database, and thus misclassification of exposure (particularly, start and end dates of pregnancies), outcome, and other factors cannot be ruled out. However, our sensitivity analyses support the results of our main analysis, and as noted above the TLC database has been previously validated for accuracy [12].

A final, and critical, limitation is that, while it is tempting to interpret the adjusted rate ratios reported in Table 2 as statements of causality (e.g., if we were to intervene on factor X, the rate of pregnancy would change by Y), such causal statements are not justifiable without substantial further assumptions and caveats [22]. Without further study, the numbers reported in Table 2 should be considered associations and predictions, not statements of causality.

In this large study of nearly 6,000 antiretroviral therapy-naïve women initiating HAART in Johannesburg, we found a high rate of pregnancy, especially among younger women. With very high numbers of HIV-infected young women in South Africa [5], incident pregnancy among women receiving HAART is an important issue with implications both for maternal response to HAART [11] as well as potentially for mother-to-child-transmission of HIV. It will be critical in coming years both to integrate contraceptive counseling and/or antenatal care into settings where HAART is provided [23] as well as to ensure that women who get reproductive or antenatal care in other facilities are able to transition between care centers smoothly and without becoming lost to care. In addition, such a high rate of pregnancy makes it critical that we better understand the impact and timing of pregnancy after HAART initiation on outcomes of HAART, as well as of pregnancy in both mother and child.

Authors' Contribution

D. Westreich cleaned the data, performed statistical analysis, and wrote the first draft of the paper as well as edited subsequent drafts. M. Maskew collected data, helped manage the database, helped clean the database, and helped write and edit the paper. D. Rubel, P. MmacDonald, P. Majuba, and I. Jaffray collected data, performed clinical investigation of efavirenz-exposed infants, and reviewed drafts of the paper. All authors have approved the final version of the paper.

Ethical Approval

This analysis of de-identified research was declared exempt from review by both the University of the Witwatersrand (Protocol M060626, 30 June 2006) and Duke University (Protocol Pro00025267, 13 October 2010). The clinical followup of efavirenz-exposed infants was approved by the University of the Witwatersrand (Protocol M070706, 16 August 2007).

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Conflict of Interests

The authors declared that they have relevant interests to disclose.

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References

[1] UNAIDS, "2009 AIDS epidemic update," http://www.unaids.org/en/dataanalysis/epidemiology/2009aidsepidemicupdate/.

[2] S. O. Mepham, R. M. Bland, and M. L. Newell, "Prevention of mother-to-child transmission of HIV in resource-rich and -poor settings," *An International Journal of Obstetrics and Gynaecology*, vol. 118, no. 2, pp. 202–218, 2011.

[3] UNAIDS/WHO, "AIDS Epidemic Update 2007," Tech. Rep., Geneva, Switzerland, 2007.

[4] A. E. Pettifor, H. V. Rees, I. Kleinschmidt et al., "Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey," *AIDS*, vol. 19, no. 14, pp. 1525–1534, 2005.

[5] Q. A. Karim, A. B. M. Kharsany, J. A. Frohlich et al., "Stabilizing HIV prevalence masks high HIV incidence rates amongst rural and urban women in KwaZulu-Natal, South Africa," *International Journal of Epidemiology*, vol. 40, no. 4, Article ID dyq176, pp. 922–930, 2011.

[6] L. Myer, R. J. Carter, M. Katyal, P. Toro, W. M. El-Sadr, and E. J. Abrams, "Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study," *PLoS Medicine*, vol. 7, no. 2, Article ID e1000229, 2010.

[7] WHO, "Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector," Progress Report, September 2010, http://www.who.int/hiv/pub/2010progressreport/.

[8] M. S. Cohen, Y. Q. Chen, M. McCauley et al., "Prevention of HIV-1 infection with early antiretroviral therapy," *New England Journal of Medicine*, vol. 365, no. 6, pp. 493–505, 2011.

[9] R. French and P. Brocklehurst, "The effect of pregnancy on survival in women infected with HIV: a systematic review of the literature and meta-analysis," *British Journal of Obstetrics and Gynaecology*, vol. 105, no. 8, pp. 827–835, 1998.

[10] S. MacCarthy, F. Laher, M. Nduna, L. Farlane, and A. Kaida, "Responding to her question: a review of the influence of pregnancy on HIV disease progression in the context of expanded access to HAART in sub-Saharan Africa," *AIDS and Behavior*, vol. 13, no. 1, pp. S66–S71, 2009.

[11] D. Westreich, S. R. Cole, S. Nagar, M. Maskew, C. van der Horst, and I. Sanne, "Pregnancy and virologic response to antiretroviral therapy in South Africa," *PLoS One*, vol. 6, no. 8, Article ID e22778, 2011.

[12] I. M. Sanne, D. Westreich, A. P. Macphail, D. Rubel, P. Majuba, and A. Van Rie, "Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study," *Journal of the International AIDS Society*, vol. 12, article 38, 2009.

[13] M. P. Fox, M. Maskew, A. P. Macphail et al., "Cohort profile: the Themba Lethu clinical cohort, Johannesburg, South Africa," *International Journal of Epidemiology*. In press.

[14] S. B. Brogly, M. J. Abzug, D. H. Watts et al., "Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C," *Pediatric Infectious Disease Journal*, vol. 29, no. 8, pp. 721–727, 2010.

[15] K. M. Knapp, S. B. Brogly, D. G. Muenz et al., "Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals," *Pediatric Infectious Disease Journal*, vol. 31, no. 2, pp. 164–170, 2012.

[16] N. Ford, L. Mofenson, K. Kranzer et al., "Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts," *AIDS*, vol. 24, no. 10, pp. 1461–1470, 2010.

[17] D. Westreich, D. Rubel, P. Macdonald et al., "Pregnancy, efavirenz, and birth outcomes in Johannesburg, South Africa," in *Proceedings of the 17th Conference on Retroviruses and Opportunistic Infections*, San Francisco, Calif, USA, 2010.

[18] D. Westreich, D. Evans, C. Firnhaber, P. Majuba, and M. Maskew, "Prevalent pregnancy, biological sex, and virologic response to antiretroviral therapy," *Journal of Acquired Immune Deficiency Syndromes*. In press.

[19] B. Sha, C. Tierney, S. Cohn et al., "Postpartum viral load rebound in HIV-1-infected women treated with highly active antiretroviral therapy: AIDS clinical trials group protocol A5150," *HIV Clinical Trials*, vol. 12, no. 1, pp. 9–23, 2011.

[20] W. A. Ray, "Evaluating medication effects outside of clinical trials: new-user designs," *American Journal of Epidemiology*, vol. 158, no. 9, pp. 915–920, 2003.

[21] S. R. Schwartz, S. H. Mehta, T. E. Taha, H. V. Rees, F. Venter, and V. Black, "High pregnancy intentions and missed opportunities for patient-provider communication about fertility in a south african cohort of HIV-positive women on antiretroviral therapy," *AIDS and Behavior*, pp. 1–10, 2011.

[22] J. M. Robins, "Data, design, and background knowledge in etiologic inference," *Epidemiology*, vol. 12, no. 3, pp. 313–320, 2001.

[23] J. Moodley, R. Pattinson, C. Baxter, S. Sibeko, and Q. Abdool Karim, "Strengthening HIV services for pregnant women: an opportunity to reduce maternal mortality rates in Southern Africa/sub-Saharan Africa," *An International Journal of Obstetrics and Gynaecology*, vol. 118, no. 2, pp. 219–225, 2011.

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Research Article

The Changing Face of HIV in Pregnancy in Rhode Island 2004–2009

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Meeting the needs of HIV-infected pregnant women requires understanding their backgrounds and potential barriers to care and safe pregnancy. Foreign-born women are more likely to have language, educational, and economic barriers to care, but may be even more likely to choose to keep a pregnancy. Data from HIV-infected pregnant women and their children in Rhode Island were analyzed to identify trends in demographics, viral control, terminations, miscarriages, timing of diagnosis, and adherence to followup. Between January 2004 and December 2009, 76 HIV-infected women became pregnant, with a total of 95 pregnancies. Seventy-nine percent of the women knew their HIV status prior to becoming pregnant. Fifty-four percent of the women were foreign-born and 38 percent of the 16 women who chose to terminate their pregnancies were foreign-born. While the number of HIV-infected women becoming pregnant has increased only slightly, the proportion that are foreign-born has been rising, from 41 percent between 2004 and 2005 to 57.5 percent between 2006 and 2009. A growing number of women are having multiple pregnancies after their HIV diagnosis, due to the strength of their desire for childbearing and the perception that HIV is a controllable illness that does not preclude the creation of a family.

1. Introduction

Understanding and supporting HIV-infected women's awareness of their own status and their options regarding pregnancy requires an understanding of their backgrounds and the potential barriers to care and safe pregnancy. Studies have shown that both social pressures and concerns for vertical transmission play a large role in HIV-infected women's choices about pregnancy [1–3]. Information from around the world supports the fact that since the introduction of reliable methods for the prevention of mother-to-child transmission (PMTCT), fewer HIV-infected women are choosing terminations and many are choosing to become pregnant, even to have multiple pregnancies, after their HIV diagnosis [2, 4–6].

Options for safe conception, especially in serodiscordant couples, now include artificial insemination and "sperm washing" [7]. These methods, even where they are available, however, remain relatively unknown and infrequently recommended by many healthcare providers, even in developed countries [8] and may be prohibitively expensive or inaccessible for some couples. In addition to these planned pregnancies, a large number of pregnancies remain unplanned [9, 10]. Women who live in developing countries, where safer methods of conception are relatively unknown or unavailable, are nevertheless choosing to become pregnant after their HIV diagnosis. A survey of 459 HIV-infected men and women in Cape Town, South Africa found that two-thirds of women, who became pregnant after commencing highly active antiretroviral therapy (HAART), had intended

to become pregnant [11]. Furthermore, 50% of HIV-infected men and women were open to the possibility of conceiving children after their HIV diagnosis; being on HAART had no significant impact on whether or not men intended to pursue pregnancy, but did make women more likely to consider pregnancy [11]. It is unclear what impact moving from a developing to a developed country may have on childbearing intentions, but it is possible that this change in their socioeconomic environment and perceived options for care and support may play a role in women's childbearing intentions.

Women in the USA, who are HIV-infected and foreign-born, may have additional issues to consider during pregnancy. They are more likely to have language, educational, and economic barriers to care and to exercising their options, but may be even more likely to choose to keep a pregnancy because of cultural emphasis on childbearing and negative views of termination. Women who are born in areas of the world where fertility rates are between 5 and 7 children per woman, especially Africa and parts of South and Southeast Asia [12], may experience particular spousal and familial pressure to become pregnant, even if they have disclosed their HIV status [13, 14]. A cross-sectional study done in Canada revealed that 69% of 490 HIV-infected women desired future pregnancy and African ethnicity was significantly correlated with intention to become pregnant [15].

Although foreign-born persons with HIV living in the US appear to be a growing proportion of the HIV-infected population [16], current national sociodemographic data do not accurately reflect this demographic, as they are generally listed under their ethnicity without distinction about place of birth [17, 18]. Thus, persons who are originally from Sub-Saharan Africa, where the highest number of HIV-infected individuals exists, are listed as black/African-American in data used for determining funding and resource allocation. African-born persons often live within their own communities and may not be reached by programs that target African-Americans [19, 20]. In Washington state, for example, the HIV diagnosis rate among blacks in the state is five times higher than the rate among whites, and 40% of all HIV diagnoses among blacks in Washington state have been among foreign-born persons [21]. Similar data collected from five different states and high-prevalence areas show that across all areas, up to 41% of diagnoses in women and up to 50% of diagnoses in blacks occurred among African-born individuals [16]. Additionally, we should not presume all foreign-born persons were necessarily infected with HIV prior to arrival in the USA. Data suggest that in some parts of the country, especially those parts with high numbers of Hispanic immigrants, patients are more likely to have been infected after arrival [22], which may indicate increased vulnerability among foreign-born persons.

Unfortunately, the complex social issues that contribute to women becoming HIV-infected often present barriers to adherence with prescribed medication regimens and prenatal followup, as well as with ensuring adequate testing and followup of the HIV-exposed infant. Studies have shown that 45% of mothers of HIV-infected infants had missed opportunities for perinatal HIV prevention [23], indicating that although appropriate protocols are in place, additional factors contribute to transmission.

Rhode Island, the smallest state in the United States, had an HIV prevalence of 209 per 100,000 population by the end of 2009 [24]. Among the general population, 81% of persons identified themselves as White, 12% identified themselves as Hispanic, and 6% identified themselves as black or African-American [25]. Amongst the 3,080 HIV-infected persons who have been diagnosed in Rhode Island since 1982, 54% identified themselves as White, 26% identified themselves as African-American, and 19% identified themselves as Hispanic [25]. Thus, 45% of HIV cases in the state have occurred in the 18% of the population identified as Hispanic or African-American. No data is available on the percentage of HIV-infected persons in the state who are immigrants or foreign-born.

Following the lead of several other states, Rhode Island adopted a law mandating testing of pregnant women during pregnancy or their children immediately after birth. This was done in order to ensure that children receive medication to prevent mother-to-child transmission in a timely manner, and that women are appropriately identified if they need HIV-related services [26]. This law has already led to increased rates of HIV testing during pregnancy, from 52.8% in 2005-2006 to greater than 95% after the law changed in 2007 [27], but it is unclear if it has led to an increased number of HIV diagnoses. We seek to describe the experiences of HIV-infected pregnant women and their children followed at a large HIV clinic in Rhode Island.

2. Materials and Methods

The Immunology Center at the Miriam Hospital in Providence, Rhode Island, is an urban HIV clinic with 1400 active patients. In 2009, 25% of HIV patients followed at the Miriam Immunology Center were uninsured or covered only by the hospital's free care program and 32% were foreign-born. All HIV-infected patients in Rhode Island have access to antiretrovirals either through health insurance or through the Ryan White Program, provided they have been registered as Rhode Island residents. The Immunology Center has been caring for HIV-infected women before, during, and after their pregnancies since its establishment in 1986. The Hasbro Children's Hospital Pediatric Infectious Diseases II Clinic in Providence generally sees all the HIV-exposed infants delivered to these women. These clinics follow DHHS guidelines for perinatal prevention of mother-to-child transmission and follow-up testing for HIV-exposed infants. The two clinics are the largest providers for HIV-infected women and their children in Rhode Island. This study aims to characterize and understand the recent trends in the HIV-infected pregnant population and HIV-exposed children in Rhode Island.

Social and clinical data from HIV-infected pregnant women collected regularly by the Immunology Center staff for care and research purposes were analyzed to identify and characterize trends in demographics, viral control, terminations, miscarriages, timing of diagnosis,

and adherence to followup. Data on the adherence with follow-up appointments and testing for the HIV-exposed infants were obtained from paper and online charts from both Hasbro Children's Hospital's primary care clinics and Pediatric Infectious Diseases II Clinic. Data were analyzed for means of continuous variables (viral load, CD4 counts, etc.), percentages of descriptive variables (US-born versus foreign-born, outcome of pregnancy, mode of delivery, etc.) and significant correlations between variables using Statistical Package for the Social Sciences (SPSS) Version 17.0 (Chicago, IL, USA). Statistical significance was assessed using a chi-square test. This project was reviewed and approved by the Miriam and Rhode Island Hospital (including Hasbro Children's Hospital) Institutional Review Boards.

3. Results

Between January 2004 and December 2009, 321 HIV-infected women between 18 and 45 years old were seen at the Immunology Center. Seventy-six HIV-infected women became pregnant, with a total of 95 pregnancies. Seventeen women had more than one pregnancy, and two women had three pregnancies. Fifty-five percent of these women were foreign-born. Sixteen of the women (21%) were diagnosed with HIV during their pregnancy while 79% knew their HIV status prior to becoming pregnant. Sixteen of the women chose to terminate their pregnancies (17% of total pregnancies in this cohort); two of these women were diagnosed during this pregnancy and both were US-born. Seven women suffered miscarriages. The trends by year and breakdown of specifics between foreign-born and US-born women are presented in Tables 1 and 2. The breakdown by continent/region of origin of the women is shown in Figure 1. Among the thirty women from Africa, sixteen were from Liberia, three from Burundi, two from Guinea, Kenya, and Senegal and one each from Angola, Ghana, Ivory Coast, Mali, and Sierra Leone. Among the seven women from Latin America, there were three women from the Dominican Republic, two from Guatemala, and one each from Venezuela and Argentina.

While the number of HIV-infected women becoming pregnant increased only slightly over the years of the study, the proportion of women that were foreign-born rose from 41% between 2004 and 2005 to 57.5% between 2006 and 2009. There was no significant difference between US-born and foreign-born women in terms of their likelihood of being diagnosed with HIV during pregnancy, choosing termination or choosing to have a second or third pregnancy. US-born women were more likely to have fewer than two visits during the pregnancy or Department of Children, Youth & Families (DCYF) involvement with their children.

Of the 72 women who had pregnancies that did not end in miscarriage or termination, mode of delivery was known for 49. Seventeen (35%) delivered vaginally, twenty-five (51%) underwent elective caesarian section, and seven (14%) required emergency caesarian sections. Sixty-three women had CD4 counts and plasma viral loads (PVL) measured during pregnancy. Fifteen (24%) women had detectable plasma viral loads on their last test prior to delivery, and all but one of them underwent caesarian section (information on the mode of delivery for one woman is missing). Thirty women had both information on viral load prior to delivery and mode of delivery available. Of these, sixteen (53%) had undetectable viral loads and six (20%) had viral loads less than 1000. Only eight of the women who underwent caesarian section had viral loads above 1000, and five of these women had either repeat caesarian section or underwent the procedure due to emergency indications unrelated to viral load. Nine women were considered to have AIDS at the time of delivery, based on a last CD4 count prior to delivery less than 200 cells/μL. Seven of these women were foreign-born. The mean CD4 count prior to delivery was 480 cells/μL.

Three children in this cohort were confirmed to be perinatally-infected. All of them were born to mothers with psychological and/or social issues that had a significant impact on their ability to adhere to appropriate followup and preventive measures. One mother was a young perinatally-infected teenager at the time of her first pregnancy. She received care in both Rhode Island and Massachusetts, but was unable to adhere adequately to care and treatment at either site. The second child was born to a woman from West Africa who had been diagnosed with HIV three years before the pregnancy upon immigration to the USA. She did not adhere to her medication regimen during pregnancy and DCYF was involved soon after the child was born. The third child was born to a US-born woman who had been diagnosed with HIV during a prior pregnancy. She had delivered an HIV-negative child at that time, who was subsequently removed from her custody. She had been out of care and off HIV medications for many months when she presented to the emergency department with complaint of abdominal pain. She was quickly determined to be in active labor. She denied knowing that she had been pregnant and had received no prenatal care.

4. Discussion

As has been seen around the world, our data suggest that HIV-infected women are increasingly choosing to become pregnant and to keep pregnancies that may have been unplanned. The number of terminations has remained low. This is consistent with other studies that have shown that fewer HIV-infected women are choosing termination now that the efficacy of methods for prevention of mother-to-child transmission (PTMCT) are well-known and well-validated [2, 4–6]. Additionally, a growing number of women are having second and even third pregnancies after their HIV diagnosis. This trend likely reflects both the strength of the desire to have children and the perception of HIV as a controllable illness that does not preclude the creation of a family.

Our data indicate that Rhode Island's relatively new opt-out law for HIV testing among pregnant women, and the resultant increased rate of testing, has not resulted in a higher number of HIV diagnoses; however, its effects may not yet be reflected in our data as this law was only passed in July 2007. In addition, Rhode Island is known to have a low prevalence of HIV, and the increased testing may

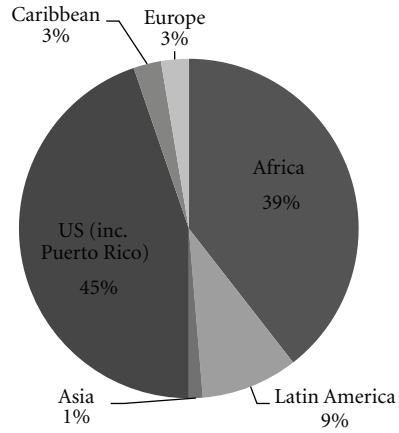

Figure 1: Continent/region of origin among HIV-infected pregnant women in RI.

Table 1: Trends in pregnancies among HIV-infected women followed by the Immunology Center.

Year	Number of pregnant HIV+ women	Women in 2nd/3rd pregnancy	Percent foreign-born women	Number of terminations	Number of miscarriages	Number diagnosed HIV+ in pregnancy
2004	10	0	40%	1	0	4
2005	12	0	42%	4	2	0
2006	21	2	62%	4	2	3
2007	21	10	52%	5	2	3
2008	15	5	60%	2	0	1
2009	16	4	56%	0	1	5
Total	95	21	54%	16	7	16

not result in a significantly higher number of diagnoses. Furthermore, laws to encourage testing during physician encounters outside of pregnancy may negate any potential increase in diagnoses during pregnancy.

While the number of HIV-infected women becoming pregnant in our clinic has increased only slightly, the proportion that are foreign-born has been steadily rising, from an average of 41% between 2004 and 2005 to 57.5% between 2006 and 2009. Now that the Obama administration has lifted the travel ban on HIV-infected persons entering the USA (as of January 2010), this trend may increase as the number of foreign-born HIV-infected women entering the USA continues to grow. However, the numbers seen in Rhode Island may also decline, as the freedom to enter any state may lead to some choosing to settle elsewhere. Previously, Rhode Island was one of the few states that was allowed to accept HIV-infected individuals emigrating to the USA under the travel ban.

Available virologic control data for our clinic indicate that most women have favorable CD4 counts and undetectable viral loads prior to delivery. All the women who had detectable viral loads underwent caesarian section, which is associated with a lower risk of viral transmission for women with HIV plasma viral loads >1000 copies/mL near the time of delivery. The three cases of perinatal transmission are not necessarily representative of the overall outcomes of pregnancy among HIV-infected women. However, they are indicative of the fact that while PMTCT protocols are now able to reduce the risk of HIV transmission to less than 2%, they cannot do so if patients are unable to adhere to them. In our small state, during the time period of this study, there was essentially one clinic and one HIV-trained obstetrician/gynecologist who saw the women during pregnancy, one hospital where they delivered, and one pediatric infectious disease clinic where the children were followed. Each of these settings has robust medical, social work and support staff that fully supported each HIV-infected pregnant woman in order to optimize her care and adherence to therapy. These data highlight the fact that despite this level of coordination and support, nonadherence does occur and perinatal HIV transmission may ensue. Further study to identify "at-risk" women may be warranted, in order to target further medical and psychosocial interventions in order to improve outcomes and decrease maternal-to-child transmission.

These study results support prior trends noted from US and international studies that HIV-infected women are increasingly choosing to become pregnant or to continue a pregnancy. Studies are needed to determine the knowledge and attitudes of foreign-born and US-born HIV-infected women regarding childbearing and prevention of maternal-to-child transmission. Additionally, comparative studies among women in high HIV-prevalence regions and women who have moved from those regions to resource-rich settings would help healthcare providers and systems to anticipate and meet the needs of a growing population of HIV-infected

Table 2: Pregnancy outcomes among foreign-born versus US-born women.

	Foreign-born HIV-infected women $n = 150$	US-born HIV-infected women $n = 149$	Total $n = 321$	P value
Number of pregnancies	51	44	95	0.41
Number diagnosed during pregnancy ($n = 76$ women)	8	8	16 (21%)	0.75
Number of terminations	6	10	16 (17%)	0.154
Number of miscarriages	3	4	7 (7%)	0.55
Number of C-sections (of those with known mode of delivery)	20/29	12/20	32/49 (65%)	0.51
Number of 2nd and 3rd pregnancies	10	11	21 (22%)	0.53
Number with undetectable viral load prior to delivery (of those with test data available)	32/38	16/25	48/63 (76%)	0.065
2 or more clinic visits during pregnancy	36	22	58 (61%)	0.04
DCYF involvement	4	12	16 (17%)	0.012

*Of the 321 women between 18–45 years seen from 1/04 to 12/09, place of birth is unknown for 22.
DCYF = Department of Children, Youth & Families.

women who may have different understandings of, and barriers to, exercising options for safe pregnancy.

5. Conclusion

The face of HIV in pregnancy is changing. HIV-infected women in Rhode Island are more likely to be foreign-born, to know their HIV status prior to pregnancy, and to actively choose to become pregnant or to continue pregnancies, whether planned or unplanned. Despite increasing rates of HIV testing in pregnancy, an increased number of HIV diagnoses has not been seen. When HIV-infected pregnant women engage with appropriate prenatal care, virologic control is generally excellent and outcomes are good for mother and child. However, risks for HIV transmission beyond lack of awareness of HIV status are emerging, especially among women with psychological or social issues, which may preclude adherence to PMTCT protocols and lead to unnecessary infection of infants. Foreign-born women are a growing percentage of the population of HIV-infected women becoming pregnant in the USA and may benefit from further study and targeted interventions. Identifying "at-risk" women during their pregnancy and providing extra social, psychological, and other support to them may be an important additional focus for PMTCT programs in order to continue to prevent perinatal HIV transmission.

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References

[1] B. Nattabi, J. Li, S. C. Thompson, C. G. Orach, and J. Earnest, "A systematic review of factors influencing fertility desires and intentions among people living with HIV/AIDS: implications for policy and service delivery," *AIDS and Behavior*, vol. 13, no. 5, pp. 949–968, 2009.

[2] S. B. Kirshenbaum, A. E. Hirky, J. Correale et al., ""Throwing the dice": pregnancy decision-making among HIV-positive women in four U.S. cities," *Perspectives on Sexual and Reproductive Health*, vol. 36, no. 3, pp. 106–113, 2004.

[3] B. H. B. Van Benthem, I. De Vincenzi, M. C. Delmas, C. Larsen, A. Van Den Hoek, and M. Prins, "Pregnancies before and after HIV diagnosis in a European cohort of HIV-infected women," *AIDS*, vol. 14, no. 14, pp. 2171–2178, 2000.

[4] S. K. Whitmore, X. Zhang, A. W. Taylor, and J. M. Blair, "Estimated number of infants born to HIV-infected women in the United States and five dependent areas, 2006," *Journal of Acquired Immune Deficiency Syndromes*, vol. 57, no. 3, pp. 218–222, 2011.

[5] A. S. Bryant, R. M. Leighty, X. Shen et al., "Predictors of repeat pregnancy among HIV-1-infected women," *Journal of Acquired Immune Deficiency Syndromes*, vol. 44, no. 1, pp. 87–92, 2007.

[6] A. Sharma, J. G. Feldman, E. T. Golub et al., "Live birth patterns among human immunodeficiency virus-infected women before and after the availability of highly active antiretroviral therapy," *American Journal of Obstetrics and Gynecology*, vol. 196, no. 6, pp. 541.e1–541.e6, 2007.

[7] L. Bujan, L. Hollander, M. Coudert et al., "Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREAThE network," *AIDS*, vol. 21, no. 14, pp. 1909–1914, 2007.

[8] T. Newmeyer, S. N. Tecimer, D. Jaworsky et al., "Case series of fertility treatment in HIV-discordant couples (male positive, female negative): the Ontario experience," *PLoS One*, vol. 6, no. 9, Article ID e24853, 2011.

[9] M. R. Loutfy, J. M. Raboud, J. Wong et al., "High prevalence of unintended pregnancies in HIV-positive women of reproductive age in Ontario, Canada: a retrospective study," *HIV Medicine*, vol. 13, no. 2, pp. 107–117, 2012.

[10] P. J. Orner, M. De Bruyn, R. M. Barbosa, H. Boonstra, J. Gatsi-Mallet, and D. D. Cooper, "Access to safe abortion: building choices for women living with HIV and AIDS," *Journal of the International AIDS Society*, vol. 14, no. 1, Article ID 54, 2011.

[11] D. Cooper, J. Moodley, V. Zweigenthal, L. G. Bekker, I. Shah, and L. Myer, "Fertility intentions and reproductive health care needs of people living with HIV in Cape Town, South Africa: implications for integrating reproductive health and HIV Care services," *AIDS and Behavior*, vol. 13, no. 1, pp. S38–S46, 2009.

[12] Central Intelligence Agency, US Government, "Country comparison: total fertility rate," https://www.cia.gov/library/publications/the-world-factbook/rankorder/2127rank.html.

[13] N. Suryavanshi, A. Erande, H. Pisal et al., "Repeated pregnancy among women with known HIV status in Pune, India," *AIDS Care*, vol. 20, no. 9, pp. 1111–1118, 2008.

[14] B. K. Chi, V. Rasch, N. Thi Thúy Hanh, and T. Gammeltoft, "Pregnancy decision-making among HIV positive women in Northern Vietnam: reconsidering reproductive choice," *Anthropology & Medicine*, vol. 18, no. 3, pp. 315–326, 2011.

[15] M. R. Loutfy, T. A. Hart, S. S. Mohammed et al., "Fertility desires and intentions of HIV-positive women of reproductive age in Ontario, Canada: a cross-sectional study," *PloS one*, vol. 4, no. 12, p. e7925, 2009.

[16] J. R. Castillo-Mancilla and M. Carten, "The need for a US registry of HIV in foreign-born people," *The Lancet Infectious Diseases*, vol. 10, no. 6, pp. 370–371, 2010.

[17] Centers for Disease Control and Prevention (CDC), "Racial/ethnic disparities in diagnoses of HIV/AIDS—33 states, 2001–2004," *Morbidity and Mortality Weekly Report*, vol. 55, no. 5, pp. 121–125, 2006.

[18] Centers for Disease Control and Prevention (CDC), "Racial/ethnic disparities among children with diagnoses of perinatal HIV infection—34 states, 2004–2007," *Morbidity and Mortality Weekly Report*, vol. 59, no. 4, pp. 97–101, 2010.

[19] R. P. Kerani, J. B. Kent, T. Sides et al., "HIV among African-born persons in the United States: a hidden epidemic?" *Journal of Acquired Immune Deficiency Syndromes*, vol. 49, no. 1, pp. 102–106, 2008.

[20] E. E. Foley, "HIV/AIDS and African immigrant women in Philadelphia: structural and cultural barriers to care," *AIDS Care*, vol. 17, no. 8, pp. 1030–1043, 2005.

[21] J. B. Kent, "Impact of foreign-born persons on HIV diagnosis rates among Blacks in King County, Washington," *AIDS Education and Prevention*, vol. 17, pp. 60–67, 2005.

[22] N. T. Harawa, T. A. Bingham, S. D. Cochran, S. Greenland, and W. E. Cunningham, "HIV prevalence among foreign- and US-born clients of public STD clinics," *American Journal of Public Health*, vol. 92, no. 12, pp. 1958–1963, 2002.

[23] V. B. Peters, K. L. Liu, L. G. Robinson et al., "Trends in perinatal HIV prevention in New York City, 1994–2003," *American Journal of Public Health*, vol. 98, no. 10, pp. 1857–1864, 2008.

[24] Centers for Disease Control and Prevention (CDC), "Rates of adults and adolescents living with a diagnosis of HIV infection, year-end 2009—46 states and 5 U.S. Dependent Areas," http://www.thebody.com/content/art59071.html.

[25] Rhode Island Department of Health Division of Community Family Health and Equity, Office of HIV/AIDS & Viral Hepatitis, "2010 Rhode Island HIV/AIDS Epidemiologic Profile with Surrogate Data," September 2011, http://www.health.ri.gov/publications/epidemiologicalprofiles/2010HIVAIDSWithSurrogateData.pdf.

[26] Rhode Island Department of Health, "HIV testing in pregnancy," http://www.health.ri.gov/publications/factsheets/HIVTestingInPreganancy.pdf.

[27] N. E. Alexander, B. Alverson, R. Neale, and C. G. Beckwith, "The implementation of the CDC's revised recommendations for HIV testing in medical settings: a Rhode Island update and call for action," *Medicine and Health, Rhode Island*, vol. 92, no. 7, pp. 247–248, 2009.

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Research Article

Efavirenz Conceptions and Regimen Management in a Prospective Cohort of Women on Antiretroviral Therapy

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Use of the antiretroviral drug efavirenz (EFV) is not recommended by the WHO or South African HIV treatment guidelines during the first trimester of pregnancy due to potential fetal teratogenicity; there is little evidence of how clinicians manage EFV-related fertility concerns. Women on antiretroviral therapy (ART) were enrolled into a prospective cohort in four public clinics in Johannesburg, South Africa. Fertility intentions, ART regimens, and pregnancy testing were routinely assessed during visits. Women reporting that they were trying to conceive while on EFV were referred for regimen changes. Kaplan-Meier estimators were used to assess incidence across ART regimens. From the 822 women with followup visits between August 2009–March 2011, 170 pregnancies were detected during study followup, including 56 EFV conceptions. Pregnancy incidence rates were comparable across EFV, nevirapine, and lopinavir/ritonavir person-years (95% 100/users ($P = 0.25$)); incidence rates on EFV were 18.6 Confidence Interval: 14.2–24.2). Treatment substitution from EFV was made for 57 women, due to pregnancy intentions or actual pregnancy; however, regimen changes were not systematically applied across women. High rates of pregnancy on EFV and inconsistencies in treatment management suggest that clearer guidelines are needed regarding how to manage fertility-related issues in. women on EFV-based regimens.

1. Introduction

Although HIV reduces fertility, an increase in pregnancy incidence has been documented in HIV-infected women using antiretroviral therapy (ART) [1–3]. Combination first-line regimens in Sub-Saharan Africa typically are comprised of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and one nonnucleoside reverse transcriptase inhibitor (NNRTI). The NNRTI drugs commonly used in the region are nevirapine (NVP) and efavirenz (EFV); the drugs have comparable clinical performance, but different toxicity profiles [4]. Due to concerns over possible EFV teratogenicity, treatment management for women must account for reproductive potential in addition to drug interactions and toxicities.

Efavirenz-related pregnancy concerns are largely based on a study in cynomolgus monkeys in which anencephaly, a neural tube defect (NTD), was linked to EFV exposure during pregnancy; a case of microphthalmia and one case of cleft palate were also observed in the monkeys exposed to EFV [5]. Six retrospective cases and one prospective NTD have been reported in human infants exposed to EFV during pregnancy [6]. Based on this evidence, EFV is considered potentially teratogenic and is contra-indicated for the first trimester of pregnancy when NTDs occur. Systematic reviews, however, have found no association between EFV exposure and birth defects [7–9]; recent reports from West Africa and South Africa similarly found no evidence of EFV-related teratogenicity [10, 11]. Despite these assurances, concerns remain and the most recent adult HIV treatment guidelines from the World Health Organization (WHO) and the South African Department of Health, which has the largest ART treatment program in the world, counsel against first trimester EFV exposure [12, 13].

The frequency of EFV conceptions is largely unknown. Most pregnancy-related data on EFV conceptions is reported from pregnancy registries and retrospective file review, from which incidence estimates are typically underestimated as pregnancies not carried to term due to spontaneous abortion or elective termination are frequently not captured through registry and file review. Information on how providers manage fertility-related issues in women on EFV is also limited. WHO guidelines recommend substituting EFV with either NVP or a protease inhibitor (PI) if the pregnancy is ≤28 days gestation [12]. South African National Treatment Guidelines recommend substituting EFV for NVP in the first 12 weeks of pregnancy; the guidelines do not refer to CD4 cell count in relation to drug choice for regimen substitution. How closely these guidelines are followed is unknown. Neither WHO nor South African guidelines provide direction for regimen changes amongst women trying to conceive who are already using EFV.

The objectives of this study are to prospectively compare pregnancy rates by ART regimens in an operational setting and to assess HIV treatment management of fertility-related issues amongst women on EFV-based regimens.

2. Methods

2.1. Cohort Description. Women on ART or being initiated onto ART were enrolled for prospective followup in four public-run HIV clinics in Johannesburg, South Africa, from August 2009 to January 2010. A t the time of study enrollment, lifelong ART was freely available for adults in South Africa with CD4 counts <200 cells/μL (this was universally increased to 350 cells/μL in August 2011, well after study enrollment was complete). First-line regimens include EFV or NVP and 2 NRTIs; second-line therapy is typically comprised of 2 NRTIs and a PI (lopinavir/ritonavir). The study examined fertility-related outcomes in women on ART and has been previously described [14]. Briefly, 850 women were enrolled and followed for incident pregnancy for one year; women who conceived during study followup were followed throughout the duration of their pregnancies in order to obtain pregnancy outcomes. Followup for the primary pregnancy incidence endpoint was completed in March 2011; followup of pregnancy outcomes was completed in December 2011. Women were eligible for enrollment if they were aged 18–35 years, on ART, not pregnant, not breastfeeding, sexually active in the past year, and had not been previously sterilized. Pregnancy testing was conducted at enrollment to exclude prevalent pregnancies.

2.2. Assessment of Exposure and Outcome Variables. Structured interviews covering an array of questions on demographics, health, and reproductive histories were conducted at study enrollment. Fertility intentions, contraceptive use, and urine-based pregnancy testing were prospectively measured by study staff during participants' routine clinic visits. As this was a clinical cohort established within an operational care setting, visit schedules were determined by providers; on average, participants were seen every two months.

At baseline, women were asked about their current and future fertility plans. During followup, fertility intentions were assessed at each visit by asking participants if they were currently trying to get pregnant. Pregnancy was assessed at each visit through urine-based testing for human chorionic gonadotropin (hCG); repeat urine testing was immediately performed for all positive pregnancy tests. Pregnancy was defined as having two same-day positive pregnancy tests. Conception dates were assigned to two weeks following the last menstrual period or if unknown, to 266 days before the due date determined by ultrasound and recorded in antenatal records. Ultrasound was done free of charge at the discretion of participants' health providers. Pregnancies occurring during the study were followed through pregnancy duration.

ART treatment and clinical data were confirmed through pharmacy records, medical chart review, and laboratory records. Due to EFV-related teratogenicity concerns, all women conceiving or trying to conceive on EFV during the study were referred for a regimen change. Women conceiving on EFV were counseled about potential risks, reassured that termination was not required because of the EFV conception, and referred for free fetal abnormality scans at a tertiary clinic.

The study was approved by the University of the Witwatersrand Human Research Ethics Committee, Johannesburg, South Africa; all participants provided written informed consent.

2.3. Statistical Analysis. Survival analysis was used to assess time-to-pregnancy by ART regimen. The origin for the survival analyses was study enrollment, and the outcome of interest was incident pregnancy. Women were censored when they experienced the outcome, died, were lost-to-followup or completed the study. For women with multiple pregnancies during study followup, only the first pregnancy was included in the survival analyses. Kaplan-Meier estimators were used to assess one-year cumulative incidence for pregnancy. Equality of failure functions was assessed through log-rank analysis. Both a "*per-protocol*" and a "*per routine care*" analyses were conducted to assess the impact of the study on EFV-related conceptions. In the *per-protocol* analysis, ART regimens were treated as time-varying; ART treatment was lagged one visit to ensure that treatment exposure reflected participants' regimens at time of conception. Per study protocol, women trying to conceive on EFV were referred for regimen changes due to safety concerns. In the absence of this study intervention (patient referrals), regimen changes would have been unlikely, as fertility intentions are not routinely assessed by providers after ART initiation and no consistent policies are in place to change women stable on EFV to other regimens if they are trying to conceive. The *per routine care* analysis assessed one-year pregnancy incidence according to participant regimens at time of study enrollment; this likely would have been the counterfactual regimen at time-of-conception had the research study not intervened.

Pregnancy incidence by ART regimen according to time on ART was also assessed using Kaplan-Meier estimators.

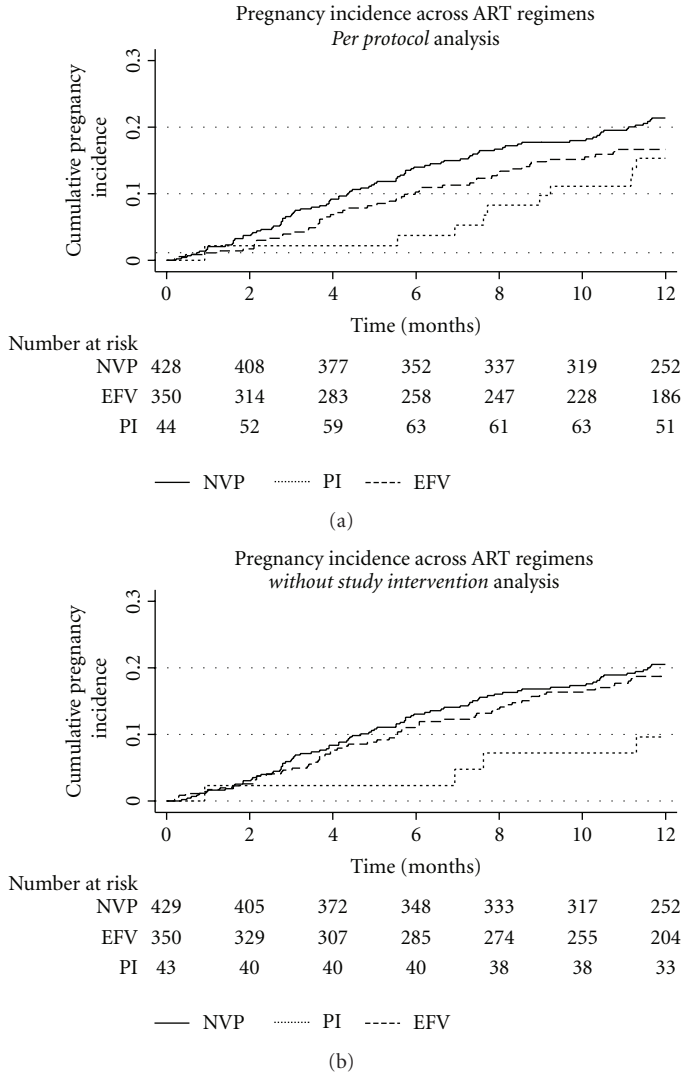

Figure 1: Pregnancy incidence across antiretroviral therapy (ART) regimens according to (a) treatment at time of conception and (b) treatment had the study not intervened to refer participants for regimen change. *NVP: Nevirapine; EFV: Efavirenz; PI: Protease Inhibitor (lopinavir/ritonavir).*

The outcome of interest for this analysis was incident pregnancy, and the key exposure was time-varying ART. The time origin for this analysis was ART initiation; the analysis thus allowed for individuals in the study to have late entries and early exits from the analysis according to their time on ART. Censoring, multiple pregnancies, and comparisons were handled as described above. Comparisons of medians and proportions between groups were assessed using Wilcoxon rank-sum tests and chi-square statistics.

3. Results

Of the 850 women enrolled into the study, 822 (97%) had at least one followup visit between August 2009 and March 2011 and 734 (86%) completed study followup. Participants contributing to followup had a median of 6 visits over 12 months. The median time-on-ART at enrollment into the study was 13 months (interquartile range [IQR]: 5–24), and the median CD4 count was 320 cells/μL (IQR: 178–473). At enrollment, 429 women were on NVP, 350 on EFV and 43 on LPV/r-based regimens.

Overall 170 incident pregnancies were detected in 161 women (8 women were pregnant >1 time). Women contributed a total of 745 person-years (PY) at-risk for pregnancy; only time-at-risk for first pregnancy during study followup was included in the incidence analysis. Pregnancy incidence rates by regimen were 24.3/100 PY (95% Confidence Interval [CI]: 19.9–29.7) on NVP, 18.6/100 PY (95% CI: 14.2–24.2) on EFV and 18.8/100 PY (95% CI: 10.7–33.1) on LPV/r. Kaplan-Meier curves (Figure 1) demonstrate the one-year cumulative incidence of pregnancy across treatment arms. Incidence rates in the per-protocol analysis were slightly higher in women on NVP as compared to EFV throughout study followup (Figure 1(a)), although rates

were not statistically significantly different between the two groups (log-rank NVP versus EFV: $P = 0.11$). Because the research study intervened with patient care to refer women trying to conceive on EFV for regimen changes, the per-routine care analysis (Figure 1(b)) illustrates pregnancy rates by regimen at study enrollment. In this analysis, differences in pregnancy incidence between the NVP and EFV arms were minimal (log-rank NVP versus EFV: $P = 0.48$).

Kaplan-Meier curves in Figure 2 assess the cumulative incidence of pregnancy on ART regimens during the 12 months of study followup, according to time on ART. Incidence across ART regimens was not statistically significantly different between EFV and NVP users (log-rank $P = 0.09$) and illustrates similar inferences to the previous analyses. Figure 2 also demonstrates, however, that the cumulative burden of pregnancy on EFV will be high over time, as women of reproductive age continue treatment on this regimen. In this analysis, 40% of women on EFV who had already been on ART for 3 years upon study entry, conceived on EFV during followup.

Details of fetal exposure to EFV and fertility-related ART regimen substitutions are presented in Table 1. In total, 56 EFV conceptions were detected in 54 women. Twenty-five women with EFV conceptions received regimen changes during pregnancy; average time to regimen change amongst those actually changed was 6 weeks after conception [IQR: 4–8]. Nine pregnant women continued on EFV due to late detection ($n = 4$), clinic delays ($n = 1$), and indecision over pregnancy termination ($n = 4$). Thirty-four percent of EFV conceptions were terminated prior to regimen changes.

Amongst sexually active women not trying to conceive, hormonal contraceptive use over followup was 32.9% in women on NVP, 25.7% on EFV, and 37.5% on LPV/r ($P < 0.01$). Hormonal contraceptive use amongst women not trying to conceive was also lower in EFV versus non-EFV users at enrollment (EFV 28% versus non-EFV 35%, $P = 0.06$). One EFV conception was attributed to an injectable contraceptive failure. Pregnancy incidence rates amongst hormonal contraception users on EFV versus NVP were 1.5/100 PY [95% CI: 0.2–10.9] and 7.1/100 PY [95% CI: 3.4–14.9], respectively; contraceptive failures were too infrequent and confidence intervals too wide for meaningful comparisons across hormonal contraceptive methods.

During followup, 96/350 (27%) women on EFV at enrollment had at least one visit in which they were trying to conceive on EFV, including fifteen women with planned pregnancies while on EFV-based regimens. All women trying to conceive on EFV were referred for regimen changes; however, records and patient reports suggested many providers would only substitute regimens after an established pregnancy to avoid unnecessary treatment changes. Thirty-two women received preventive regimen changes from EFV due to their fertility intentions; of these, 6 (19%) became pregnant during followup.

A total of 57 fertility-related regimen changes were made during the study due to either EFV conceptions or intention to conceive while on EFV. NVP was substituted for EFV 67% of the time and LPV/r 33% of the time. Women switched to LPV/r versus NVP had higher median CD4 counts (573 versus 257 cells/μL, $P < 0.01$). Median viral load and acute liver damage (measured through alanine aminotransferase) were equivalent across groups ($P = 0.76$ and $P = 0.80$).

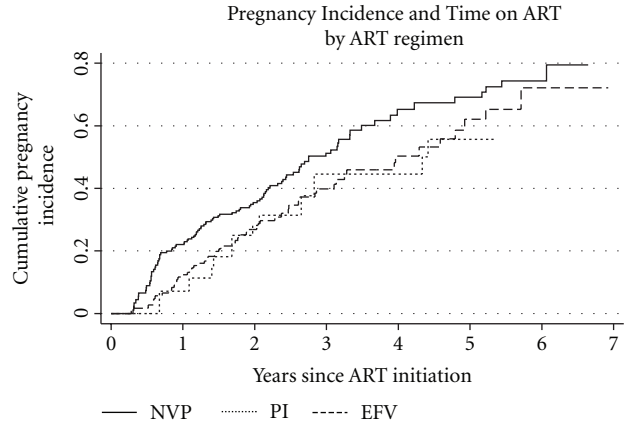

Figure 2: Cumulative incidence of pregnancy during study followup by years on antiretroviral therapy (ART); regimen arms represent time-varying treatment exposure during study followup. *NVP: nevirapine-based regimen*; *EFV: efavirenz-based regimen*; *PI: boosted-protease inhibitor-(lopinavir/ritonavir) based regimen*.

Pregnancy outcomes for the 56 EFV conceptions were: live birth ($n = 26$), termination of pregnancy ($n = 19$), miscarriage ($n = 9$), and loss to followup ($n = 2$); no birth defects were detected in infants. Rates of pregnancy termination in EFV versus NVP users were 34% versus 23% ($P = 0.15$); rates of miscarriage between the two groups were 18% versus 16% ($P = 0.71$), respectively.

4. Discussion

This is one of the first prospective studies of which we are aware to report pregnancy incidence rates on EFV-based regimens in a clinic setting. Although EFV remains contraindicated during the first trimester of pregnancy in South African guidelines, the pregnancy incidence rate on EFV was very high, 18.6/100 PY. This was observed despite counseling and systematic referrals for regimen changes. Overall, 54 of the 350 women on EFV at enrollment conceived at least once on EFV during study followup. As illustrated in Figure 1, the rate of conceptions on EFV may have been higher in the absence of the study as we routinely screened for fertility intentions and systematically referred women trying to conceive for same day regimen reassessment and change according to the discretion of the facility providers. In the absence of this intervention, the rate of EFV conceptions observed in Figure 1(a) would likely have been even higher and more closely matched incidence rates by participant regimen at the time of study enrollment (Figure 1(b)).

Pregnancy on both EFV and NVP was common in this study, with 170 pregnancies detected amongst 850 women over 12 months of followup. The high rate of pregnancies on EFV resulted from a combination of unplanned pregnancies and planned pregnancies. Fertility intentions and contraceptive use are screened by providers at ART initiation

Table 1: EFV conceptions and regimen substitutions.

EFV conceptions ($n = 56$)	n (%)
Pregnancies carried forward on EFV	9 (16%)
Women receiving regimen substitutions	25 (45%)
Pregnancies miscarried prior to regimen substitution	3 (5%)
Pregnancies terminated	19 (34%)
Extent of EFV exposure during pregnancy	Median (IQR)
Time from EFV conception to detection ($n = 56$), weeks	4 [1–6]
Time from pregnancy detection to regimen change ($n = 25$), days	1 [1–28]
Total time of first trimester EFV exposure in pregnancies carried to term ($n = 34$), weeks	8 [5–13]
Fertility-related regimen substitutions to NVP or LPV/r[†]	
Clinical characteristics of women changed from EFV to NVP, n = 38 (67%)	Median (IQR)
CD4 count, cells/μL	257 (185–412)
Log_{10} Viral load, copies/mL	1.7 (1.7–2.1)
Alanine aminotransferase (ALT) levels, U/L	26 (21–39)
Clinical characteristics of women changed from EFV to Lopinavir/Ritonavir, $n = 19$ (33%)	Median (IQR)
CD4 count, cells/μL	573 (333–684)
Log_{10} Viral load, copies/mL	1.7 (1.7-1.7)
Alanine aminotransferase (ALT) levels, U/L	25 (19–44)

[†]Includes regimen changes for EFV conceptions and preventive changes for women trying to conceive.
EFV: Efavirenz; NVP: Nevirapine; LPV/r: Lopinavir/ritonavir.

but are not routinely reassessed over time and may change. This study cohort was a mix of women with ART experience and recently initiating treatment and demonstrates that pregnancy rates on EFV compared to NVP may be lower in the first year after ART initiation, but the overall burden will steadily climb over time (Figure 2). While the overall pregnancy rates reported are higher than those reported by Myer et al. in another South African study [3], pregnancy testing was routinely done at each clinic visit in this cohort and many pregnancies miscarried or terminated would likely have been missed had routine testing not taken place. Amongst women on EFV alone, 50% of pregnancies were not carried to term. Women on EFV had nonstatistically significantly higher rates of termination of pregnancy than women on NVP, however, the sample size for this analysis was limited. To what extent the terminations were due to concerns over fetal exposure to EFV is not known; however, counseling was provided to all women to ensure that messages about the low frequency of risk were stressed.

In contrast to guideline recommendations that women on EFV be using a reliable method of contraception, use of hormonal contraception was actually lower amongst women on EFV-based regimens than on NVP. This finding was not expected and further emphasizes the need to reevaluate both fertility intentions and contraceptive use, as method discontinuation amongst women in Sub-Saharan Africa is frequently high [15]. In our data, high rates of EFV conceptions did not appear to be related to reduced efficacy of hormonal contraception amongst EFV users.

The average EFV exposure from conception to regimen change was 6 weeks; this is within the 12-week timeframe recommended for regimen change in the South African treatment guidelines, but beyond what is recommended by the WHO (28 days). Nine women had pregnancies in which the regimen was not changed; the median duration of first trimester EFV exposure amongst all EFV conceptions carried to term was 8 weeks. Regimen substitution after conception is unlikely to happen as quickly in routine clinical practice, as our study tested regularly for pregnancy regardless of last menstrual period or pregnancy symptoms. A South African study of EFV conceptions using pregnancy registry data reported a median gestational age at presentation for regimen change of 19 weeks—well beyond the time of risk for NTD [11]. These results indicate that if regimen changes are delayed amongst women planning conception until pregnancy is detected, fetal exposure to EFV will often be extensive and any potential for harm will likely have already occurred.

We previously reported high rates of fertility intentions at baseline on EFV-based regimens [14]. In the followup data reported here, we also see that many women on EFV are trying to conceive. As noted above, in routine care settings, this will frequently occur as fertility intentions may change after ART initiation, but in the absence of systematic screening, providers may not be aware of these changes. However, our data suggest that routine screening for fertility intentions alone is not sufficient to prevent EFV conceptions, as no consistent approach is being employed to address regimen changes amongst women known to be trying to conceive on EFV. In our study, some women intentionally conceived on EFV despite referrals for regimen changes, as these changes were deferred by providers until pregnancy was established. South African guidelines are clear about what regimens to use at time of initiation if women want children and also specify when to switch regimens in the event of pregnancy. However, the guidelines do not mention how to manage EFV-related fertility concerns amongst stable women trying to conceive before she is pregnant. Clarity is needed

regarding whether a regimen change should be made for these women and if so, what drugs should be substituted. Inconsistencies in regimen changes may result from lack of specific guidance.

Amongst women receiving regimen changes, either due to EFV conceptions or to prevent EFV conceptions, CD4 count seemed to drive drug substitution choice. Current South African guidelines recommend changing women with EFV conceptions to NVP and do not mention CD4 cell count as a factor that should influence the regimen substitution. Our findings suggest that in practice the guidelines are often not followed, even in sites with relatively strong training programs, and many women appear to have been unnecessarily changed to second-line therapy. This is likely due to hepatotoxicity concerns despite evidence that NVP initiation at higher CD4 counts is safe in women stable on ART [16–18].

Given the weak body of evidence surrounding EFV teratogenicity, there is a need to balance a possible risk to the fetus associated with EFV, with the treatment gains that may be achieved amongst adult women. In a recent simulation analysis based on clinical data from Côte d'Ivoire, Ouattara et al. reported that EFV-based regimens would result in substantially fewer deaths at 10 years as compared with NVP use, with only a small increase in birth defects resulting from fetal EFV exposure [19]. The United Kingdom and Malawi have both recently amended ART treatment guidelines to allow for EFV use throughout pregnancy [20, 21]. While it is not the intention of this analysis to advocate for a shift in policy, our findings suggest that there is a need for clarity in the guidelines to foster consistent messages to patients and providers, which will either be intended to reduce rates of conceptions on EFV or to prevent unnecessary regimen changes amongst pregnant women or those trying to conceive while on EFV.

The strength of this study is that it was explicitly designed to compare pregnancy incidence across EFV and NVP users. Pregnancy was routinely and frequently assessed for during followup, and data on fertility intentions and contraceptive use were collected at each study visit. Reasons for changing regimens or continuing on EFV regimens were also collected. The study was not designed, however, to assess EFV teratogenicity; we provide limited data on this; however, the number of live births which were exposed to EFV was too small to provide meaningful information on teratogenicity. Our primary objective was to assess the frequency of pregnancy on EFV and to assess whether guidelines are being followed at the clinic level and whether or not they adequately specify how to address situations experienced in an implementation setting.

5. Conclusions

The implications from this study are that high rates of EFV conceptions will take place due to both unplanned pregnancies amongst women not using effective contraception, but also due to planned pregnancies. Delays in providing regimen changes for women trying to conceive on EFV in an environment in which extensive sensitization to possible EFV teratogenicity has previously taken place are notable. For women stable on EFV, clarity over when it is appropriate to substitute regimens and whether women can be changed to NVP at higher CD4 counts should be specified in national and international guidelines. The evidence around EFV teratogenicity is equivocal and many providers may believe that the potential for harm caused to women by changing ART regimens is greater than the risks associated with fetal EFV exposure. However, neither South African nor WHO guidelines reflect this sentiment and consistent guidance around this issue is necessary.

Earlier initiation of ART improves individual survival and has recently been shown to reduce HIV transmission [22, 23]. Given NVP-related hepatotoxicity concerns, EFV utilization may increase in Sub-Saharan Africa as women initiate ART earlier. Consensus over how to manage EFV use in women with reproductive potential is important in order to minimize either the fetal exposure to EFV or unnecessary regimen changes.

Conflict of Interests

The authors have no conflicts of interests to declare.

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References

[1] R. H. Gray, M. J. Wawer, D. Serwadda et al., "Population-based study of fertility in women with HIV-1 infection in Uganda," *Lancet*, vol. 351, no. 9096, pp. 98–103, 1998.

[2] J. Homsy, R. Bunnell, D. Moore et al., "Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study," *PLoS ONE*, vol. 4, no. 1, Article ID e4149, 2009.

[3] L. Myer, R. J. Carter, M. Katyal, P. Toro, W. M. El-Sadr, and E. J. Abrams, "Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan

Africa: a cohort study," *PLoS Medicine*, vol. 7, no. 2, Article ID e1000229, 2010.

[4] F. van Leth, P. Phanuphak, K. Ruxrungtham et al., "Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study," *Lancet*, vol. 363, no. 9417, pp. 1253–1263, 2004.

[5] SUSTIVA, *Important Change in SUSTIVA (efavirenz) Package Insert- Change from Pregnancy Category C to D*, SUSTIVA, Washington, DC, USA, 2005.

[6] SUSTIVA, *Updated Label Information for Sustiva (efavirenz)*, SUSTIVA, Washington, DC, USA, 2010.

[7] N. Ford, L. Mofenson, K. Kranzer et al., "Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts," *AIDS*, vol. 24, no. 10, pp. 1461–1470, 2010.

[8] World Health Organization, *A Systematic Review of the Teratogenicity of Efavirenz*, World Health Organization, Geneva, Switzerland, 2009.

[9] N. Ford, A. Calmy, and L. Mofenson, "Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis," *AIDS*, vol. 25, no. 18, pp. 2301–2304, 2011.

[10] D. K. Ekouevi, P. A. Coffie, E. Ouattara et al., "Pregnancy outcomes in women exposed to efavirenz and nevirapine: an appraisal of the IeDEA West Africa and ANRS databases, abidjan, Côte d'Ivoire," *Journal of Acquired Immune Deficiency Syndromes*, vol. 56, no. 2, pp. 183–187, 2011.

[11] E. Bera, K. McCausland, R. Nonkwelo, B. Mgudlwa, S. Chacko, and B. Majeke, "Birth defects following exposure to efavirenz-based antiretroviral therapy during pregnancy: a study at a regional south african hospital," *AIDS*, vol. 24, no. 2, pp. 283–289, 2010.

[12] World Health Organization, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach-2010 rev*, World Health Organization, Geneva, Switzerland, 2010.

[13] South African Department of Health, *Clinical Guidelines for the Management of HIV & AIDS in Adults and Adolescents*, South African Department of Health, Cape Town, South Africa, 2010.

[14] S. R. Schwartz, S. H. Mehta, T. E. Taha, H. V. Rees, F. Venter, and V. Black, "High Pregnancy Intentions and Missed Opportunities for Patient-Provider Communication About Fertility in a South African Cohort of HIV-Positive Women on Antiretroviral Therapy," *AIDS and Behavior*, pp. 1–10, 2011.

[15] K. Nanda, C. S. Morrison, C. Kwok et al., "Discontinuation of oral contraceptives and depot medroxyprogesterone acetate among women with and without HIV in Uganda, Zimbabwe and Thailand," *Contraception*, vol. 83, no. 6, pp. 542–548, 2011.

[16] F. van Leth, S. Andrews, B. Grinsztejn et al., "The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART," *AIDS*, vol. 19, no. 5, pp. 463–471, 2005.

[17] E. De Lazzari, A. León, J. A. Arnaiz et al., "Hepatotoxicity of nevirapine in virologically suppressed patients according to gender and CD4 cell counts," *HIV Medicine*, vol. 9, no. 4, pp. 221–226, 2008.

[18] A. Antela, A. Ocampo, R. Gómez et al., "Liver toxicity after switching or simplifying to nevirapine-based therapy is not related to cd4 cell counts: results of the TOSCANA study," *HIV Clinical Trials*, vol. 11, no. 1, pp. 11–17, 2010.

[19] E. N. Ouattara, X. Anglaret, A. Y. Wong et al., "Projecting the clinical benefits and risks of using efavirenz-containing antiretroviral therapy regimens in women of childbearing age," *AIDS*, vol. 26, no. 5, pp. 625–634, 2012.

[20] British HIV Association (BHIVA), *Guidelines for the Management of HIV Infection in Pregnant Women 2012. Working Draft*, British HIV Association, London, UK, 2012.

[21] E. J. Schouten, A. Jahn, D. Midiani et al., "Prevention of mother-to-child transmission of HIV and the health-related millennium development goals: time for a public health approach," *The Lancet*, vol. 378, no. 9787, pp. 282–284, 2011.

[22] M. M. Kitahata, S. J. Gange, A. G. Abraham et al., "Effect of early versus deferred antiretroviral therapy for HIV on survival," *New England Journal of Medicine*, vol. 360, no. 18, pp. 1815–1826, 2009.

[23] M. S. Cohen, Y. Q. Chen, M. McCauley et al., "Prevention of HIV-1 infection with early antiretroviral therapy," *New England Journal of Medicine*, vol. 365, no. 6, pp. 493–505, 2011.

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Research Article

Reproductive Healthcare Needs and Desires in a Cohort of HIV-Positive Women

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Background. The aim of this study was to determine current contraceptive use, contraceptive desires and knowledge, future fertility desires, and sterilization regret in a cohort of HIV-positive women. *Study Design.* 127 HIV-positive women receiving care at an urban infectious disease clinic completed a survey addressing their contraceptive and reproductive histories as well as their future contraceptive and fertility desires. *Results.* The most common forms of contraception used were sterilization (44.4%) and condoms (41.3%). Less than 1% used a long-term reversible method of contraception (LARC) despite these being the methods that best fit their desired attributes of a contraceptive method. Overall, 29.4% desired future fertility. Only 50.6% of those sexually active had spoken with a provider within the last year regarding their contraceptive plans. There was a high degree of sterilization regret (36.4%), and 18.2% of sterilized women desired future fertility. Multivariate analysis found women in a monogamous relationship had a statistically increased rate of regret compared to women who were not sexually active (OR 13.8, 95% CI 1.6–119, $P = 0.17$). *Conclusion.* Given the diversity in contraceptive and fertility desires, coupled with a higher rate of sterilization regret than is seen in the general population, integration of comprehensive family planning services into HIV care via increased contraceptive education and access is imperative.

1. Introduction

Since the mean desired fertility rate in the United States is 2 [1], American women spend most of their reproductive lives attempting to space or prevent pregnancies; however, nearly half of all pregnancies in the USA are unintended (unwanted or mistimed) [2]. Women at highest risk for unintended pregnancies are also at highest risk for HIV and sexually transmitted infection acquisition, including women of minority race, lower education level, and lower socioeconomic status [3]. Approximately 100,000 women of reproductive age in the USA are infected with HIV, and women of color disproportionately account for 80% of HIV-infected women [4].

The prognosis for people living with HIV has greatly improved and therefore the healthcare community is able to focus on quality-of-life issues rather than only length of life issues [5]. For example, the availability and use of highly active antiretroviral therapy (HAART) has dramatically reduced mother-to-child transmission and allowed HIV-positive women to live longer, healthier lives which in turn has affected their fertility desires [6, 7]. Cohort studies of HIV-positive women have noted a high use of sterilization and a low use of hormonal contraception, despite desire for future fertility [8, 9]. Reasons for low use of hormonal or other effective contraception were not explored.

Given their HIV status, often coupled with a lower socioeconomic status, these women represent a vulnerable cohort in need of objective support in regards to their reproductive choices. It remains unclear how advances in HIV therapy have influenced HIV-positive women's reproductive needs and choices. Our study was designed to assess the contraceptive needs and fertility desires of an HIV-positive population of women in order to help direct evidence-based, effective, integrated family planning services into the current HIV care setting.

2. Material and Methods

From December 2008 through January 2010, we recruited a convenience sample of HIV-positive women presenting to outpatient medical care at the Infectious Disease Clinic associated with the Grady Health System in Atlanta, GA, USA. This clinic provides care to a predominately urban and underinsured population of HIV-positive men and women. Inclusion criteria included females 18–50 years old, HIV-positive, nonpregnant, and able to speak, read, understand, and consent in English. Exclusion criteria included women with uncontrolled psychiatric illness, unknown HIV status, pregnancy, history of hysterectomy, or who were unable or unwilling to consent to the study. The Institutional Review Board at the Emory University and the Grady Research Committee approved this study protocol, and all subjects provided verbal informed consent.

Participants completed a self-administered, 35-question written survey. To assure confidentiality, surveys were completed in a private room beside the waiting area. The survey inquired about the subject's demographic characteristics, obstetrical history, HIV medical history, most recent contraception usage, desired contraceptive attributes, knowledge of safety and availability of various contraceptives to HIV-positive women, desire for future fertility, sterilization rates and regret, and whether they have discussed their reproductive choices/desires with their physician. Many of the survey questions had been previously validated in other reproductive healthcare surveys. Prior to study initiation, the survey was piloted with 30 participants in the clinic to assess the understandability and feasibility of administering the survey instrument in this population.

2.1. Statistical Analysis. All statistical analyses were completed using SPSS version 17.0. Tests with P values <0.05 were considered statistically significant. Outcomes of interest included contraceptive use, desired contraceptive attributes, contraceptive knowledge, future fertility desires, and sterilization regret. Descriptive statistics were generated. Continuous variables were compared using Student's t-test while categorical variables were compared using Chi-square test. Logistic regression was used to generate odds ratios and 95% confidence intervals for multivariate analyses to identify factors that were associated with sterilization regret and future fertility desire.

3. Results

A total of 127 women were surveyed. The subjects had a mean age of 37.8 years (standard deviation 8.4) with a range 18–50 years. The vast majority of subjects self-reported as black (95%). Subjects' educational background was diverse. The majority of subjects (67.7%) were unemployed. Most had been pregnant in the past (91.3%) and had borne children (81.6%), and 37.3% of subjects had 4 or more prior pregnancies. Nearly half (47.2%) were in a monogamous relationship, and 27.6% were not currently in a sexual relationship. The majority (60.6%) reported always using condoms when they had sex. Nearly half (49.6%) of the women surveyed had been diagnosed with HIV for greater than 10 years, and 28.8% reported being diagnosed less than 5 years. Overall, 40.9% had been diagnosed with AIDS and 75.6% were currently taking antiretroviral medications as prescribed (Table 1).

Table 1: Demographics.

	Number	Valid %
Age		
18–25	13	10.2%
26–35	32	25.2%
36–45	58	45.7%
46–50	24	18.9%
Ethnicity		
Black	120	94.5%
Hispanic	1	0.8%
White	4	3.1%
Other	1	3.1%
Missing	1	
Education		
Did not complete high school	48	37.8%
Completed high school/GED	39	30.7%
At least some college of technical school	32	25.2%
Completed college or above	8	6.3%
Missing	1	
Reproductive history		
Gravida 1 or more	115	91.3%
Para 1 or more	102	81.6%
Missing	2	
Sexual relationship		
Monogamous	60	47.2%
Non-monogamous	10	7.9%
Not currently sexually active	35	27.6%
Not sure	17	13.4%
Missing	5	
HIV history		
Diagnosed <5 years ago	34	28.8%
Diagnosed 5–10 years ago	27	21.3%
Diagnosed >10 years ago	63	49.6%
AIDS diagnosis	52	40.9%
Currently taking HAART	96	75.6%

3.1. Contraceptive Use and Desires. When asked to state the last contraceptive method used, most women reported using female sterilization (44.4%) or condoms (41.3%), with only 24.4% using any type of hormonal method, and less than 1% using long-term reversible contraception (LARC) defined as an IUD or implant (Table 2). While less than 60% of women knew about each of the LARC methods, the most common methods subjects stated they wished to learn more about were the LARC methods and the Nuvaring. Most (91.3%) thought condoms were safe for HIV-positive women; however, less than half of the participants thought

Table 2: Last contraceptive method used.

Method	Number*	Percentage
Sterilization	56	44.4%
Condoms	52	41.3%
Depo-Provera	20	15.9%
Abstinence	8	6.3%
None	8	6.3%
Pill	7	5.6%
Patch	3	2.4%
Withdrawal	2	1.6%

*$n = 126$, 1 missing.
Overall, 0.8% each used IUD, diaphragm, or cervical cap, NuvaRing, and natural family planning.

Table 3: Contraceptive methods HIV-positive subjects have heard of/think are safe to use.

Method	Have heard of number (%)	Think are safe number (%)
Condoms	115 (92.7%)	115 (91.3%)
Pill	114 (91.6%)	55 (43.7%)
Sterilization	112 (90.3%)	41 (32.5%)
Depo-Provera	112 (90.3%)	46 (36.5%)
Patch	93 (75.0%)	30 (23.8%)
Abstinence	77 (62.1%)	78 (61.9%)
Implant	72 (58.1%)	23 (18.3%)
IUD	68 (54.8%)	26 (20.6%)
Diaphragm	65 (52.4%)	28 (22.2%)
Withdrawal	61 (49.2%)	28 (22.2%)
Plan B	54 (43.5%)	22 (17.5%)
Nuvaring	51 (41.4%)	23 (18.3%)
Missing	3	1

the pill, Depo-Provera, the patch, the IUD, the Nuvaring, or implant were safe (Table 3).

Subjects were asked how satisfied they were with their current contraceptive method: 58.1% were very satisfied, 17.9% were somewhat satisfied, and 23.9% were somewhat or not at all satisfied. When asked to choose the three most important factors to them when choosing a birth control method, the most frequently cited attribute was ease of use, followed by efficacy at preventing pregnancy, and low risk of side effects (Table 4). Subgroup analyses of contraceptive use and desires in women ≤45 years of age were not significantly different with the exception that knowledge of sterilization was lower (76.0% versus 90.3%, $P = 0.005$).

3.2. Desire for Fertility and Discussion with Providers. Overall, 29.4% of those surveyed desired future fertility. Of these almost half (46.0%) were unsure of when they desired to become pregnant in the future, and only 8.1% desired to become pregnant within the next year. The factor most strongly correlated with future fertility desire was age. Univariate analysis found that women with greater than 4 prior live births were significantly less likely to desire future pregnancy; however, when controlling for age, this association was no longer significant. In a multivariate model looking at predictors of future fertility desire, age was found to be significantly associated (OR 1.17, 95% CI 1.08–1.26, $P < 0.001$) with younger age associated with increased fertility desire. In addition, women not currently in a relationship were significantly less likely to desire future fertility compared to women in a monogamous relationship (OR 0.26, 95% CI 0.09–0.77, $P = 0.015$). In multivariate analyses, education, reproductive history, HIV history, having a diagnosis of AIDS, or using HAART was not associated with future fertility desire. Only 50.6% of those sexually active had spoken with a provider in the past year regarding their contraceptive plans. Approximately one-third (32.1%) reported that they had either never spoken to a provider or it was greater than 5 years ago.

Table 4: Most important attributes of contraceptive method (women were asked to pick their top 3 attributes).

Attribute	Number*	Percentage
Easy to use	80	64.5%
Works well at preventing pregnancy	50	40.3%
Low in side effects	44	35.5%
Low in cost	41	33.1%
Decreases menstrual cycles	31	24.8%
Works on the long term	25	20.2%
Maintains regular menstrual cycles	24	19.4%
Decreases period symptoms	22	17.7%
Quickly reversible	10	8.1%
Hormone-free	8	6.5%
No action required during sex	4	3.2%

*$n = 124$, 3 missing.

3.3. Female Sterilization. The mean age of sterilization was 28 years of age with a range 21–39 years. More than half (56.4%) reported that HIV/AIDS was one of the reasons they chose to be sterilized. Sterilization regret was reported in 36.4%, and 18.2% of these women desired to become pregnant in the future. Multivariate analysis looking at age, education, reproductive history, sexual relationship, HIV history, AIDS diagnosis, and use of HAART medication found that women in a monogamous relationship had a statistically increased rate of regret compared to women who were not sexually active (OR 13.8, 95% CI 1.6–119, $P = 0.017$). Age at sterilization and reporting that HIV/AIDS was a factor in deciding to become sterilized were not significantly associated with regret.

4. Discussion

Our sample represented an older reproductive-aged, predominantly black and parous, urban, underinsured cohort, with a high percentage functioning with a long-term diagnosis of HIV. Female sterilization was the most commonly used form of contraception in our subjects (44.4%). Massad et al. reported 23% use of sterilization, 30% use of barrier

methods, and less than 10% use of hormonal methods among US HIV-positive women in a 2007 study [8]. The increased rate of sterilization we found may be related to the characteristics of our cohort as it is similar to the 46.4 rate reported in age-comparable samples of the general US population [10]. Although a substantial number of these HIV-positive women had undergone sterilization, their contraceptive and fertility desires suggest that effective, reversible contraceptive methods are more suitable.

Only 22.9% of subjects were using any type of hormonal method, and less than 1% used long-term reversible contraception (LARC). Again, this is similar to age-comparable rates of method use reported in the general population [10]. This may be in part due to the fact that less than half of the subjects thought the pill or Depo-Provera was safe for HIV-positive women to use and less than a quarter thought the LARC methods were safe. Concern in the literature exists regarding hormonal contraceptive use in women with HIV. Several studies of hormonal contraceptive use in HIV-positive women have indicated an association with increased shedding of HIV-1 DNA in the genital tract, HIV acquisition and transmission, or clinical disease progression [11–14]. However, multiple other studies have failed to demonstrate a link between contraceptive use and HIV-1 acquisition, transmission, and progression [15–18]. The World Health Organization (WHO) in February 2012 concluded, upon the strength of the epidemiological evidence and analysis of risks and benefits to country programmes, that no restrictions (MEC category 1) be placed on the use of any hormonal contraceptive method for women living with HIV [19]. In addition, based on systematic reviews of all available literature, the Centers for Disease Control USA Medical Eligibility Criteria (MEC) for Contraceptive Use classifies all hormonal and LARC methods as acceptable for use (category 1 or 2) in HIV-positive women. Information regarding medical eligibility for all contraceptive methods in women with HIV/AIDS is available at http://www.cdc.gov/reproductivehealth/usmec.

Although small studies have noted decreased hormonal levels in the plasma of women using certain classes of antiretrovirals, there is no evidence that this leads to an increase in contraceptive failure in this population. The USA Department of Health and Human Services recommends additional or alternative (nonoral hormonal) contraception for HIV-infected women taking most nonnucleoside reverse-transcriptase inhibitors or protease inhibitors and recommends avoiding coadministering combined OCs with fosamprenavir [20]. Alternatively, Depo-Provera was found to have no interactions with several antiretroviral agents [21, 22]. Consistent use of condoms in addition to hormonal contraceptives is strongly recommended to prevent HIV transmission and in addition may compensate for any potential reduction in efficacy or increased viral shedding with hormonal contraceptives. Our results suggest that additional patient counseling is required to educate HIV-infected women regarding their risks as they appeared to underestimate the safety profile of most effective, reversible contraceptive methods.

When asked which attributes the subjects most desired from their contraceptive method, they chose ease of use, effectiveness, and low risk of side effects. Given these factors, it is not surprising that so many subjects chose female sterilization; however, given the substantial rate of sterilization regret, the most suitable methods appeared to be LARC methods. Like sterilization, the LARC methods (progestin-only IUD, copper IUD, and the progestin-only implant) are all rated as having "top tier efficacy" per the World Health Organization because they have a typical-use failure rate of less than 1% [23]. Also like sterilization, typical-use failure rates of LARC methods are comparable to their perfect-use failure rates because little action is required by the user. Because LARC provides either the lowest hormonal levels (progestin-only IUD, progestin-only implant) or no hormones, they have low side effect profiles and few contraindications to use. Per The US Medical Eligibility Criteria for Contraceptive Use, even women with AIDS can have implants placed (category 1) and may have IUDs placed with close followup or if no other method is available or acceptable (category 2 or 3). Perhaps most important to this population, the reversibility of LARC enables the use of highly effective contraception without the risk of sterilization regret. The World Health Organization and the American Congress of Obstetricians and Gynecologist (ACOG) state that intrauterine devices (IUDs) are a safe contraceptive method for HIV-infected women [4].

Of the women in the study who had been sterilized, one-third (36.4%) regretted their sterilization, and 18.2% reported they desired children in the future. Stanwood et al. found similar rates of HIV-positive women sterilized (47%) and wanting children after sterilization (12%) [9]. However, the United States Collaborative Review of Sterilization found an overall rate of sterilization regret of 7.5% at 7 years in the general population [24]. It is also interesting that in our sample, an additional 18.2% stated they regret their tubal sterilization although they do not currently desire future fertility. A prior systematic review evaluating age and risk of sterilization regret found that women under 30 were about twice as likely as those over 30 to express regret [25]. Our findings were not consistent with this; however, we did find that women currently in a monogamous relationship had statistically higher rates of regrets than those not in a relationship. Future relationship status may be a much more difficult factor to foresee preoperatively than one's age as a predictor of future regret. Nevertheless, our results indicate the need for more in-depth preprocedure counseling in an attempt to decrease the rate of regret in this population.

The relatively high rates of tubal ligation and of tubal regret in our population highlight the importance of our need to counsel HIV-positive women on highly effective reversible contraceptive methods, especially as they are greatly underused and yet appear to suit their contraceptive desires. It also highlights the importance of screening them regarding their future fertility desires. ACOG currently recommends that reproductive plans, including preconception counseling and counseling regarding reversible methods of contraception, should be discussed with HIV-infected women of childbearing age [4].

Our study has the following limitations. As this survey included sensitive topics, social desirability and stigma may have biased respondents' answers. Our study population received care in an academic, urban setting and therefore may not be generalizable to all HIV-positive women in care. As this was a cross-sectional study, we can only make findings of associations, not definitive conclusions on cause and effect.

5. Conclusions and Implications

Women acquiring HIV through heterosexual relationships are currently the largest growing group of HIV-positive patients. Given current therapies, this population is living longer, healthier lives with access to HIV care. Therefore it is important that providers ask HIV-positive women about their reproductive needs and discuss contraception and STI prevention as part of their routine care. Based on our results this population is most commonly using sterilization for contraception despite an unfortunately high level of regret. In addition, this population is under-using LARCs despite these being the type of method they most desire. It is important that providers ask HIV-positive women about their reproductive needs and desires, discuss contraception, and provide preconception counseling if appropriate. There has been little progress integrating family planning services and HIV/AIDS care. Often clinic staff views family planning and HIV prevention as independent services and are not trained to administer them together [26]. Governments and funding agencies have a growing awareness of the need to address the reproductive choices of HIV-positive women and agree that HIV/STI and family planning services should be integrated [27, 28]. Partnerships between HIV/AIDS services and family planning services may be more responsive to the needs of reproductive-age HIV-positive women and may be more likely to provide complete, high-quality care.

References

[1] S. K. Henshaw, "Unintended pregnancy in the United States," *Family Planning Perspectives*, vol. 30, no. 1, pp. 24–46, 1998.

[2] L. B. Finer and S. K. Henshaw, "Disparities in rates of unintended pregnancy in the United States, 1994 and 2001," *Perspectives on Sexual and Reproductive Health*, vol. 38, no. 2, pp. 90–96, 2006.

[3] UNAIDS, "Report on the global AIDS epidemic: a UNAIDS 10th anniversary special edition: executive summary," Joint United Nations Programme on HIV/AID, UNAIDS, Geneva, Switzerland, 2006.

[4] ACOG Committee on Practice Bulletins–Gynecology, "ACOG Practice Bulletin No. 117: gynecologic care for women with human immunodeficiency virus," *Obstetrics and gynecology*, vol. 116, no. 6, pp. 1492–1509, 2010.

[5] H. Boonstra, "Meeting the sexual and reproductive health needs of people living with HIV," *Issues in Brief (Alan Guttmacher Institute)*, no. 6, pp. 1–4, 2006.

[6] Centers for Disease Control and Prevention, "Epidemiology of HIV/AIDS—United States, 1981–2005," *Morbidity and Mortality Weekly Report*, vol. 55, no. 21, pp. 589–592, 2006.

[7] E. Z. Aaron and S. M. Criniti, "Preconception health care for HIV-infected women," *Topics in HIV Medicine*, vol. 15, no. 4, pp. 137–141, 2007.

[8] L. S. Massad, C. T. Evans, T. E. Wilson et al., "Contraceptive use among U.S. women with HIV," *Journal of Women's Health*, vol. 16, no. 5, pp. 657–666, 2007.

[9] N. L. Stanwood, S. E. Cohn, J. R. Heiser, and M. Pugliese, "Contraception and fertility plans in a cohort of HIV-positive women in care," *Contraception*, vol. 75, no. 4, pp. 294–298, 2007.

[10] W. D. Moshe and J. Jones, "Use of contraception in the United States: 1982–2008. National Center for Health Statistics," *Vital and Health Statistics*, vol. 23, no. 29, 2010.

[11] D. B. A. Clemetson, G. B. Moss, D. M. Willerford et al., "Detection of HIV DNA in cervical and vaginal secretions: prevalence and correlates among women in Nairobi, Kenya," *Journal of the American Medical Association*, vol. 269, no. 22, pp. 2860–2864, 1993.

[12] A. Kovacs, S. S. Wasserman, D. Burns et al., "Determinants of HIV-1 shedding in the genital tract of women," *Lancet*, vol. 358, no. 9293, pp. 1593–1601, 2001.

[13] C. C. Wang, R. S. McClelland, J. Overbaugh et al., "The effect of hormonal contraception on genital tract shedding of HIV-1," *AIDS*, vol. 18, no. 2, pp. 205–209, 2004.

[14] R. Heffron, D. Donnell, H. Rees et al., "Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis," *Lancet Infectious Diseases*, vol. 12, pp. 19–26, 2012.

[15] C. S. Morrison, B. A. Richardson, F. Mmiro et al., "Hormonal contraception and the risk of HIV acquisition," *AIDS*, vol. 21, no. 1, pp. 85–95, 2007.

[16] I. De Vincenzi, R. A. Ancelle-Park, J.-B. Brunet et al., "Comparison of female to male and male to female transmission of HIV in 563 stable couples," *British Medical Journal*, vol. 304, no. 6830, pp. 809–813, 1992.

[17] E. M. Stringer, M. Giganti, R. J. Carter, W. El-Sadr, E. J. Abrams, and J. S. A. Stringer, "Hormonal contraception and HIV disease progression: a multicountry cohort analysis of the MTCT-Plus Initiative," *AIDS*, vol. 23, no. 1, supplement 1, pp. S69–S77, 2009.

[18] K. M. Curtis, K. Nanda, and N. Kapp, "Safety of hormonal and intrauterine methods of contraception for women with HIV/AIDS: a systematic review," *AIDS*, vol. 23, no. 1, pp. S55–S67, 2009.

[19] "Hormonal contraception and HIV technical statement," World health organization, 2012, http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.08_eng.pdf.

[20] "Panel on Antiretroviral Guidelines for Adults and Adolescents," Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services; 2009, http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGl.pdf.

[21] K. Nanda, E. Amaral, M. Hays, M. A. M. Viscola, N. Mehta, and L. Bahamondes, "Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy," *Fertility and Sterility*, vol. 90, no. 4, pp. 965–971, 2008.

[22] D. H. Watts, J. G. Park, S. E. Cohn et al., "Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093," *Contraception*, vol. 77, no. 2, pp. 84–90, 2008.

[23] R. A. Hatcher, J. Trussell, A. Nelson, W. Cates, D. Kowal, and M. Policar, *Contraceptive Technology*, Ardent Media, Atlanta, Ga, USA, 20th edition, 2011.

[24] S. D. Hillis, P. A. Marcheanks, L. R. Tylor, and H. B. Peterson, "Poststerilization regret: findings from the United

States collaborative review of sterilization," *Obstetrics and Gynecology*, vol. 93, no. 6, pp. 889–895, 1999.

[25] K. M. Curtis, A. P. Mohllajee, and H. B. Peterson, "Regret following female sterilization at a young age: a systematic review," *Contraception*, vol. 73, no. 2, pp. 205–210, 2006.

[26] D. Daley, "Reproductive health and AIDS-related services for women: how well are they integrated?" *Family Planning Perspectives*, vol. 26, no. 6, pp. 264–269, 1994.

[27] W. Cates, Q. Abdool Karim, W. El-Sadr et al., "Global development. Family planning and the millennium development goals," *Science*, vol. 329, no. 5999, p. 1603, 2010.

[28] W. Cates Jr. and K. M. Stone, "Family planning, sexually transmitted diseases and contraceptive choice: a literature update. Part II," *Family Planning Perspectives*, vol. 24, no. 3, pp. 122–128, 1992.

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Clinical Study

HIV Mother-to-Child Transmission, Mode of Delivery, and Duration of Rupture of Membranes: Experience in the Current Era

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Objective. To evaluate whether the length of time of rupture of membranes (ROM) in optimally managed HIV-positive women on highly active antiretroviral therapy (HAART) with low viral loads (VL) is predictive of the risk of mother to child transmission (MTCT) of the human immunodeficiency virus (HIV). *Study Methods*. A retrospective case series of all HIV-positive women who delivered at two academic tertiary centers in Toronto, Canada from January 2000 to November 2010 was completed. *Results*. Two hundred and ten HIV-positive women with viral loads <1,000 copies/ml delivered during the study period. VL was undetectable (<50 copies/mL) for the majority of the women (167, 80%), and <1,000 copies/mL for all women. Mode of delivery was vaginal in 107 (51%) and cesarean in 103 (49%). The median length of time of ROM was 0.63 hours (range 0 to 77.87 hours) for the entire group and 2.56 hours (range 0 to 53.90 hours) for those who had a vaginal birth. Among women with undetectable VL, 90 (54%) had a vaginal birth and 77 (46%) had a cesarean birth. Among the women in this cohort there were no cases of MTCT of HIV. *Conclusions*. There was no association between duration of ROM or mode of delivery and MTCT in this cohort of 210 virally suppressed HIV-positive pregnant women.

1. Introduction

In economically developed countries, the human immunodeficiency virus (HIV) infection is now considered a chronic disease, with life expectancy approaching that of the general population [1]. Many HIV-positive women choose to pursue pregnancies [2]. Management of the HIV-positive pregnant patient should focus on both decreasing the risk of mother to child transmission (MTCT) and minimizing maternal and neonatal complications.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) and American College of Obstetricians and Gynecologists (ACOG) recommend that elective cesarean section (cesarean section before labor or rupture of membranes (ROMs) be performed for delivery when viral load is detectable [3] or greater than 1000 copies/mL [4] as there is a 12-fold increased risk of MTCT [3, 5]. This is based on several studies that showed that the combination of intrapartum zidovudine (ZDV) and elective cesarean section significantly decreased vertical transmission compared to other delivery modes [6–8]. With the addition of highly active antiretroviral therapy (HAART), the risk of vertical transmission has continued to decrease [5].

ROM increases fetal exposure to maternal blood and vaginal fluids, and prolonged duration of ROM has been shown to be a significant risk factor for vertical transmission [6, 9–11]. Evidence exists that after 4 hours of ROM the risk of MTCT rises and the protective effect of a cesarean section is lost [9, 10]. However, these conclusions were based on studies in which only intrapartum monotherapy with ZDV was used and maternal VL was not known. Since the addition of HAART, subsequent research has been performed to determine if prolonged duration of ROM remains an important risk factor for vertical transmission. These studies have demonstrated that there is no increased risk of transmission with ROM longer than 4 hours and no protective effect of cesarean section [5, 12]. Given that postpartum morbidity from cesarean section is potentially higher in HIV-positive women [13], achieving a vaginal birth in this population is beneficial.

Given the paucity of literature addressing this question, the objective of this study was to review our experience and evaluate whether the effect of duration of ROM or mode of delivery on MTCT still exists among optimally managed HIV-positive women on HAART.

2. Methods

Following ethical approval, we performed a retrospective chart review of all HIV-positive women who delivered at Mount Sinai and St. Michael's Hospitals in Toronto, Canada, between January 2000 and November 2010.

Women were defined as "optimally managed" if they were taking antepartum HAART and had a VL less than 1000 copies/mL at the time of delivery. Thus, eligibility criteria included pregnant women with a predelivery diagnosis of HIV, adherence to antepartum HAART, VL less than 1000 copies/mL at the time of delivery, and delivery at either of the two sites. If a woman had had multiple deliveries during the time period, the most recent delivery data was collected. Women not on HAART or with viral loads greater than 1000 copies/mL were excluded.

Information regarding the patient's age, ethnic background, gravidity, parity, administration of intravenous ZDV, time of ROM, time of birth, mode of delivery, and intrapartum procedures (artificial rupture of membranes (AROMs), fetal scalp electrodes) were all recorded from the antenatal charts and/or from the medical records. The VL closest to the date of birth was recorded. Duration of ROM was expressed as total length of time in minutes from time of ROM to time of birth. The proportion of women receiving intravenous ZDV, with vaginal birth or cesarean section, and with any invasive procedures was determined.

All children born to HIV-positive mothers were prescribed a 6-week course of oral zidovudine and referred for follow-up care in the pediatric HIV clinic, at the Hospital for Sick Children, in Toronto. The rate of MTCT was determined in collaboration with this clinic.

3. Results

During the study period, 213 HIV-positive women delivered at the participating centers. Of these, 3 were excluded due to a viral load > 1000 copies/m—therefore the final study cohort consisted of 210 women. During the 10-year study period, the number of HIV-positive pregnant women seeking care steadily increased over time.

Demographic characteristics are reported in Table 1. The majority of the group (135, 64%) was of African descent. Eighty (38%) women gave birth to their first child. A high rate (16%) of preterm birth, defined as delivery <37 weeks gestational age, was observed in our cohort. The average gestational age at birth was 38 weeks and 2 days with a range of 24 weeks and 6 days to 41 weeks and 3 days.

Of the 210 women, 200 had a recorded VL prior to delivery. The other 10 women had a VL recorded as "less than 1000 copies/mL". Of those 200 patients with known VL, the majority of the group ($n = 167$, 84%) had an undetectable VL (less than 50 copies/mL) at the time of delivery. The highest viral load in this cohort was 706 copies/mL. The majority of women ($n = 179$, 85%) received adequate intrapartum ZDV, defined as having received a loading dose followed by 3 hours of maintenance infusion prior to delivery.

In the entire cohort, 107 women (51%) had a vaginal birth and 103 (49%) had a cesarean birth. Among women with cesarean birth, 75 (73%) were performed electively (prior to labor) and 28 (27%) were performed in labor. Among women with undetectable VL, 90 (54%) had a vaginal birth, and 77 (46%) had a cesarean birth.

In this cohort, 46 women had AROM. Of those, 20 women had dilation between 0 and 4 cm, 20 had greater than 4 cm but less than 10 cm, and 6 were ruptured just prior to delivery. Among the 107 women with a vaginal birth, six had a vacuum-assisted vaginal delivery and one had a fetal scalp electrode placed.

The median length of time of rupture of membranes for the entire cohort was 0.63 hours (0.00–77.87). The median length of time of rupture of membranes for the vaginal birth group was 2.56 hours (0.00–53.90) and cesarean birth group was 0.02 hours (0.00–77.87) ($P < 0.0001$). For those women with an undetectable VL, the median length of time of rupture of membranes was 0.62 hours (0.00–77.87) and for those with a detectable VL was 0.57 hours (0.00–33.63) ($P > 0.92$). When removing those who were ruptured less than 0.03 hours (elective cesareans, precipitous vaginal deliveries, etc.), there were 131 patients whose membranes were ruptured for 0.05 hours or longer. Their median length of time of rupture was 3.53 hours (0.05–77.87). In total, 59 (28%) women had rupture of membranes for 4 hours or longer. For women who were less than 37 weeks at the time of delivery, the median length of time of rupture was 0.63 hours (0.00–77.87), and 0.66 hours (0.00–53.90) for those greater than 37 weeks. The median lengths of time of rupture and gestational ages are shown in Figure 1.

There were no cases of MTCT in this cohort of HIV-positive pregnant women.

Table 1: Optimally managed HIV-positive women who delivered between January 2000 and November 2010.

Characteristic	
Mean age	32 years (range 16–43)
Race	
African	135 (64%)
Caucasian	23 (11%)
Asian	16 (8%)
Caribbean	17 (8%)
Other	11 (5%)
Missing	8 (4%)
Average gravidity	3
Average parity	1
Gestational Age >37 weeks at delivery	177 (84%)

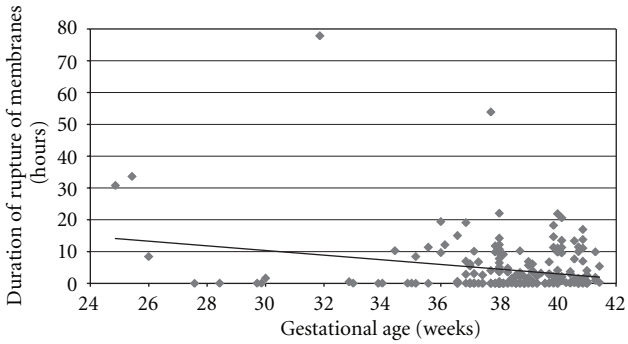

Figure 1: Gestational age and median lengths of time of rupture.

4. Discussion

This study suggests that, in a group of 210 optimally managed HIV-positive women who gave birth over a 10-year period, increasing the duration of ROM did not increase the likelihood of MTCT. Since the use of HAART, little has been published specifically exploring the role of duration of ROM and MTCT in optimally managed women [11, 12].

In this cohort of women, the median length of time of ROM for the entire group was 0.63 hours with a range of 0 to 77.87 hours. A large proportion of the group was ruptured for minutes only, and when removing those women, the median increases to 3.53 hours, with a range from 0.05 hours to 77.87 hours. The median for the undetectable VL women was similar to the entire group, at 0.65 hours, which follows since the majority of the group had undetectable VL. It is clear that some women certainly had ROM longer than the previously recommended time limit of 4 hours [9, 10], but given that this recommendation is based on studies where women were not on HAART and maternal VL was not known, this recommendation may not apply to women who are optimally managed. In all of our subgroups, the range extends outside the 4-hour recommendation without increasing the association with MTCT.

Previous literature has stated that even in women with undetectable VL, elective cesarean birth reduces MTCT; however when adjusted for HAART, the effect was no longer significant [5]. In our study the median times of ROM for the vaginal (2.56 hours) and cesarean groups (0.02 hours) were statistically different, but neither group had a case of MTCT. This is consistent with previous literature that for women on HAART, mode of delivery does not influence risk of MTCT, even if the length of time of ROM increased.

The adherence rate for IV ZDV prior to delivery in this study was 85%, which is similar to rates in other studies [14]. All women who did not receive adequate IV ZDV prior to delivery either had precipitous deliveries or operative deliveries for emergency indications (cord prolapse, footling breech in labor). In the majority of cases, the ZDV was started on admission using preprinted orders, but delivery occurred before three hours of maintenance infusion could be completed.

Our cesarean birth rate was 49%, which is well above the national average of approximately 26% [15]. This may be related to several factors. First, the majority of the group was multiparous, accounting for two-thirds of the women who underwent cesarean. Many of these women chose to undergo a repeat cesarean, similar to HIV-negative women in Canada [14]. Second, some HIV-positive women choose to undergo an elective cesarean regardless of previous delivery status or VL [3]. A large proportion of women in this study originate from resource-poor countries where different strategies are employed, such as cesarean birth, to prevent MTCT [15].

In our cohort of HIV-positive women, the preterm birth rate was 16%, which is double the average preterm birth rate in Canada of 8%. This increased preterm birth rate has been observed in other studies of HIV-positive women on HAART [5, 16]. In previous work done at one of our institutions, the preterm delivery rate in a cohort of HIV-positive women was similar to the control group (in press). Possible reasons for the increased rate in the current cohort could include earlier induction of labor for abnormal liver function tests or preeclampsia, or spontaneous preterm labor. These factors could also be a contributor to the high cesarean birth rate observed in this study. More research is urgently required to further explore these relationships.

Preterm premature rupture of membranes (PPROMs) in optimally managed HIV-positive women poses a clinical dilemma for management when weighing the risk of prematurity over the risk of MTCT. Our study did not specifically address the issue of PPROM; however there was a small number of preterm patients who were ruptured for greater than the 4-hour recommendation without a case of MTCT. Overall though, the median lengths of time of rupture for both the preterm and term patients were similar. More studies with a larger number of optimally managed patients with PPROM are required to further explore this complex issue.

Traditionally, the use of invasive procedures during labor in HIV-positive women has been discouraged because of the potential for increasing MTCT [5–10]. In this study, AROM was employed for labor induction and during the active phase of labor in 46 women without increasing the likelihood

of vertical transmission. One patient did have a fetal scalp electrode placed, although this is not typical practice even among optimally managed women and is not recommended.

During the study period of ten years, we observed a trend of an increasing number of deliveries. There are many possible reasons for this, including an increase in the proportion of women among HIV-positive persons, changing immigration patterns, and better long-term management of HIV resulting in better overall health and an increased desire for childbearing. Since the introduction of HAART in 1998, there has been a steady decline in antenatal monotherapy use in Ontario, with an increasing acceptance of and adherence to HAART regimens [14]. This also may have resulted in an increasing number of women who met inclusion criteria of antenatal HAART use and low VL over time. Given the number of cases from January to November 2010, the number for 2011 is projected to be similar to 2008 and 2009.

This study has several strengths. We had a large cohort of HIV-positive women managed by a small number of practitioners at only two geographic sites. This resulted in a cohort of optimally managed and virally suppressed women, with the majority having undetectable VL and all having VL less than 1,000 copies/mL. Physicians and nurses at these two sites have experience in the antenatal and intrapartum care of these women, which increases the likelihood of appropriate decision-making regarding medication use and labor management. Finally, complete follow-up of children born to women in this study allows us to evaluate MTCT rates over time. There are also some limitations. Due to the relatively small proportion of HIV-positive women delivering in Canada, our ability to examine larger cohorts of women is limited without employing a multicentre approach. The size of our cohort prevents us from determining small differences in transmission rate. To more accurately investigate the relationship of duration of ROM and MTCT of HIV in optimally managed women, a larger multicenter study would be required.

With no cases of MTCT, we were unable to evaluate patient-specific or labor and delivery characteristics predictive of transmission. However, we found no association with increasing duration of ROM or mode of delivery and MTCT. It is reassuring that, in the current era and among women with low VL, allowing length of time of ROM to increase beyond four hours does not appear to increase the risk of MTCT.

5. Conclusion

In a cohort of over 200 optimally managed HIV-positive women on HAART with low VL, there were no cases of MTCT. Increasing the duration of ROM did not increase the likelihood of MTCT. Further, MTCT was not related to mode of delivery. Allowing optimally managed women with low VL to continue in labor beyond four hours of ROM is acceptable. Additional studies with larger numbers of women are important to further evaluate the impact of duration of ROM and mode of delivery on MTCT among HIV-positive women in the current era.

References

[1] Antiretroviral Therapy Cohort Collaboration, "Life expectancy of individuals on combination antiretrovrial therapy in high-income countries: a collaborative analysis of 14 cohort studies," *Lancet*, vol. 372, no. 9635, pp. 293–299, 2008.

[2] M. R. Loutfy, T. A. Hart, S. S. Mohammed et al., "Fertility desires and intentions of HIV-positive women of reproductive age in Ontario, Canada: a cross-sectional study.," *PloS Nne*, vol. 4, no. 12, Article ID e7925, 2009.

[3] M. Boucher, H. Cohen, A. Gruslin, D. Money, M. Steben, and T. Wong, "Mode of delivery for pregnant women infected by the human immunodeficiency virus," *Journal of the Society of Obstetricians and Gynaecologists of Canada*, vol. 23, no. 4, pp. 348–350, 2001.

[4] ACOG Committee Opinion, "Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection," *The American College of Obstetricians and Gynecologists*, no. 234, 2000.

[5] European Collaborative Study, "Mother-to-Child transmission of HIV infection in the era of highly active antiretroviral therapy," *Clinical Infectious Diseases*, vol. 40, pp. 458–465, 2005.

[6] The International Perinatal HIV Group, "The mode of delivery and the risk of vertical transmission of human immunodificiency virus type 1," *New England Journal of Medicine*, vol. 340, pp. 977–987, 1999.

[7] L. Mandelbrot, J. Le Chenadec, A. Berrebi et al., "Perinatal HIV-1 transmission: Interaction between zidovudine prophylaxis and mode of delivery in the French perinatal cohort," *Journal of the American Medical Association*, vol. 280, no. 1, pp. 55–60, 1998.

[8] F. Parazzini, E. Ricci, E. Di Cintio et al., "Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial," *Lancet*, vol. 353, no. 9158, pp. 1035–1039, 1999.

[9] H. Minkoff, D. N. Burns, S. Landesman et al., "The relationship of the duration of ruptured membranes to vertical transmission of human immunodeficiency virus," *American Journal of Obstetrics and Gynecology*, vol. 173, no. 2, pp. 585–589, 1995.

[10] S. Landesman, L. Kalish, D. Burns et al., "Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. The Women and Infants Transmission Study," *New England Journal of Medicine*, vol. 334, no. 25, pp. 1617–1623, 1996.

[11] A. Garcia-Tejedor, A. Perales, and V. Maiques, "Duration of ruptured membranes and extended labor are risk factors for HIV transmission," *International Journal of Gynecology and Obstetrics*, vol. 82, no. 1, pp. 17–23, 2003.

[12] A. Garcia-Tejedor, V. Maiques, A. Perales, and J. Lopez-Aldeguer, "Influence of Highly Active Antiretroviral Treatment (HAART) on risk factors for vertical HIV transmission," *Acta Obstetricia et Gynecologica Scandinavica*, vol. 88, pp. 882–887, 2009.

[13] J. S. Read and M. K. Newell, "Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1," *Cochrane Database of Systematic Reviews*, no. 4, Article ID CD005479, 2005.

[14] S. Gahir, G. J. Anger, M. Ibrahim, S. Read, and M. Piquette-Miller, "Management of hiv positive pregnancies in ontario: Current status," *Canadian Journal of Clinical Pharmacology*, vol. 16, no. 1, pp. e68–e77, 2009.

[15] Canadian Institute for Health Information, "Giving Birth in Canada: Regional Trends from 2001-2002 to 2005-2006," July 2007, http://secure.cihi.ca/cihiweb/en/downloads/Childbirth_AiB_FINAL_E.pdf.

[16] C. Rudin, A. Spaenhauer, O. Keiser et al., "Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data," *HIV Medicine*, vol. 12, no. 4, pp. 228–235, 2011.

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Clinical Study

Pharmacokinetic Interactions between the Hormonal Emergency Contraception, Levonorgestrel (Plan B), and Efavirenz

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Objectives. Compare the Plan B levonorgestrel (LNG) area under the concentration- time curve (AUC_{12}) prior to and with efavirenz (EFV). *Design*. Prospective, open-label, single-arm, equivalence study. *Methods*. Healthy HIV-negative subjects underwent 12 hr intensive pharmacokinetic (PK) sampling following single dose LNG alone and after 14 days of EFV. Geometric means, Geometric Mean Ratios, and 90% confidence intervals (CI) are reported for PK Parameters. *T*-tests were utilized. Clinical parameters and liver function tests (LFTs) were assessed. *Results*. 24 women enrolled and 21 completed the study. With EFV, LNG AUC_{12} was reduced 56% (95% CI: 49%, 62%) from 42.9 to 17.8 ng∗hr/mL, and maximum concentration (C_{max}) was reduced 41% (95% CI: 33%, 50%) from 8.4 to 4.6 ng/mL. LNG was well tolerated with no grade 3 or 4 treatment-related toxicities. *Conclusions*. EFV significantly reduced LNG exposures. Higher LNG doses may be required with EFV. These results reinforce the importance of effective contraception in women taking EFV.

1. Introduction

The majority of women with human immunodeficiency virus −1 (HIV) are of reproductive age and may use an efavirenz- (EFV-) containing antiretroviral (ARV) regimen [1, 2]. EFV is a nonnucleoside reverse transcriptase inhibitor (NNRTI) indicated in combination with other antiretroviral agents for the treatment of HIV [3]. EFV is an FDA pregnancy category D drug based on animal studies and human case reports of fetal neural tube defects [3–6]. Thus, preventing pregnancy is critical in HIV-infected women receiving EFV.

Pregnancy rates for HIV-infected women range from 6.0 to 8.2 pregnancies per 100 person-years, and in 2001, 49% of all pregnancies in the United States were unintended [7–9]. Women with HIV not desiring pregnancy are advised to use dual methods of contraception to prevent pregnancy and HIV transmission to their partners. Some women use emergency hormonal contraception to prevent pregnancy after unprotected sex or contraceptive failure (condom breakage).

Plan B is a levonorgestrel- (LNG-) containing emergency contraceptive pill indicated for pregnancy prevention following unprotected intercourse or a known or suspected contraceptive failure [10]. It is taken as soon as possible within 72 hours after unprotected intercourse either as a single dose (LNG 1.5 mg) or as two doses (0.75 mg) taken twelve hours apart. LNG use for emergency hormonal contraception has been shown to reduce pregnancy rates by 85% [11]. The mechanism of action of Plan B is not fully elucidated. It may inhibit ovulation, fertilization, or implantation [10, 11]. The minimum effective LNG plasma concentration is unknown.

Few data are available on the pharmacokinetics (PK) of progesterone-based contraceptives with NNRTIs. A study of depomedroxyprogesterone acetate (DMPA) depot injections in HIV-infected women on antiretroviral therapy revealed no significant change in plasma levels of MPA or EFV,

nevirapine, or nelfinavir [12]. However, in a study of EFV and the combination oral contraceptive pill OrthoTriCyclen-Lo and OrthoCyclen (25 mcg ethinyl estradiol plus 0.18–0.25 mg norgestimate), LNG area under the concentration time curve from 0 to 12 hours (AUC_{12}), maximum concentration (C_{max}), and minimum concentration (C_{min}) were decreased by 80%, 83%, and 86%, respectively [13]. A case of contraceptive failure with ectopic pregnancy in an HIV-infected woman occurred with the etonogestrel contraceptive implant and EFV [14]. No PK interaction studies of Plan B and concomitant efavirenz have been performed [14].

2. Methods

2.1. Subjects. Subjects were HIV-seronegative women ages 18–45 years with normal body mass index and no recent use of hormonal contraceptive agents (oral or vaginal hormonal contraception use within 60 days or injectable hormonal contraception use within 180 days of study entry; subjects with Mirena IUD were excluded) or other medications/therapies known to interact with EFV. Subjects who had not undergone surgical sterilization used 2 nonhormonal types of contraception throughout the study period and for 2 weeks following study completion.

The protocol was approved by the institutional review board at participating sites, and informed consent was obtained from each woman before participation.

2.1.1. Study Design. This was a prospective, open-label, single-arm, two-period, PK equivalence study. The primary objective was to compare Plan B LNG AUC_{12} prior to and during steady-state EFV. Secondary objectives included (1) characterization of other LNG plasma PK parameters, (2) assessment of the safety and tolerability of coadministration of Plan B and EFV, and (3) evaluation of potential effects of LNG on EFV AUC_{24} with comparison to previous data in HIV+ women. Study participants received LNG 0.75 mg at time 0 and 12 hours at baseline (visit 1-day 0) and after steady state EFV dosing (visit 2-day 17). Subjects were begun on EFV 600 mg at bedtime on empty stomach 72 hours after visit 1 for a total duration of 14 days. Participants fasted at least 12 hours prior to the PK study visits and ate a standardized breakfast with LNG dosing (600 kcal; 15% protein, 30% fat, and 55% carbohydrates). Serial blood (plasma) sampling for LNG PK analysis was performed after LNG dosing at 0 (predose), 2, 3, 4, 6, 8, 10, and 12 hours at Visit 1 and 2. Blood (plasma) sampling for EFV PK analysis was performed prior to LNG dose, 6 and 12 hours after LNG dose at visit 2 only (corresponding to approximately 10, 16, and 22 hours from EFV dosing). Relevant clinical adverse events were assessed at study and 4 telephone visits (study days 4, 11, 16, and 20–28). Safety and laboratory profiles and pregnancy testing were performed at screening and visits 1, 2 (LFT's only), and 3. EFV adherence was assessed by subject self-report at telephone visits approximately 7 and 17 days after EFV was initiated.

2.2. Bioanalyses. LNG plasma concentrations were determined with a liquid chromographic assay with MS/MS detection linear in the range of 50–25000 pg/mL. Accuracy and precision were within ±11% using a 0.5 mL plasma sample. EFV plasma concentrations were determined using a validated HPLV/UC method linear in the range of 20–20,000 ng/mL. Accuracy and precision were within ±15% with 0.2 mL plasma. Samples were frozen and shipped to PPD, Inc. for LNG analysis and University of Colorado Pharmacology lab for EFV analysis.

2.3. Data Analyses. Sample size calculations assumed that expected LNG AUC_{12} was 123.1 ng∗hr/mL with a standard deviation of 50.1 [15]. Assuming equal variances and a modest correlation of 0.5, the standard deviation of the difference is also 50.1. 18 subjects were required to detect a difference of 49.2 (a 40% change) in LNG AUC_{12} using a two-sided, paired t-test with a significance level of 0.05 and 97.5% power. To account for drop-outs, we enrolled 24 participants.

LNG PK was determined by noncompartmental methods (WinNonLin V5.2.1, Pharsight Corporation, Mountain View, CA). LNG AUC_{12} was calculated with the linear-log trapezoidal rule and LNG C_{min}, C_{max}, and time to C_{max} (T_{max}) determined visually. LNG half-lives ($t_{1/2}$) were calculated as 0.693 divided by λz, where λz was the terminal elimination rate constant. LNG total apparent oral clearance (CL/F) was determined as dose divided by AUC_{12}. Apparent volume of distribution (V/F) was determined by CL/F divided by λz.

A post hoc Bayesian approach (NONMEM vVI) was used to estimate each subject's EFV AUC_{24} based on the three measured EFV levels. The estimated AUC_{24} was compared to data from a previous PK study of HIV+ women using a 2-sample t-test [16].

For the primary hypothesis, equivalence was defined as a decrease of less than 40% LNG AUC_{12} after addition of EFV based on previous studies utilizing a 40% difference in contraceptive steroid hormone AUC as that which is clinically relevant [12]. Percent change was calculated from the raw (untransformed) data. The null hypothesis of equivalence was rejected if the corresponding 95% confidence interval included values ≤40%.

PK data were log transformed. Point estimates and 90% confidence intervals for geometric means of LNG AUC_{12}, C_{max}, C_{min}, V/F and CL/F, and $t_{1/2}$ were determined for LNG dosed alone and with EFV. Geometric mean ratios (GMR) for LNG AUC_{12}, C_{max}, and C_{min} with versus without EFV were calculated. Relevant clinical adverse events and liver function test elevations were summarized. Paired t-tests were used.

3. Results

3.1. Demographics. Twenty-four women enrolled, and 23 subjects commenced study visits and treatments. Three subjects discontinued; 2 for adverse events and 1 for personal reasons. Evaluable PK data was generated for 21 women who had a mean age of 31 years (range 21–45) and BMI of 27

Table 1: Estimated LNG PK parameters.

PK parameter	Percent change raw scale (95% CI)	LNG GM (90% CI)	LNG + EFV GM (90% CI)	*P* value	GMR (90% CI)
AUC_{12} (ng∗hr/mL)	−56% (−49%, −62%)	42.9 (38.0, 48.5)	17.8 (15.5, 20.5)	<0.0001	0.42 (0.36, 0.48)
C_{max} (ng/mL)	−41% (−33%, −50%)	8.4 (7.6, 9.3)	4.6 (4.0, 5.4)	<0.0001	0.55 (0.49, 0.63)
C_{min} (ng/mL)	−67% (−59%, −74%)	2.04 (1.7, 2.3)	0.6 (0.5, 0.7)	<0.0001	0.31 (0.26, 0.36)
V/F (L)	110% (−155%, 176%)	144 (120, 173)	256 (217, 301)	0.0001	—
CL/F (L/hr)	260% (159%, 364%)	9.7 (8.0, 11.6)	32.1 (27.6, 37.3)	<0.0001	—
$t_{1/2}$ (hr)	−34% (−17%, −55%)	10.3 (8.1, 13.2)	5.5 (4.6, 6.7)	0.0001	—

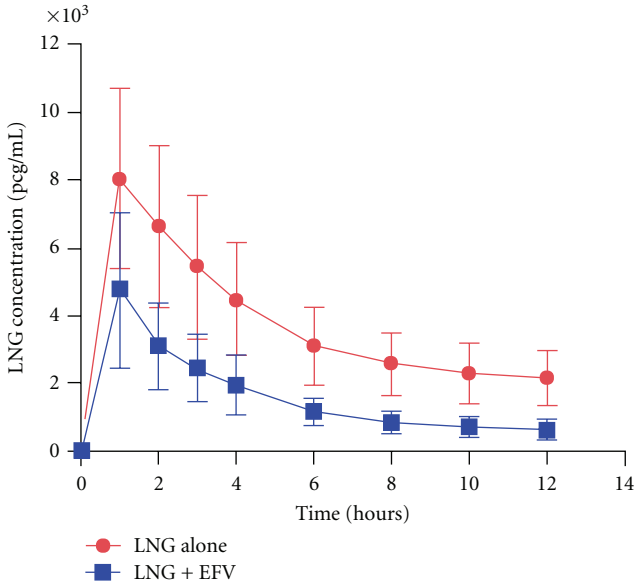

Figure 1: Mean plasma concentration versus time profile for LNG. Mean (±SD) levonorgestrel concentration-time profile in 21 healthy volunteers administered alone (red) and after 14 days of pretreatment with efavirenz (blue).

(range 21–35). The majority of subjects were white (62%), and 24% were Latina and 10% Black. Contraception use included condoms, spermicide, diaphragm, abstinence, and intrauterine device.

3.2. LNG and EFV Pharmacokinetics. The estimated percent decrease in LNG AUC_{12} with EFV was 56% (Table 1), and the corresponding 95% confidence interval (49%, 62%) excluded a change of ≤40% ($P < 0.0001$), such that the equivalence hypothesis was rejected. A decrease in LNG AUC_{12} of >40% was observed in 90.5% (95% CI: 0.70%, 0.99%) of women. LNG C_{max} and C_{min} GMR were 0.55 and 0.31, respectively. LNG concentration time curves are shown in Figure 1. The geometric mean EFV AUC_{24} in combination with LNG was 69597 ng∗hr/mL. (90% CI 27629, 175316 ng∗hr/mL). This value was compared to a previous study of EFV PK in HIV-infected females which demonstrated an EFV geometric mean AUC_{24} of 61361 ng∗hr/mL (90% CI 19076, 197379 ng∗hr/mL) (P value = 0.35) [15]. Study participants had a >95% adherence with EFV dosing, and all had detectable EFV levels.

3.3. Safety and Tolerability. Headache, abdominal pain, diarrhea, and menstrual cycle changes were the most common adverse events occurring in >10% of subjects after Plan B dosing alone. The incidence of abdominal pain, diarrhea, and menstrual cycle changes was decreased, while incidence of fatigue was increased with EFV. The occurrence of rash, pruritus, abnormal dreams, and insomnia was similar to previous studies of EFV [3]. Changes in LFT's were rare and resolved with discontinuation of EFV. Adverse events were mild (Grade 1) to moderate (Grade 2) in majority and were resolved at follow-up visits. Two subjects discontinued study secondary to adverse events. One subject had a grade 2 rash likely related to study treatment (EFV) and resolved at follow-up visits. One subject had grade 3 syncope not related to study treatment and attributed to a vasovagal reaction with phlebotomy.

4. Discussion

Data are limited regarding the use of hormonal contraception in HIV-infected women on antiretroviral therapy. Interactions have been described between steroid hormones and both protease inhibitors and NNRTI which could lead to decreased protection from pregnancy or increased contraceptive side effects [17]. Previous studies have focused predominantly on combined oral contraceptive pills, injectable DMPA, and one small study evaluated PK with the transdermal contraceptive patch [12, 13, 18]. Women taking EFV are specifically advised to avoid pregnancy due to this agents' potential role in fetal neural tube defects [3, 19]. Thus, emergency hormonal contraception, like Plan B, may be even more important for these women.

We sought to evaluate the effect of EFV on plasma concentration of LNG in Plan B in healthy HIV-negative women. We found that pretreatment with EFV for 14 days was associated with a 56%, 41%, and 67% decrease in LNG AUC_{12}, C_{max}, and C_{min}, respectively.

The mechanism for this interaction is likely EFV induction of LNG metabolism. EFV is an inducer of CYP3A and uridine-diphosphate glucuronosyl transferases (UGTs) in vivo [3]. LNG exposures are reduced approximately 40% with the anticonvulsants phenytoin and carbamazepine (inducers of CYP3A) and 19% with lamotrigine (an inducer of glucuronidation enzymes) [20, 21]. A study of rifampin and oral contraception demonstrated considerable reduction in contraceptive hormone levels; however, ovulation suppression persisted [22].

These findings may have important ramifications with regard to the efficacy of Plan B when taken with this ARV. However, the clinical relevance of this finding is unclear as the minimal effective LNG plasma concentration is unknown. We did not monitor for ovulation which may signal failed contraception. It is possible the alternate Plan B single dosing of LNG 1.5 mg would mitigate this effect; however, this is unlikely given the magnitude of our observed difference. Further clinical studies of Plan B and EFV are thus needed to inform providers of potential need for Plan B dosing adjustments for these women. HIV providers' role in providing family planning services including contraception and preconception counseling is significant given the inherent complexities with HIV and antiretroviral therapy.

Conflict of Interests

Drs. M. L. Carten, J. J. Kiser, A. Kwara, and S. Cu-Uvin have no conflict of interests to report.

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References

[1] HIV/AIDS Surveillance Report, *Cases of HIV and AIDS in the United States and Dependent Areas*, 2007.

[2] UNAIDS, AIDS Epidemic Update: December 2005.

[3] *Sustiva (Efavirenz) Capsule and Tablets.US Prescribing Information*, Bristol-Myers-Squibb, Princeton, NJ, USA, 2010.

[4] A. Saitoh, A. D. Hull, P. Franklin, and S. A. Spector, "Myelomeningocele in an infant with intrauterine exposure to efavirenz," *Journal of Perinatology*, vol. 25, no. 8, pp. 555–556, 2005.

[5] C. Fundarò, O. Genovese, C. Rendeli, E. Tamburrini, and E. Salvaggio, "Myelomeningocele in a child with intrauterine exposure to efavirenz," *AIDS*, vol. 16, no. 2, pp. 299–300, 2002.

[6] M. De Santis, B. Carducci, L. De Santis, A. F. Cavaliere, and G. Straface, "Periconceptional exposure to efavirenz and neural tube defects," *Archives of Internal Medicine*, vol. 162, no. 3, p. 355, 2002.

[7] L. S. Massad, G. Springer, L. Jacobson et al., "Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV," *AIDS*, vol. 18, no. 2, pp. 281–286, 2004.

[8] B. H. Van Benthem, I. De Vincenzi, M. C. Delmas et al., "Pregnancy bfore and after HIV diagnosis in a European cohort of HIV-infected women. European study on the natural history of HIV infection in women," *AIDS*, vol. 14, no. 14, pp. 2171–2178, 2000.

[9] L. B. Finner and S. K. Henshw, "Disparities in rates of unintended pregnancy in the United States, 1994–2001," *Perspect Sex Reprod Health*, vol. 38, no. 2, pp. 9–96, 2006.

[10] Plan B (LNG0.75) Tablets, *US Prescribing Information*, Barr Pharmaceuticals Inc., Pomona, NY, US, 2006.

[11] Task Force on Postovulatory Methods of Fertility Regulation, "Randomized controlled trial of levonorgestrel versus the yuzpe regimen of combined oral contraceptives for emergency contraception," *The Lancet*, vol. 352, no. 9126, pp. 428–433, 1998.

[12] S. E. Cohn, J. G. Park, D. H. Watts et al., "Depo medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 2, pp. 222–227, 2007.

[13] H. Sevinsky, T. Eley, A. He, D. Persson et al., "Effect of efavirenz on the pharmacokinetics of ethinyl estradiol and norgestimate in healthy female subjects," in *Proceedings of the 48th Annual ICAAC/IDSA 46th Annual Meeting*, Washington, DC, USA, October 2008.

[14] A. Matiluko, L. Soundararjan, P. Hodston et al., "Early contraceptive failure of implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz," *Journal of Family Planning and Reproductive Health Care*, vol. 33, no. 4, pp. 277–278, 2007.

[15] K. Kook, H. Gabelnick, and G. Duncan, "Pharmacokinetics of levonorgestrel 0.75 mg tablets," *Contraception*, vol. 66, no. 1, pp. 73–76, 2002.

[16] M. Gandhi, L. Benet, P. Bacchetti et al., "Nonnucleoside reverse transcriptase inhibitor pharmacokinetics in a large unselected cohort of HIV-infected women," *Journal of Acquired Immune Deficiency Syndromes*, vol. 50, no. 5, pp. 482–491, 2009.

[17] S. El-Ibiary and J. Cocohoba, "Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives," *European Journal of Contraception and Reproductive Health Care*, vol. 13, no. 2, pp. 123–132, 2008.

[18] M. Vogler, K. Patterson, L. Kamemoto et al., "Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: pharmacokinetic results of ACTG trial A5188," *Journal of Acquired Immune Deficiency Syndromes*, vol. 55, no. 4, pp. 473–482, 2010.

[19] Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, "US Department of Health and Human Services," 2010, http://www.aidsinfo.nih.gov/guidelines/adult/AA 100606.pdf.

[20] P. Crawford, D. J. Chadwick, C. Martin, J. Tjia, D. J. Back, and M. Orme, "The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids," *British Journal of Clinical Pharmacology*, vol. 30, no. 6, pp. 892–896, 1990.

[21] J. Sidhu, S. Job, S. Singh, and R. Philipson, "The pharmacokinetic and pharmacodynamic consequences of the coadministration of lamotrigine and a combined oral contraceptive in healthy female subjects," *British Journal of Clinical Pharmacology*, vol. 61, no. 2, pp. 191–199, 2006.

[22] P. Barditch-Crovo, C. B. Trapnell, E. Ette et al., "The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive," *Clinical Pharmacology and Therapeutics*, vol. 65, no. 4, pp. 428–438, 1999.