Contraception, fertility planning and HIV-1 risk among African HIV-1 serodiscordant couples

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Abstract

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The studies within this dissertation describe contraception and fertility planning and their relationship to HIV-1 risk among African HIV-1 serodiscordant couples. Specifically, this work 1) describes correlates of contraceptive use, 2) assesses the relationship between contraceptive use and HIV-1 transmission risk, and 3) explores whether new prevention strategies would be a welcomed option.

Hormonal contraception lies at the interface of reproductive health and HIV-1 prevention programs. Safe and effective contraception can reduce maternal mortality and improve infant and maternal health through birth spacing. With these benefits, however, hormonal contraceptive use among women with and at-risk for HIV-1 is low and is correlated with less frequent condom use. Some epidemiological studies–including ours–have demonstrated an increased HIV-1 acquisition risk among women using hormonal contraception, further linking the family planning and HIV-1 prevention communities. At this time, the evidence is inconclusive and recommendations to modify family planning guidelines for women at high HIV-1 risk are not warranted but this question remains of great public health importance. Low rates of contraceptive use may be indicative of high fertility desires and antiretrovirals may offer HIV-1 serodiscordant couples strategies to reduce their HIV-1 transmission risk when they desire children. Not all HIV-1 infected participants in our study indicated willingness to initiate antiretrovirals for HIV-1 prevention purposes, however, and incorporating individual preferences into HIV-1 prevention counseling will remain imperative.

The work detailed in this dissertation will be potentially used to guide HIV-1 prevention and family planning programs for African HIV-1 serodiscordant couples and the results have already contributed landmark findings to these fields. Much work remains to control the African HIV-1 epidemic but the promise of HIV-1 prevention programs that incorporate antiretrovirals and are integrated with reproductive health services are fueling policy makers, researchers and providers to ensure these programs are successfully implemented to achieve great impact.

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DEDICATION

For Matt and Liza Heffron

CHAPTER 1: Introduction

This dissertation addresses unanswered questions about HIV-1 transmission and prevention and will potentially guide HIV-1 prevention program planning with its efforts reduce new HIV-1 infections. In sub-Saharan Africa, an estimated 1.7 million people are newly infected with HIV-1 each year and 61% of HIV-1 infections are in women.[1] The HIV-1 prevention community is engaged to determine best practices for implementing novel antiretroviral-based HIV-1 prevention methods that can be rolled out with widespread coverage and greatly curb the spread of HIV-1 in sub-Saharan Africa.

An important strategy to prevent vertical HIV-1 transmission and improve maternal and child health is for women to avoid unintended pregnancies by using hormonal contraception. Family planning programs have successfully introduced and maintained hormonal contraceptive usage at modest levels in sub-Saharan Africa for nearly 40 years and work is ongoing to increase the level of uptake. Unintended pregnancies currently account for 14-58% of all births in Sub-Saharan Africa and contraception prevents approximately 173,000 neonatal HIV infections per year.[2, 3] Since the most common mode of HIV-1 transmission in Africa is heterosexual intercourse, reproductive health and HIV-1 prevention strategies often have the opportunity to be linked and programs that integrate family planning and HIV-1 prevention are recognized as efficient and cost effective.[4]

There are concerns, however, about whether hormonal contraceptives may increase women's risk of acquiring or transmitting HIV-1 to male partners. The current biologic and epidemiologic data addressing this question provide mixed results and without sufficiently large groups of women with similar behaviors among whom to test for this link, this question has quietly lingered in the minds of reproductive health and HIV-1 prevention specialists without a clear direction forward.[5] Any conclusive data demonstrating an increase in HIV-1 risk would have very important implications.

HIV-1 serodiscordant couples – in which one member is HIV-1 infected and the other is HIV-1 uninfected – can benefit greatly when HIV-1 prevention and reproductive health programs are

integrated. In sub-Saharan African, these couples are not rare – more than half of current HIV-1 infections are estimated to be among people in HIV-1 serodiscordant partnerships – although their discordancy is not always known or disclosed between partners.[1, 6] These couples are at high risk for horizontal and vertical HIV-1 transmission and prime targets for HIV-1 prevention interventions, yet their pregnancy and HIV-1 incidence rates remain as high as 10-20% per year. [7-9] These couples need strategies to reduce their HIV-1 transmission risk when they desire to conceive children and they need safe strategies to prevent pregnancy when they do not desire to conceive.

Novel antiretroviral-based HIV-1 prevention strategies may be appropriate for couples to use to prevent HIV-1 transmission within their partnership and can be used in conjunction with hormonal contraception and during peri-conception periods. These strategies have recently been tested in large HIV-1 prevention clinical trials and proven to work in highly controlled research settings.[10, 11] It is unknown, however, if HIV-1 serodiscordant couples would be willing to use these strategies to lower their HIV-1 risk and how these strategies should be implemented in a real world setting to maximize their uptake and adherence. Identifying couples willing to initiate and adhere to these strategies will be a priority for HIV-1 prevention programs.

We have conducted a series of studies to understand contraceptive use, the relationship between hormonal contraceptive use and HIV-1 risk and HIV-1 serodiscordant couples' fertility desires and perceptions of antiretroviral-based HIV-1 prevention strategies. Using a unique dataset comprised of high quality and detailed information from a prospective study of over 3,400 HIV-1 serodiscordant couples in East and southern Africa (the Partners in Prevention HSV/HIV Transmission Study), longitudinal data analyses were conducted to study correlates of contraceptive use and the relationship between hormonal contraceptive use and HIV-1 acquisition and transmission risk. Additionally, new data collection from an ongoing large prospective HIV-1 prevention study among HIV-1 serodiscordant couples (the Partners PrEP

Study) permitted an investigation of couples' willingness and preferences for antiretroviral-based HIV-1 prevention. Through these studies, we have contributed to the understanding of the relationship between hormonal contraceptive use and HIV-1 risk, and we have begun to understand user preferences related to antiretroviral-based HIV-1 prevention for HIV-1 serodiscordant couples.

Contraceptive use by HIV-1 infected and uninfected women: Chapter 2

What are the patterns and correlates of contraceptive use among women with and at high-risk for HIV-1?

Understanding women's contraceptive choices can improve public health efforts to increase its uptake and long-term use by women. Safe and effective contraception is vital for women's health. Reductions in maternal mortality and morbidity as well as infant health have resulted directly from increases in birth spacing and the prevention of unintended pregnancy. Despite its importance, use of effective contraception remains low among African women, partially due to fertility intentions that are influenced by complex cultural expectations and sexual behavior. Among women with and at-risk for HIV-1 infection, dual contraception, the practice of combining condom use with an effective hormonal contraceptive, is widely recommended to prevent unintended pregnancies and HIV-1 transmission, including prevention of vertical transmission.[4, 12] Strategies to promote uptake and acceptability of dual contraception, however, have often fallen short and hormonal contraceptive use is frequently associated with reduced condom use.[13, 14] Studies have shown that condom use is more often motivated by a desire to prevent pregnancy than sexually transmitted infections and this motivation may be responsible for a decline in condom use when hormonal contraception is initiated.[15, 16] Multinational studies from Africa examining correlates of contraceptive use, particularly the

relationship between contraception and condom use, can be used to tailor counseling for fertility planning and HIV-1 prevention and foster its uptake for HIV-1 serodiscordant couples.

We conducted a longitudinal study of HIV-1 infected and uninfected women in HIV-1 serodiscordant partnerships to examine their contraceptive practices and patterns. The data presented in Chapter 2 highlight the continued need to increase contraceptive uptake among women, identify novel messages to promote dual contraception, and increase the contraceptive method mix that is accessible and acceptable.

Hormonal contraception and HIV-1 risk: Chapter 3

What is the association of hormonal contraceptive use and HIV-1 acquisition risk among women in HIV-1 serodiscordant relationships?

What is the association of hormonal contraceptive use by HIV-1 infected women and the risk of HIV-1 transmission to their male partners?

The prospect that hormonal contraception may increase HIV-1 risk could have important public health implications for women in high HIV-1 risk settings. Some, but not all, observational studies have demonstrated a moderate increase in the risk of HIV-1 acquisition among women using hormonal contraception.[5] Injectable contraceptives, specifically depot medroxyprogesterone acetate (DMPA) with its large progesterone dose and accompanying high systemic levels immediately following administration, have been specifically highlighted as the formulation most commonly associated with increased risk. Epidemiologic studies have been conducted using different methods and most are limited by at least one of the issues presented in Table 1. Prior to 2011, the two studies with arguably the fewest methodological limitations include a study among female sex workers in Mombasa, Kenya [17] and family planning attendees in Uganda and Zimbabwe (Table 2).[14, 18] Both of these studies suggest a moderate increase in HIV-1 risk for women using DMPA but only the study among Kenyan sex workers found increased risk with the use of oral contraceptive pills (OCP).

Table 1. Common methodological limitations in studies of hormonal contraception and HIV-1 risk

1. Inability to discern temporal relationship between contraceptive use and the acquisition of HIV-1 infection
2. Small sample size resulting in imprecision and an inability to disaggregate hormonal contraceptive types
3. Infrequent measurement of hormonal contraceptive use and/or HIV-1 serostatus (i.e. more than 6 months between study visits)
4. Poor follow up rates resulting in selection bias
5. The inclusion of hormonal contraceptive users in the unexposed group
6. Insufficient control of confounding
7. Contraceptive use and condom use data collected via self report without data on adherence, specific brand of contraceptive used or dates when user-independent methods were administered

In response to early studies noting higher HIV-1 infection rates in women using hormonal contraceptives, biologists have conducted experiments to examine potential mechanisms through which hormonal contraceptives could increase HIV-1 susceptibility, including physiologic and/or immunologic changes.[17, 18] Early experiments investigated the effect of exogenous hormones on cervical ectopy and vaginal epithelial thinning as potential biological mechanisms mediating the increase in risk. These findings were not confirmed in studies among women, however.[19] More recent studies have suggested that cytokine regulation may play a role but these also lack definitiveness since multiple cytokines have been identified in different studies and the amount of up or down regulation has been inconsistent.[20-23] The biological experiments investigating this question have been conducted using different animal models, strains of HIV and formulations of exogenous hormones. Thus, similar to the epidemiologic data among women, the biologic evidence from animal and human studies is inconsistent and further research is needed.

Table 2. Highest quality observational studies conducted prior to 2011 of the association of hormonal contraception and HIV-1 acquisition risk

First author, year	Population	Frequency of study visits	Hormonal contraceptive groups assessed	Primary results
Baeten, 2007	Kenya, Sex workers, N=1206	Monthly	OCP, DMPA, none	OCP aHR 1.5 (1.0-2.1) DMPA aHR 1.7 (1.3-2.3)
Morrison, 2007, 2010	Uganda, Zimbabwe Family planning clinic, N= 4439	3-monthly	OCP, DMPA, none	From 2007 analysis: OCP aHR 1.0 (0.7-1.4) DMPA aHR 1.3 (0.9-1.8) From 2010 analysis: OCP aHR 1.2 (0.8-1.8) DMPA aHR 1.5 (1.0-2.2)

OCP: oral contraceptive pills; DMPA: depot medroxyprogesterone acetate; aHR: adjusted hazard ratio

The study that we present in Chapter 3 is longitudinal, among nearly 3800 women with quarterly measurement of contraceptive use, sexual behavior and HIV-1 serostatus, high rates of follow up and we used sophisticated statistical techniques to adjust for confounding factors. Our data demonstrate a two-fold increase in the risk of HIV-1 acquisition among women using injectable contraceptives as well as a two-fold increase in the risk of HIV-1 transmission to men by HIV-1 infected women, which may be partially explained by genital HIV-1 levels. Prior to this dissertation, there has never been a published study with sufficient numbers of HIV-1 serodiscordant couples (where the female is the HIV-1infected partner), longitudinal follow u,p distribution of hormonal contraceptive use and viral linkage data to assess the effect of hormonal contraceptive use by HIV-1 infected women on HIV-1 transmission to male partners.

Accounting for potential confounding by sexual behavior is critical in observational analyses of hormonal contraception and HIV-1 risk. Women who choose to use hormonal contraception have different sexual behaviors than women who do not use hormonal contraception and are inherently at a greater HIV-1 risk due to their sexual behavior. Multivariate proportional hazards regression models have traditionally been used to statistically account for differences in sexual behavior but a new method, marginal structural modeling, may achieve better control when time dependent covariates are confounding factors and intermediary to prior and current exposure.[24, 25] We conducted our study of hormonal contraception and HIV-1 risk employing Cox proportional hazards regression and marginal structural models. For our analysis using marginal structural models, we used time dependent data on sexual behavior and pregnancy to create stabilized weights and redistribute the population in our final model. With the stabilized weights, the distribution of time dependent covariates in the weighted dataset is more similar between exposure groups, mimicking the distribution of these factors that would have resulted if hormonal contraceptive use had been randomized.

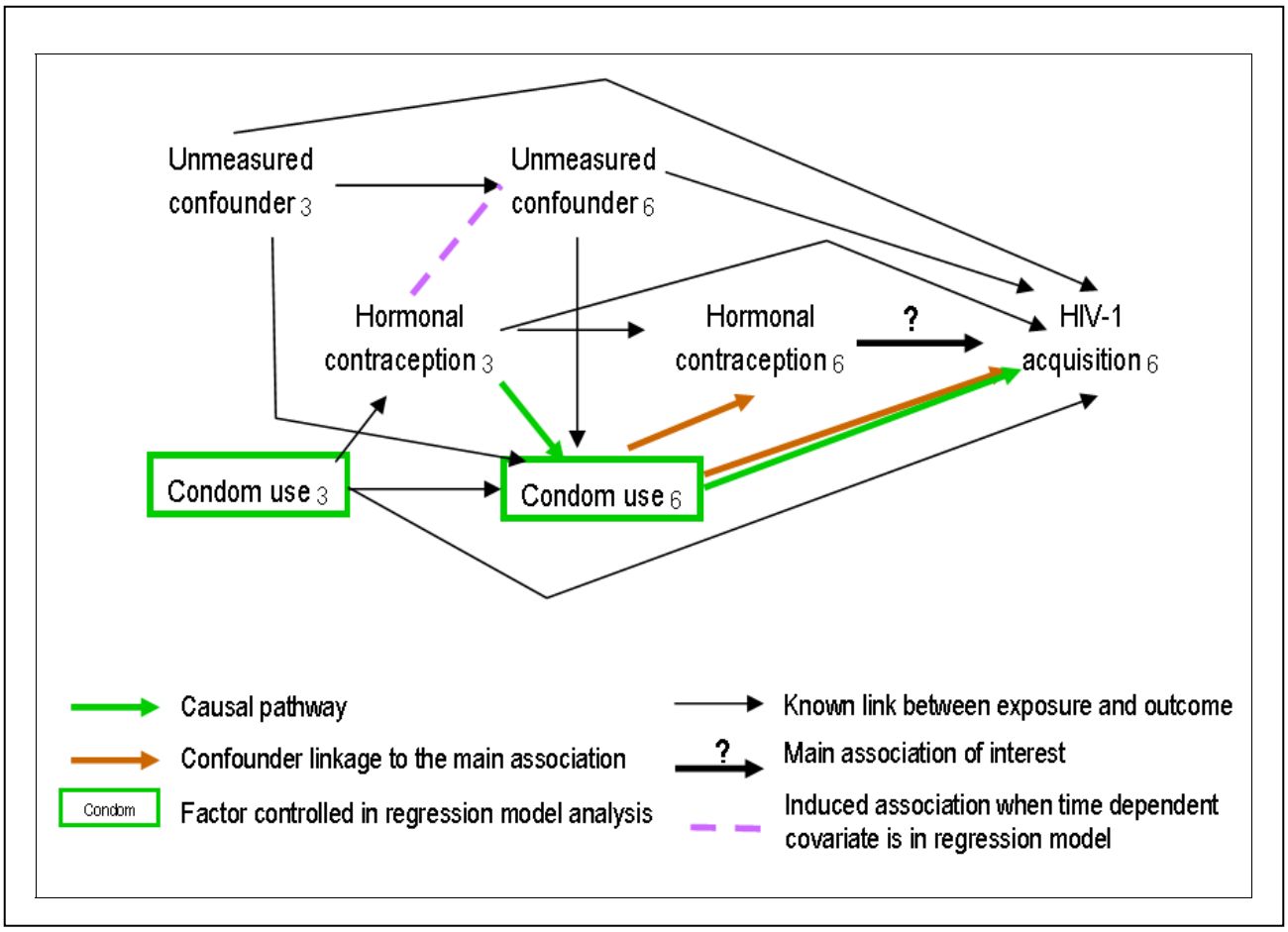
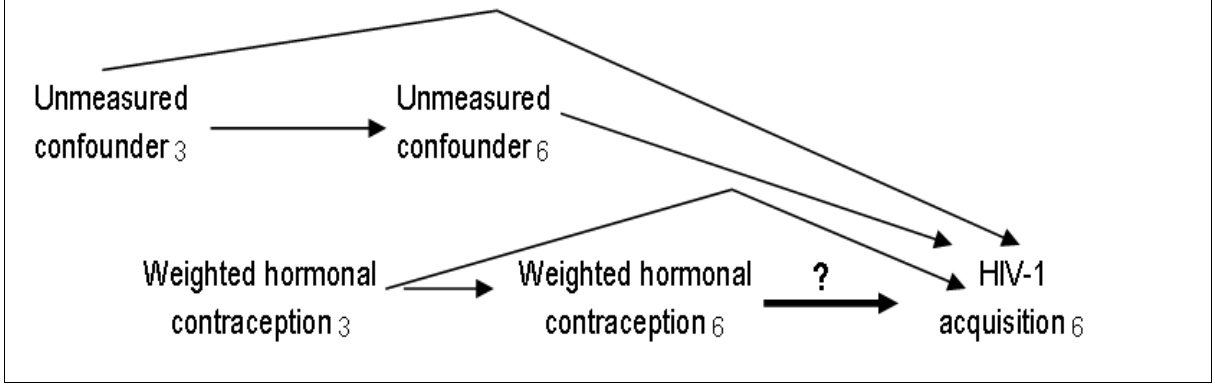


Figure 1. Directed acyclic graph showing relationships of time dependent hormonal contraceptive use and HIV-1 risk utilized by a multivariate Cox proportional hazards model

Directed acyclic graphs (DAGs) can be used to demonstrate the theoretical difference between statistical models represented through Cox proportional hazards models and marginal structural models. The first DAG below (Figure 1) depicts the relationships between hormonal contraceptive use, HIV-1 infection and sexual behavior (i.e. condom use) over two time periods (study months 3 and 6) when Cox modeling is used. Condom use is a time dependent covariate in this model. In our study, pregnancy is also a time dependent covariate but for simplicity, this figure shows only condom use. The red arrows mark the role of condom use as a potential confounder and the green arrows mark the role of past hormonal contraceptive use in predicting current condom use. When a multivariate model adjusts for a covariate that is intermediary to the exposure and outcome, such as condom use is here, an association

between an unmeasured confounder and hormonal contraception is induced because the



unmeasured variable is associated with condom use and HIV-1 acquisition. Thus the inclusion

Figure 2. Directed acyclic graph showing relationships of time dependent hormonal contraception and HIV-1 risk utilized by a marginal structural model

or exclusion of a time dependent covariate in a multivariate Cox model, may result in a biased effect estimate. With a marginal structural model (Figure 2), it is not necessary to include the time dependent covariates in the final regression model because the weights equalize the distribution of the time dependent covariates among exposed and unexposed individuals. In this way, marginal structural modeling accounts for time dependent covariates without including them in the final regression model and is potentially less biased than Cox proportional hazards regression.

Using high quality data and sophisticated statistical techniques, we have conducted one of the largest studies to date of hormonal contraceptive use and HIV-1 risk. Our results have received worldwide attention and sparked passionate debate about the hazardous effects of hormonal contraceptive discontinuation, unintended pregnancy, and HIV-1 risk and the limitations of epidemiologic data to address this question.[26, 27] Guidance from the WHO and Ministries of Health in Kenya and Uganda have been instrumental in assisting HIV-1 prevention and reproductive health providers to navigate the response to our data and provide women with important messages about the importance of using dual contraception.[28, 29]

Antiretroviral-based HIV-1 preferences and fertility desires of HIV-1 serodiscordant couples: Chapter 4 and Chapter 4 Addendum

Are HIV-1 infected partners in HIV-1 serodiscordant partnerships willing to use antiretrovirals and are their HIV-1 uninfected partners willing to use PrEP for an extended period of time for HIV-1 prevention.

What is the level of fertility intention and HIV-1 risk perception among HIV-1 serodiscordant couples and would couples with fertility intentions be willing to use antiretroviral-based HIV-1 prevention?

New strategies for HIV-1 prevention employ antiretrovirals and have the potential to change the course of the HIV-1 epidemic if wide coverage and high levels of adherence are achieved. In 2011, a landmark clinical trial (HPTN 052) found that antiretrovirals nearly eliminated HIV-1 transmission (reducing risk by 96%) when used to suppress HIV-1 viral levels among HIV-1 infected participants [10], demonstrating the utility of antiretrovirals for HIV-1 prevention as well as treatment. A direct outcome from this trial is new WHO guidelines that recommend considerations of antiretrovirals for HIV-1 infected members of HIV-1 serodiscordant couples, regardless of CD4 count, to reduce transmission to the uninfected partner [30]. Despite the tremendous benefits of antiretrovirals for HIV-1 prevention, however, not all HIV-1 infected individuals have demonstrated willingness to initiate antiretrovirals even when they have a clinical need for them.[31-35] For HIV-1 uninfected members of HIV-1 serodiscordant couples, antiretrovirals used as pre-exposure prophylaxis (PrEP) have demonstrated efficacy rates of 75%.[11] PrEP is an important tool for HIV-1 serodiscordant couples to use to provide additional protection to the HIV-1 uninfected partner prior to antiretroviral uptake and/or viral suppression by the HIV-1 infected partner. Adherence is key to HIV-1 prevention with PrEP, as it also is with the use of antiretroviral treatment as prevention.[36] HIV-1 serodiscordant couples are prime populations for targeted HIV-1 prevention interventions that include PrEP and

antiretrovirals due to their natural provision of adherence support to one another and their motivation to protect their unborn child from HIV-1 infection.[37-41]

Couples with future fertility desires need HIV-1 prevention strategies that go beyond consistent condom use and will allow conception. For these couples, antiretroviral-based HIV-1 prevention strategies could provide protection against HIV-1 transmission during peri-conception periods. Identifying these couples and whether their fertility desires are tied to their HIV-1 risk perception can help HIV-1 prevention programs target couples who are most likely to initiate and adhere to antiretroviral-based HIV-1 prevention.

We conducted a cross-sectional survey among HIV-1 infected and uninfected participants in the Partners PrEP Study in Thika, Kenya to determine fertility desires, HIV-1 risk perception and willingness and preferences for antiretroviral-based HIV-1 prevention. The data presented in Chapter 4 highlight the importance of incorporating antiretroviral user preferences into HIV-1 prevention counseling recommendations for couples and suggesting alternatives if a couple or individual is unwilling to adhere to them. In the Chapter 4 addendum, data demonstrate that fertility desires are high and HIV-1 risk perception is low among HIV-1 serodiscordant couples despite their actual high risk for HIV-1 transmission. Research to design and test strategies to promote safer conception by reducing HIV-1 transmission risk during peri-conception periods is urgently needed in resource-limited settings.

There is a great interface between HIV-1 prevention and reproductive health promotion and the results from this dissertation stress the importance of integrating public health programs to achieve greater health improvements. This dissertation addresses unanswered questions about contraceptive choices and fertility desires among women in high HIV-1 risk settings. In addition, it examines a potential link between hormonal contraceptive methods and increases in HIV-1 risk and whether this association is likely mediated by behavioral or biological factors. Finally, it explores the potential for real world use of antiretroviral-based HIV-1 prevention strategies that could remedy potential increases in HIV-1 risk due to hormonal contraceptive use or couples'

desires to conceive a child. The power of antiretrovirals to prevent HIV-1 infection has injected new resolve and momentum into the HIV-1 prevention community. Coupling antiretroviral-based HIV-1 prevention strategies and reproductive health promotion will provide women and men with feasible and acceptable strategies to improve their health and the quality of life for themselves and their children.

CHAPTER 2: A Prospective Study of Contraceptive Use among African Women in HIV-1 Serodiscordant Partnerships

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A Prospective Study of Contraceptive Use among African Women in HIV-1 Serodiscordant Partnerships

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Running head: Contraception in HIV serodiscordant couples

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Short summary: Contraceptive use among African women in HIV-1 serodiscordant partnerships was low and women who used contraception were more likely to report unprotected sex than women who did not use contraception.

Abstract

Background: Dual contraception is important for averting HIV-1 transmission, unintended pregnancy, and maternal-to-child HIV-1 transmission. Few studies have explored contraceptive use in HIV-1 serodiscordant couples, a population at high risk for HIV-1 transmission.

Methods: Data from a prospective study of 3407 women in HIV-1 heterosexual serodiscordant partnerships were analyzed to describe use and correlates of contraception.

Results: Among 2298 HIV-1 seropositive women, 23.5% used contraception at enrollment and 30.2% used contraception after 24 months of follow-up; among 1109 HIV-1 seronegative women, contraceptive use decreased from 21.3% to 14.2%. For both HIV-1 seropositive and seronegative women, contraceptive use was less common among women from East Africa compared to women from southern Africa (adjusted odds ratio [AOR]=0.6, 95% confidence interval [CI]:0.5-0.8 and AOR=0.6, 95% CI:0.4-0.8, respectively) and more common among women with at least one child (AOR=2.4, 95% CI:1.7-3.4 and AOR=2.3, 95% CI:1.2-4.5, respectively). Condom use increased significantly during follow-up from 71.2% to 92.6% and 73.5% to 95.6% among HIV-1 seropositive and HIV-1 seronegative women, respectively, at baseline and 24 months. However, contraceptive use was associated with unprotected sexual activity among both HIV-1 seropositive and seronegative women (AOR=1.3, 95% CI:1.1-1.5 and AOR=1.4, 95% CI:1.1-1.8, respectively), although not among women who initiated contraception during follow-up.

Conclusions: Counseling and provision of dual contraception should receive high priority in programs that care for women in HIV-1 serodiscordant partnerships.

Key words: HIV-1, serodiscordant couples, Africa, contraception, condoms

Introduction

Safe and highly effective contraception is essential for the health of women and their children. For women with or at-risk for HIV-1 infection, dual contraceptive use (i.e., condoms plus a highly effective contraceptive method) has been suggested as the optimal strategy to prevent both pregnancy and HIV-1 transmission. For women with HIV-1, contraceptive use has additionally been recognized as an important but neglected adjunctive method for prevention of HIV-1 transmission from mother to child.[3, 4, 12]

Recent population surveys and mathematical modeling studies suggest that the majority of new HIV-1 transmission in Africa occurs within stable serodiscordant partnerships – i.e., in which one partner is HIV-1 infected and the other is HIV-1 uninfected – making HIV-1 serodiscordant couples a high-risk population for HIV-1 transmission and a key group for targeting HIV-1 prevention strategies.[6] Childbearing expectations, concerns for HIV-1 risk reduction, and personal autonomy may be conflicting considerations for HIV-1 serodiscordant couples weighing contraception and condom use decisions.[42, 43] Notably, some studies among women at-risk for HIV-1 have found the initiation of effective non-condom contraception to be associated with a decrease in condom use.[13, 14, 16]

Little is known about factors that influence contraceptive use among African women in HIV-1 serodiscordant partnerships, and further study is needed to understand the relationship between use of effective contraception and condoms in this population at high risk for HIV-1 transmission. We examined data from a multinational prospective study among African HIV-1 serodiscordant couples to explore determinants of contraceptive use and the association between contraceptive use and sexual risk behavior.

Materials and Methods

Population and procedures. Data were collected as part of the Partners in Prevention HSV/HIV Transmission Study, a randomized, placebo-controlled, HIV-1 prevention trial of daily acyclovir

for herpes simplex virus type 2 (HSV-2) suppression provided to HIV-1/HSV-2 dually-infected members within heterosexual HIV-1 serodiscordant couples.[44] The trial was recently completed and did not demonstrate efficacy of acyclovir suppressive therapy in reducing HIV-1 transmission to the HIV-1 seronegative partners.[45] Longitudinal data on sexual behavior and contraceptive use were used for the present analysis.

Participating couples reported at least three episodes of vaginal intercourse during the three months prior to study screening. HIV-1 seropositive partners were ≥18 years of age, seropositive for HSV-2, had a CD4 count ≥250 cells/mm^3 and no history of AIDS-defining conditions, and were not on antiretroviral therapy (ART). HIV-1 infected women who were pregnant at the time of study screening were excluded from enrollment. HIV-1 seronegative partners were ≥18 years of age. Women and their partners were enrolled at 14 sites in East and southern Africa between December 2004 and May 2007 and follow-up was completed in October 2008.[45]

Study visits occurred monthly for HIV-1 seropositive participants and quarterly for HIV-1 seronegative participants for up to 24 months. As previously reported, 92% of HIV-1 seropositive participants and 84% of HIV-1 seronegative participants were retained in the study for 24 months.[45] Sites offered contraception either on-site and by referral, or both.[46] Although acyclovir has not been associated with safety or teratogenicity concerns in North American and European women,[47] there was limited experience with acyclovir among pregnant women in Africa at the time of study initiation and thus HIV-1 infected women who became pregnant were discontinued from study medication during the pregnancy. CD4 counts were measured every 6 months for HIV-1 seropositive participants. HIV-1 infected participants who met national guidelines for initiation of ART during follow-up were referred to local HIV-1 care clinics.

All participants received comprehensive HIV-1 prevention services, including individual and couples risk reduction counseling, free condoms, and treatment of sexually transmitted

infections. The protocol was approved by institutional review boards at the University of Washington and all study sites. Participants provided written informed consent.

Statistical analysis. All analyses were performed using SAS version 9.2. Data from enrollment and quarterly study visits were included in the analyses; visits were excluded during months when a woman was pregnant and after HIV-1 seroconversion, for those who acquired HIV-1 during follow-up. All analyses were conducted separately for HIV-1 seronegative and seropositive women.

The primary study measure was self-reported use of contraception other than condoms, defined as any current use of an intrauterine device (IUD), tubal ligation or hysterectomy, or an oral, injectable, or implanted hormonal method. Unadjusted trends in contraceptive use during study follow-up were tested via the Cochran-Armitage test for trend. The relationships between contraceptive use and baseline demographic and time-dependent behavioral characteristics were examined using generalized estimating equations (GEE). Univariate models were executed for each covariate and those with significant associations were included in multivariate models. In a secondary analysis, the frequency of sex unprotected by a condom was modeled via GEE with contraceptive use as the predictor of interest. Trends in dual contraceptive use (i.e., use of both a non-condom contraceptive method and 100% condom use during study follow-up periods) were also examined.

Results

A total of 3,407 HIV-1 serodiscordant couples were enrolled, of which 2,298 (67.5%) were couples in which the female partner was HIV-1 seropositive and 1,109 (32.5%) were couples in which the female partner was HIV-1 seronegative. The median duration of follow-up was 18.2 months (interquartile range [IQR] 12.6-24.0) for HIV-1 seropositive women and 19.5 months (IQR 14.3-24.0) for HIV-1 seronegative women. In total, HIV-1 seropositive women

contributed 15,267 visits (median per woman 7, IQR 5-9) for this analysis and HIV-1 seronegative women contributed 7,492 visits (median per woman 7, IQR 5-9). The majority of women were married, <35 years of age, had completed ≤8 years of school, did not earn any income, and had 2 or more children (Table 3).

During follow up, 21.2% of HIV-1 seropositive and 20.7% of HIV-1 seronegative women became pregnant. Pregnancy incidence rates were 16.3 (95% CI 14.9-17.7) and 15.6 (95% CI 13.6-17.6) per 100 person-years, for HIV-1 seropositive and seronegative women, respectively. Among HIV-1 seropositive women, 9.5% commenced ART during follow up; among HIV-1 seronegative women, 10.8% of their partners commenced ART during follow up.

Contraceptive use during follow-up. At baseline, 23.5% of HIV-1 seropositive women and 21.3% of HIV-1 seronegative women were using some form of non-condom contraception (Table 4). The prevalence of contraception was higher for women from southern Africa (29.9% of HIV-1 seropositive and 28.9% of HIV-1 seronegative women) compared with those from East Africa (20.1% of HIV-1 seropositive and 17.8% of HIV-1 seronegative women), with variation in prevalence of use across the study sites. After enrollment, non-condom contraceptive use was reported at 28.9% of visits attended by HIV-1 seropositive women and 17.1% of visits attended by HIV-1 seronegative women. Overall, 11.7% and 7.1% of HIV-1 seropositive and seronegative women, respectively, reported non-condom contraceptive use at every visit, and an additional 33.5% and 27.5% reported contraceptive use for part of their follow up (Table 3). The most common contraceptive method used was injectable methods (reported at 17.1% of visits by HIV-1 seropositive women and 9.0% of visits HIV-1 seronegative women) followed by oral methods (4.6% and 3.3%, respectively), tubal ligation or hysterectomy (4.4% and 3.4%), implants (1.3% and 1.0%), and IUDs (0.7% and 1.1%). Among all visits by HIV-1 seropositive women at which contraceptive use was reported, injectable methods were used at 60.9% of those visits, oral methods at 16.3%, tubal ligation or hysterectomy at 15.8%, implants at 4.4%

and IUD at 2.5%. For visits by HIV-1 seronegative women at which contraceptive use was reported, injectable methods were used at 50.5% of visits, hysterectomy or tubal ligation at 19.0%, oral methods at 18.6%, IUD at 6.2% and implants at 5.7%. Among HIV-1 seropositive women, the prevalence of contraceptive use rose significantly during the follow-up period to 30.2% at month 24 (Cochran Armitage test for trend $p<0.0001$, Figure 3) and decreased for HIV-1 seronegative women to14.2% at month 24 ($p=0.0003$, Figure 4).

Sexual behavior. Women reported sex with their study partner at most study visits (80.9% of visits by HIV-1 seropositive women and 83.9% of visits by HIV-1 seronegative women). However, sex unprotected by a condom was reported relatively infrequently. As a fraction of all study visits, unprotected sex was reported at 12.7% of visits by HIV-1 seropositive women and at 10.2% of visits by HIV-1 seronegative women, and only 9.9% and 7.3%, respectively, at study visits after the enrollment visit. However, 26.1% of HIV-1 seropositive women and 25.1% of HIV-1 seronegative women reported unprotected sex at least once after the enrollment visit.

Correlates of contraceptive use during follow-up. In multivariate analysis, contraceptive use among HIV-1 seropositive women was less frequent among those from East Africa (adjusted odds ratio [AOR]=0.6, 95% confidence interval [CI]: 0.5–0.8) and by women who were 45 years and older (AOR=0.3, 95% CI: 0.2–0.5), currently married to their study partner (AOR=0.8, 95% CI: 0.6–1.0), and who reported a live birth since their last study visit (AOR=0.6, 95% CI: 0.4–0.9) (Table 5). Contraceptive use was more common among those with at least one child living (AOR=2.4, 95% CI: 1.7–3.4 among women with one child and AOR=4.6, 95% CI: 3.3–6.3 among women with two or more children). Women who reported unprotected sex with their study partner during the prior month (AOR=1.3, 95% CI: 1.1–1.5) and women who reported sex with an outside partner during the past month (AOR=2.0, 95% CI: 1.3–3.2) were more likely to use contraception.

Among HIV-1 seronegative women, contraceptive use was significantly less frequent among those from East Africa (AOR=0.6, 95% CI: 0.4-0.8) and who reported a live birth since their last study visit (AOR=0.1, 95% CI: 0.0–0.3) and was significantly more common among those with one or more children living (AOR=2.3, 95% CI: 1.2–4.5 among women with one child and AOR=3.3, 95% CI: 1.7–6.3 among women with two or more children) and among women who reported unprotected sex with their study partner during the prior month (AOR=1.4, 95% CI: 1.1–1.8).

Characteristics of male partners were also examined, including partner age, difference in age between the male and female members of the couple, education level, income, number of children, and sexual partners other than their study partner, but none of these factors was significantly related to contraceptive use by the HIV-1 seropositive and seronegative female partners (data not shown).

Dual contraceptive use and the association between unprotected sex and contraceptive use. Dual contraceptive use was reported at 23.5% and 15.8% of visits by HIV-1 seropositive and seronegative women, respectively. Among HIV-1 seropositive women, the prevalence of dual contraceptive use increased during the study period (test for trend $p<0.0001$) while there was no change over time among HIV-1 seronegative women (test for trend $p=0.7$), consistent with the overall trend in contraceptive use reported above. Condom use for 100% of sex acts during the prior month increased during the course of study: for the comparison of baseline to the 24 month follow-up visit from 71.2% to 92.6% for HIV-1 seropositive women and from 73.5% to 95.6% for HIV-1 seronegative women (test for trend $p<0.0001$ for both).

For visits at which women reported sex with their study partner (Table 6), unprotected sex was more likely to occur at those visits at which contraception was used (AOR=1.3 for both HIV-1 seropositive and seronegative women). To more-precisely understand the relationship between contraceptive use and unprotected sex, we repeated this analysis among the subset of

women who used contraception inconsistently during the study period (thus, excluding those women who either always or never used contraception, who might have been otherwise behaviorally different from each other). Among inconsistent contraceptive users, there was no statistically significant increase in the occurrence of unprotected sex when contraception was used. Moreover, among the smaller subset of women who initiated contraception during the study (i.e., who were not using contraception at enrollment but reported use during follow up), unprotected sex was reported significantly less frequently at visits where contraception was used (12.7% vs. 17.1% for HIV-1 seropositive women, AOR=0.7, 95% CI: 0.5–0.9, and 9.4% vs. 20.1% for HIV-1 seronegative women, AOR=0.4, 95% CI: 0.3–0.7).

Discussion

In this large, prospective study of contraceptive use among African women in HIV-1 serodiscordant partnerships, we observed a low prevalence of contraceptive use at the study outset that increased among HIV-1 seropositive women but not among HIV-1 seronegative women. Contraceptive use was more common among women from southern Africa (compared with East Africa) and among women who had children. A concerning finding was that, unprotected sex was more likely to be reported by women using contraception. Condom use increased significantly during the study period, for both HIV-1 seropositive and seronegative women.

Contraceptive use in this study was similar to that detailed in a recent UNICEF report which described an overall contraceptive prevalence of 30% among women in southern and East Africa.[48] Recent Demographic and Health Survey reports have shown that contraceptive use is more common in southern Africa than Eastern Africa (32.7% among married women in Zambia and 59.8% in South Africa compared with 17.9% in Uganda and 31.5% in Kenya).[49-52] These trends may reflect regional differences in community norms about fertility,

acceptability and availability of condoms and contraceptive methods, and uptake of contraception by women who have reached their desired fertility.

Among both HIV-1 seropositive and HIV-1 seronegative women, we found that contraceptive use was associated with a modestly increased likelihood of unprotected sexual activity. This finding is consistent with previous reports describing trade-offs between contraception and condoms in high-risk populations.[13, 53] However, we did not find this association between unprotected sex and contraception among women who intermittently used contraception during the study, particularly among those who initiated contraception during study follow-up, for whom unprotected sex was actually less common when contraception was used. Together, these results suggest that women in HIV-1 serodiscordant partnerships can successfully initiate contraception accompanied by consistent condom use. We recently reported on the successful implementation of a multipronged family planning intervention that included staff training, couples family planning sessions, and free provision of hormonal contraception at one of the sites in the present study, an intervention that resulted in significantly increased nonbarrier contraceptive uptake and reduced pregnancy incidence among both HIV-1 seropositive and seronegative women.[46]

We found contraceptive use to be more common among women who had children, perhaps indicating more acceptability of fertility control once cultural childbearing norms have been achieved. An additional striking finding of our study was that contraception was less commonly used by women who had recently given birth. While lactational amenorrhea may delay subsequent pregnancies among these women, it is not as effective a contraceptive method as those considered in this study. Further attention is needed to missed opportunities during postnatal care and prevention of mother-to-child treatment counseling for the promotion of highly effective contraceptive uptake after delivery and in the postnatal period.

Contrary to an increased trend in contraceptive uptake among HIV-1 seropositive women in our cohort, the prevalence of contraceptive use decreased among HIV-1 seronegative

women over the course of the study. This may be a reflection of the frequency of study visits and hence HIV-1 prevention counseling (HIV-1 seropositive women were seen monthly while HIV-1 seronegative women were seen quarterly), differences in fertility intentions among HIV-1 seropositive and seronegative women, and a greater level of contraceptive promotion directed towards HIV-1 seropositive women by study sites, as HIV-1 seropositive women who became pregnant were required to discontinue study drug.

This study had many strengths including being a large, geographically diverse cohort of an HIV-1 high-risk population with uniform data collection and high retention over 24 months of follow-up. That the primary context for the study was a clinical trial may somewhat limit the generalizability of the findings, since the frequency of contact with participants was greater than could be expected in general clinic settings.[54] Additional limitations are that fertility intentions or perceptions of contraception were not assessed and self-report of contraception was not validated. Future inclusion of questions to address these variables would strengthen the use of these data in public health settings. Better understanding of contraceptive method choice for women with or at-risk of HIV-1 is also needed, as greater acceptability and accessibility of non-user dependent contraceptive methods, such as implants and IUDs, may offer more consistent and longer-term pregnancy prevention.

In summary, our findings about use, correlates, and temporal trends of contraceptive and condom use among African women in HIV-1 serodiscordant partnerships indicate that even in the context of regular HIV-1 prevention and couples counseling, dual contraceptive use was modest among HIV-1 infected women and decreased among HIV-1 uninfected women. Additional efforts are needed to understand fertility desires and behaviors and to increase dual contraception uptake, particularly of non-user dependent methods, in order to reduce unintended pregnancies among this population at high risk of HIV transmission and pregnancy. As dual contraceptive use has great potential to prevent unintended pregnancy and avert new

HIV-1 infections, it should be a high priority for programs counseling women in HIV-1 serodiscordant partnerships.

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Table 3. Characteristics of HIV-1 seropositive and seronegative women

Baseline characteristics				
	HIV-1 seropositive		HIV-1 seronegative	
	N	%	N	%
Region				
Eastern Africa	1486	64.7	763	68.8
Southern Africa	812	35.3	346	31.2
Age, years				
18-24	523	22.8	245	22.1
25-34	1214	52.9	491	44.3
35-44	445	19.4	279	25.2
≥ 45	115	5.0	94	8.5
Years of school completed				
≤ 8	1358	59.1	690	62.2
> 8	940	40.9	419	37.8
Earned any income				
Yes	565	24.6	288	26.0
No	1733	75.4	821	74.0
Total number of living children				
0	284	12.4	95	8.6
1	579	25.2	220	19.8
≥ 2	1435	62.5	794	71.6
Currently married to study partner				
Yes	1682	73.2	895	80.7
No	616	26.8	214	19.3
CD4 count, cells/mm^3				
≥ 500	1078	46.9	--	--
350–499	673	29.3	--	--
250–349	547	23.8	--	--
Partner CD4 count, cells/mm^3				
≥ 500	--	--	388	35.0
350–499	--	--	389	35.1
250–349	--	--	332	29.9
Characteristics during study follow-up				
Non-condom contraception pattern				
Used at every visit	269	11.7	79	7.1
Used at first visit with some use at follow up visits	272	11.8	157	14.2
No use at first visit with some use at follow up visits	498	21.7	147	13.3
Did not use at any visit	1259	54.8	726	65.5
Pregnant during follow up				
Yes	488	21.2	230	20.7
No	1810	78.8	879	79.3
Unprotected sex with study partner				
Yes	586	26.1	274	25.1
No	1662	73.9	818	74.9
Sex with outside partner				
Yes	257	11.4	84	7.7
No	1991	88.6	1009	92.3
Unprotected sex with outside partner				
Yes	224	10.0	56	5.1
No	2024	90.0	1037	94.9
Took antiretroviral medications, at any point during follow-up				
Yes	214	9.5	--	--
No	2033	90.5	--	--
Partner took antiretroviral medications, at any point during follow-up				
Yes	--	--	117	10.8
No	--	--	962	89.2

Table 4. Prevalence of contraceptive use at baseline and during follow-up among HIV-1 seropositive and HIV-1 seronegative women

	Baseline (% of visits)				Follow up (% of visits)			
	HIV-1 +		HIV-1 -		HIV-1 +		HIV-1 -	
Eastern Africa	298	20.1	136	17.8	2365	26.1	679	14.6
Kenya								
Eldoret	36	19.8	16	18.6	235	21.1	70	13.7
Kisumu	41	12.5	37	18.1	248	12.1	156	12.0
Nairobi	55	17.1	24	25.5	512	24.9	60	10.6
Thika	47	29.6	20	37.0	556	57.7	136	41.7
Rwanda								
Kigali	21	25.3	9	12.9	109	33.3	54	18.2
Tanzania								
Moshi	51	28.2	9	24.3	268	28.3	50	24.5
Uganda								
Kampala	47	20.4	21	9.6	437	27.4	153	10.6
Southern Africa	243	29.9	100	28.9	1384	35.5	411	23.7
Botswana								
Gaborone	40	19.6	24	19.8	275	24.4	110	16.3
South Africa								
Cape Town	62	40.3	22	52.4	287	45.1	84	45.2
Soweto	55	30.2	14	24.1	500	46.4	78	22.9
Orange	19	35.9	4	20.0	85	37.1	21	21.4
Zambia								
Kitwe	9	14.8	9	30.0	36	14.1	24	17.8
Lusaka	26	56.5	12	46.2	75	49.3	35	37.2
Ndola	32	28.6	15	30.6	126	30.0	59	29.1
All sites	541	23.5	236	21.3	3749	28.9	1090	17.1

Table 5. Univariate and multivariate associations between baseline and time-varying characteristics and contraceptive use during the study period

	HIV- 1 seropositive women					HIV-1 seronegative women				
		Univariate		Multivariate			Univariate		Multivariate	
	n/N (%) visits with contraception	OR (95% CI)	p-value	AOR (95% CI)	p-value	n/N (%) visits with contraception	OR (95% CI)	p-value	AOR (95% CI)	p-value
Region of Africa										
East	2663/10547 (25.3)	0.6 (0.5–0.8)	<0.0001	0.6 (0.5–0.8)	<0.0001	815/5408 (15.1)	0.5 (0.4–0.7)	<0.0001	0.6 (0.4–0.8)	0.0006
Southern	1627/4711 (34.5)	1.0	Referent	1.0	Referent	511/2079 (24.6)	1.0	Referent	1.0	Referent
Age										
18-24	724/2757 (26.3)	1.0	Referent	1.0	Referent	182/1395 (13.1)	1.0	Referent	1.0	Referent
25-34	2466/8285 (29.8)	1.2 (1.0–1.4)	0.08	0.9 (0.7–1.1)	0.2	596/3340 (17.8)	1.4 (1.0–2.1)	0.04	1.2 (0.8–1.7)	0.4
35-44	966/3386 (28.5)	1.1 (0.9–1.4)	0.4	0.7 (0.6–0.9)	0.02	429/1990 (21.6)	1.8 (1.2–2.7)	0.002	1.3 (0.9–2.0)	0.2
≥45	129/825 (15.6)	0.5 (0.3–0.8)	0.005	0.3 (0.2–0.5)	<0.0001	119/793 (15.6)	1.2 (0.7–2.1)	0.4	0.8 (0.5–1.5)	0.6
Total number of children living										
0	208/1729 (12.01)	1.0	Referent	1.0	Referent	42/567 (7.4)	1.0	Referent	1.0	Referent
1	912/3780 (24.1)	2.3 (1.7–3.3)	<0.0001	2.4 (1.7–3.4)	<0.0001	221/1427 (15.5)	2.3 (1.2–4.6)	0.02	2.3 (1.2–4.5)	0.02
≥2	3170/9749 (32.5)	3.5 (2.6–4.8)	<0.0001	4.6 (3.3–6.3)	<0.0001	1063/5493 (19.4)	3.0 (1.6–5.6)	0.0007	3.3 (1.7–6.3)	0.0003
Currently married to study partner										
Yes	3053/11586 (26.4)	0.7 (0.6–0.8)	<0.0001	0.8 (0.6–1.0)	0.02	1015/6170 (16.5)	0.6 (0.5–0.9)	0.003	0.8 (0.6–1.2)	0.3
No	1237/3672 (33.7)	1.0	Referent	1.0	Referent	311/1317 (23.6)	1.0	Referent	1.0	Referent
Reported unprotected sex with study partner *										
Yes	643/1939 (33.1)	1.3 (1.1–1.5)	0.0006	1.3 (1.1–1.5)	0.0009	171/760 (22.5)	1.4 (1.1–1.8)	0.005	1.4 (1.1–1.8)	0.01
No	3647/13319 (27.4)	1.0	Referent	1.0	Referent	1153/6719 (17.2)	1.0	Referent	1.0	Referent
Reported sex with outside partner *										
Yes	206/593 (34.7)	1.4 (1.1–1.8)	0.02	2.0 (1.3–3.2)	0.002	37/177 (20.9)	1.3 (0.7–2.3)	0.4		
No	4084/14664 (27.9)	1.0	Referent	1.0	Referent	1161/6762 (17.2)	1.0	Referent		
Reported unprotected sex with outside partner *										
Yes	160/480 (33.3)	1.3 (1.0–1.7)	0.09	0.6 (0.4–1.0)	0.07	18/95 (19.0)	1.1 (0.5–2.3)	0.8		
No	4130/14777 (28.0)	1.0	Referent	1.0	Referent	1180/6844 (17.2)	1.0	Referent		
Gave birth since last visit*										
No	4216/14948 (28.2)	1.0	Referent	1.0	Referent	1321/7295 (18.1)	1.0	Referent	1.0	Referent
Yes, live birth	36/191 (18.9)	0.6 (0.4–0.9)	0.004	0.6 (0.4–0.9)	0.005	2/169 (1.2)	0.1 (0.0–0.2)	<0.0001	0.1 (0.0–0.3)	0.0002
Yes, not a live birth	38/115 (33.0)	1.3 (0.8–1.9)	0.3	1.1 (0.8–1.7)	0.5	3/22 (13.6)	0.7 (0.2–2.4)	0.5	0.4 (0.1–1.9)	0.2
CD4 count *(results shown for HIV- women are the CD4 count of her partner)*, cells/mm^3*										
≥500	1810/6290 (28.8)	1.0	Referent			*398/2246 (17.7)*	*1.0*	*Referent*		
350-499	1166/4185 (27.9)	1.0 (0.8–1.1)	0.6			*379/2162 (17.5)*	*1.0 (0.8–1.3)*	*0.9*		
250-349	847/3018 (28.1)	1.0 (0.8–1.2)	0.7			*300/1749 (17.2)*	*1.0 (0.7–1.3)*	*0.8*		
< 250	308/1130 (26.9)	0.9 (0.7–1.2)	0.5			*119/660 (18.0)*	*1.1 (0.7–1.5)*	*0.9*		
ART use since last visit for non PMTCT reasons *(results shown for HIV- women are the ART use of her partner)**										
Yes	158/592 (26.7)	0.9 (0.7–1.3)	0.6			*68/354 (19.2)*	*1.1 (0.7–1.8)*	*0.7*		
No	4129/14662 (28.2)	1.0	Referent			*1173/6698 (17.5)*	*1.0*	*Referent*		

*Time varying characteristic.

Table 6. Association between contraceptive use and sex unprotected by condoms

	HIV-1 seropositive women					HIV-1 seronegative women				
		Univariate		Multivariate			Univariate		Multivariate	
	n/N (%) visits with unprotected sex	OR (95% CI)	p-value	AOR (95% CI)*	p-value	n/N (%) visits with unprotected sex	OR (95% CI)	p-value	AOR (95% CI)*	p-value
Non-condom contraception among all women										
Yes	643/3545 (18.1)	1.3 (1.1–1.5)	0.002	1.3 (1.1–1.5)	0.002	171/1165 (14.7)	1.3 (1.0–1.7)	0.02	1.3 (1.0–1.7)	0.03
No	1296/8792 (14.7)	1.0	Referent	1.0	Referent	589/5112 (11.5)	1.0	Referent	1.0	Referent
Non-condom contraception among inconsistent contraceptive users										
Yes	362/2125 (17.0)	1.1 (0.9–1.3)	0.4	1.1 (0.9–1.3)	0.6	114/742 (15.4)	1.1 (0.8–1.5)	0.6	1.1 (0.8–1.5)	0.5
No	346/2178 (15.9)	1.0	Referent	1.0	Referent	143/1004 (14.2)	1.0	Referent	1.0	Referent
Non-condom contraception among inconsistent contraceptive users who entered the study not using contraception but used contraception at some time during follow up										
Yes	173/1358 (12.7)	0.7 (0.5–0.9)	0.01	0.7 (0.5–0.9)	0.003	33/350 (9.4)	0.4 (0.3–0.7)	0.0002	0.4 (0.3–0.7)	0.0002
No	254/1489 (17.1)	1.0	Referent	1.0	Referent	93/463 (20.1)	1.0	Referent	1.0	Referent

*AOR are in a multivariate model including region, age, children, marital status and pregnancy.
Analyses restricted only to those visits at which women reported any sex with their study partner.

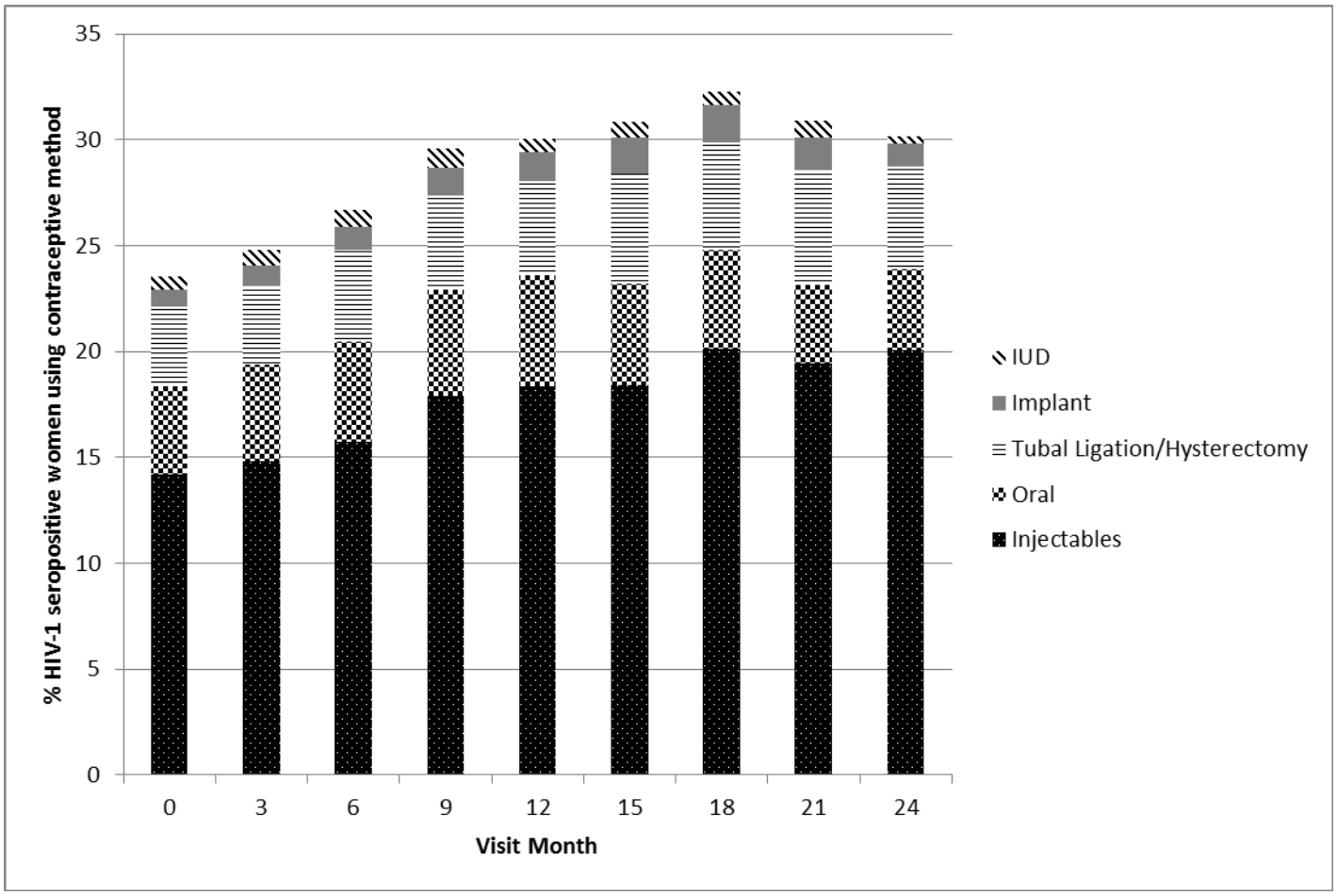

Figure 3. Contraceptive use prevalence by study visit month in HIV-1 seropositive women

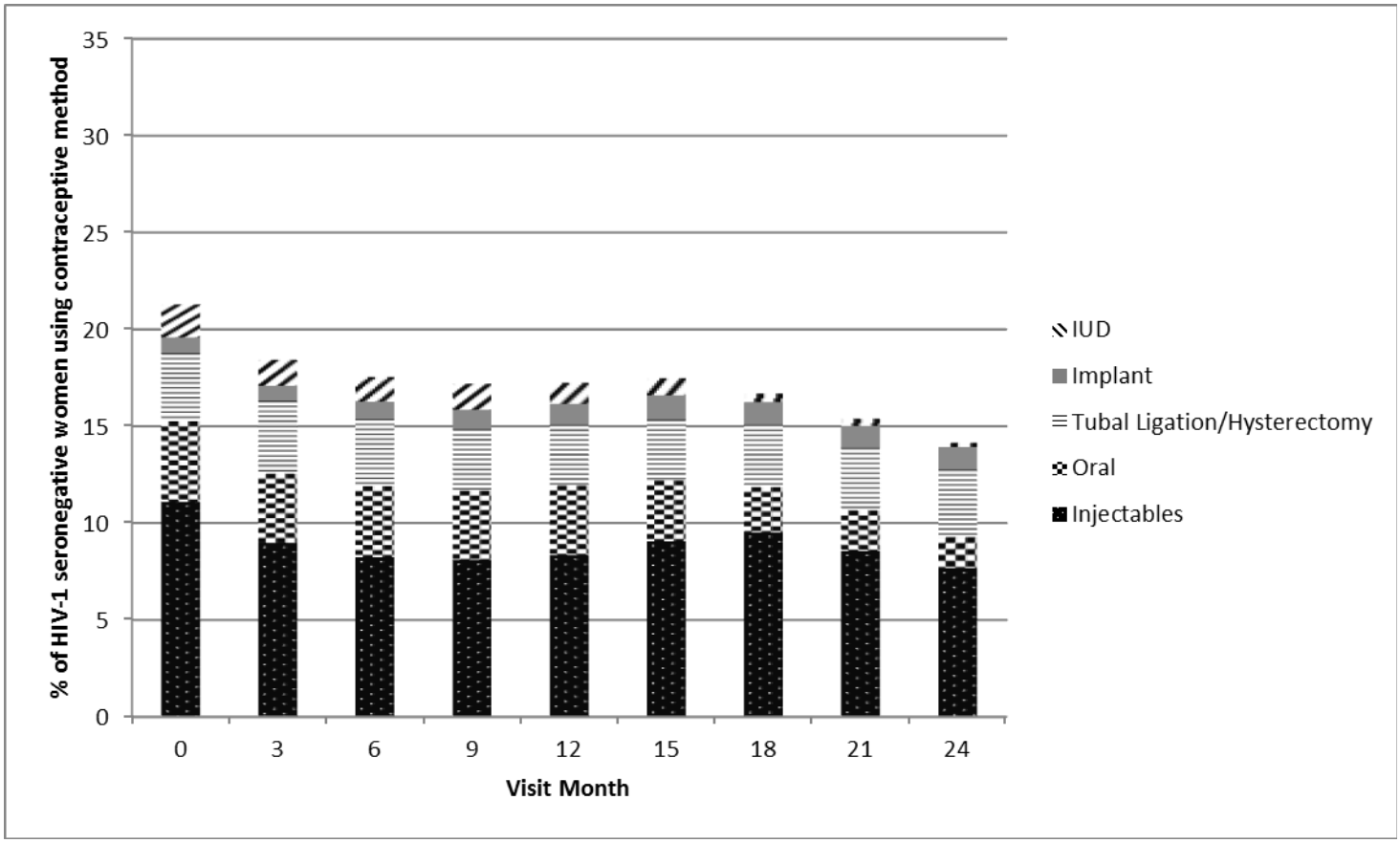

Figure 4. Contraceptive use prevalence by study visit month in HIV-1 seronegative women

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CHAPTER 3: Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis

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Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis

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Summary

Background: Hormonal contraceptives are used widely but their effects on HIV-1 risk are unclear.

Methods: In this prospective study, we followed up 3790 heterosexual HIV-1 serodiscordant couples participating in two longitudinal studies of HIV-1 incidence in seven African countries. Among injectable and oral hormonal contraceptive users and nonusers, we compared rates of HIV-1 acquisition by women and HIV-1 transmission from women to men. We used Cox proportional hazards regression and marginal structural modeling to assess the effect of contraceptive use on HIV-1 risk.

Findings: Among 1314 couples in which the HIV-1 seronegative partner was female (median follow-up 18.0 [IQR 12.6 – 24.2] months), rates of HIV-1 acquisition were 6.61 per 100 person-years in women who used hormonal contraception and 3.78 per 100 person-years in those who did not (adjusted hazard ratio 1.98, 95% CI 1.06-3.68, p=0.03). Among 2476 couples in which the HIV-1 seronegative partner was male, HIV-1 transmission rates from women to men were 2.61 per 100 person-years in couples in which women used hormonal contraception and 1.51 per 100 person-years in couples in which women did not use hormonal contraception (adjusted hazard ratio 1.97, 95% CI 1.12-3.45, p=0.02). Marginal structural model analyses generated much the same results to the Cox proportional hazards regression.

Interpretation: Women should be counseled about potentially increased risk of HIV-1 acquisition and transmission with hormonal contraception, especially injectable methods, and about the importance of dual protection with condoms to decrease HIV-1 risk. Non-hormonal or

low-dose hormonal contraceptive methods should be considered for women with or at-risk for HIV-1.

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Key words: HIV-1, serodiscordant couples, Africa, hormonal contraception

Introduction

Safe and effective family planning services are central to initiatives to reduce unintended pregnancies, promote economic development, and improve the health of women and children worldwide. Among women with and at-risk for HIV-1, the prevention of unintended pregnancy is a key component of strategies to reduce vertical HIV-1 transmission.[55, 56]

Hormonal contraceptive methods, including daily oral pills and long-acting injectables, are used by >140 million women worldwide.[57] During the past two decades, epidemiologic and laboratory studies have suggested that hormonal contraception could alter the risk of HIV-1 acquisition in women.[14, 17, 58-60] However, results have been inconsistent.[5] Only one study has addressed the effect of hormonal contraception and risk of HIV-1 transmission from women to men.[61] Increased HIV-1 risk related to hormonal contraceptive use would be of importance to global public health because of the large number of women using such methods. WHO has called for high-quality studies to assess the potential role of hormonal contraception in increased HIV-1 risk.[62, 63] We aimed to assess the association between hormonal contraceptive use and risk of HIV-1 acquisition by women and HIV-1 transmission from HIV-1 infected women to their male partners.

Methods

Study design and participants. From 2004-2010, we did two prospective studies of HIV-1 incidence among African HIV-1 serodiscordant couples (i.e. one partner with HIV-1 infection and one partner without). The Partners in Prevention HSV/HIV Transmission Study was a randomized, placebo-controlled, clinical trial of daily acyclovir herpes simplex virus type 2 (HSV-2) suppressive therapy provided to 3408 people with HIV-1 and HSV-2 as an intervention to reduce HIV-1 transmission to their heterosexual HIV-1 seronegative partners (Clinicaltrials.gov

#NCT00194519); acyclovir did not significantly reduce HIV-1 transmission.[64] Couples were from seven countries in East and southern Africa (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda and Zambia) and were followed for up to 24 months. In a parallel study at two of the clinical trial sites (Kampala, Uganda and Soweto, South Africa), we enrolled an additional 485 HIV-1 serodiscordant couples into an observational study of immune correlates of HIV-1 protection and followed them for up to 12 months. For both studies, participants were ≥18 years of age and sexually active. HIV-1 seropositive partners had no history of AIDS-defining disorders and were not using antiretroviral therapy (ART), the HIV-1 seropositive partners in the clinical trial had a CD4 count ≥250 cells/mm^3, were seropositive for HSV-2, had no known history of adverse reactions to acyclovir, and were not pregnant. Couples were recruited through study-initiated community outreach activities and referrals from HIV-1 testing and care centers, antenatal clinics, and non-governmental organizations.[65] The main reasons couples did not enroll were that they did not meet the CD4 count, HSV-2, pregnancy, or sexual activity eligibility criteria.[44]

HIV-1 uninfected partners were seen quarterly for HIV-1 serologic testing. For HIV-1 infected partners, CD4 counts were measured every six months, and participants eligible for ART initiation during follow-up were referred to local HIV-1 care clinics. All participants received comprehensive HIV-1 prevention services, including individual and couples counseling, free condoms, and treatment of sexually transmitted infections (STI). Contraceptives were offered by referral or on-site. Differences in contraceptive use occurred between sites.[66, 67]

We excluded enrolled patients who were subsequently reported to not have HSV-2 or HIV-1 infection and couples for whom the HIV-1 uninfected participant did not complete any follow-up visits for assessment of HIV-1 seroconversion. We also censored visits for couples for whom the HIV-1 infected partner started ART, because such treatment eliminated HIV-1 risk in the

study population.[68] The protocols were approved by institutional review boards at the University of Washington and collaborating institutions at each study site. Participants provided written informed consent.

Procedures. Rapid HIV-1 antibody tests were used for HIV-1 serologic testing and positive results were confirmed by ELISA.[64] For HIV-1 seroconverters, analysis of HIV-1 *env* and *gag* sequences from both members of the couple was used to establish whether transmission was linked within the partnership.[69] Nucleic-acid-amplification testing for bacterial STI was performed on samples collected from both partners at study enrollment.[44] All participants were tested for HSV-2 using HerpeSelect-2 EIA (Focus Technologies, Cypress, CA, USA) or by HSV-specific Western blot.[70] CD4 quantification was done with standard flow cytometry. Plasma HIV-1 RNA concentrations were quantified from a sample collected at study enrollment and six months later using the COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN). Concentrations of endocervical HIV-1 were quantified with the COBAS assay of swab samples collected six months after enrollment from HIV-1 infected women in the clinical trial cohort, as previously detailed.[71] The lower quantification limit for HIV-1 RNA testing was 240 copies.

At each quarterly study visit, women were asked about their current contraceptive method with a standard questionnaire. Women were classified as exposed to hormonal contraception for each quarterly period if they reported hormonal use at the quarterly visit. Contraceptive use was analyzed as a time-dependent exposure, with women assumed to have used the same method during the 3 months that elapsed between study visits. Analyses were done for exposure to any hormonal contraception and then separately for injectable and oral contraception; the comparison group was women not using hormonal contraception, which included women who had had a hysterectomy or tubal ligation, used condoms only, or used no contraceptive method.

Visits at which women reported use of implantable hormonal methods or an intrauterine device (IUD) were rare (<2% of visits) and therefore excluded. Many women reported condom use, either with or without another method for contraception; condom use was thus included in analyses as a potential confounder. HIV-1 uninfected men were classified as exposed to hormonal contraception if their HIV-1 infected female partner reported using an injectable or oral method at her corresponding study visit. For 4% of male follow-up time, missing contraceptive data from their female partners were imputed to be the method consistently reported at adjacent study visits; data were not imputed if methods during adjacent periods were inconsistent.

Statistical analysis. The primary outcome measure was HIV-1 seroconversion. We did separate analyses of the association of hormonal contraception with HIV-1 acquisition by women (male-to-female transmission) and HIV-1 transmission from women to men (female-to-male transmission). For female-to-male transmission, only genetically-linked seroconversions were included as outcomes to minimize misclassification of HIV-1 transmissions from outside partners with unknown hormonal contraceptive use, and follow-up time was censored for those men at the time they acquired HIV-1 from a partner other than the HIV-1 infected partner with whom they enrolled.

We compared participant characteristics during periods of hormonal contraceptive use and non-use using generalized estimating equations. To assess the effect of contraceptive method on HIV-1 risk, we used time-dependent Cox proportional hazards regression with robust standard errors to account for within subject correlation with repeated measurements.[72] Models were adjusted for variables that have confounded the contraception-HIV-1 risk relationship in prior analyses[14, 17] – age and time-dependent pregnancy and any sex without condoms – and plasma HIV-1 levels in the HIV-1 infected partner, a strong predictor of HIV-1 transmission.[73] We also assessed several additional variables for potential confounding: region (East versus

southern Africa), marital status of the couple and the number of children they had together, HSV-2 status of the HIV-1 uninfected partner, circumcision status of the male partner, and STI in either partner, all recorded at study enrollment, and time-dependent measures of sexual frequency (with and without condoms), sex with additional partners, CD4 count of the HIV-1 infected partner, and genital ulcer disease in either partner. None of these additional variables substantially (>10%) changed the effect estimates and thus they were not included in the final multivariate models. For analysis of HIV-1 acquisition in women, we tested for effect modification by baseline HSV-2 status and age using a likelihood ratio test, because previous results have shown that the hormonal contraception-HIV-1 risk relationship was stronger for women who were HSV-2 seronegative or who were <25 years old.[18]

We repeated our analyses with marginal structural modeling, a technique to adjust for time-dependent confounding.[24, 25] We computed stabilized inverse probability weights using logistic regression to predict the probability of hormonal contraceptive use at each visit (by plasma HIV-1 levels, age, region, and number of children) as described by Cole and colleagues;[74] the weights adjusted for time-dependent measures of pregnancy and unprotected sex. Weights for the effect of any hormonal contraception on HIV-1 risk (mean 1.00, range 0.82-1.34) were computed separately from the weights to assess the separate effects of injectable and oral contraception on HIV-1 risk (mean 1.07, range 0.19-4.56). These weights were then used in a pooled logistic regression model of hormonal contraception versus HIV-1 risk.

Finally, we assessed the prevalence and quantity of genital HIV-1 RNA in women using hormonal contraception versus those who did not by logistic and linear regression. All analyses were performed using SAS 9.2 (Cary, NC).

Role of the funding source

The sponsor of the study had no role in design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For most of the 3,790 HIV-1 serodiscordant couples, the HIV-1 infected partner was female. Most couples were married with children. The median age was in the mid-30s, and 321 (24.4%) of uninfected women were aged <25 years. Among HIV-1 seropositive participants, the median CD4 count was 455 (IQR 337-626) cells/mm^3 and median plasma HIV-1 RNA concentration was 4.10 log_{10} copies/mL (IQR 3.37-4.73). More than a quarter of women experienced a pregnancy during study follow-up (Table 7).

Twenty-seven couples enrolled in the randomized trial were subsequently found to not have HSV-2 or HIV-1 infection and were excluded from the analysis [64] as were 76 couples in which the HIV-1 uninfected participant did not complete any follow-up visits for assessment of HIV-1 seroconversion. For 350 couples (151 with an HIV-1 uninfected woman and 199 with an HIV-1 uninfected man) in which the HIV-1 infected partner initiated ART, subsequent visits were censored.

At enrollment, 194 (15%) of 1314 HIV-1 seronegative and 430 (17%) of 2476 HIV-1 seropositive women used hormonal contraception; injectable contraception was more commonly used than oral pills (477 [13%] of 3790 women used injectable vs. 147 [4%] who used oral contraception). 275 (21%) of 1314 HIV-1 seronegative and 815 (33%) of 2476 HIV-1 seropositive women used hormonal methods during study follow-up. Most women did not switch contraceptive methods during follow-up (1085 [83%] of 1314 HIV-1 seronegative women and 1909 [77%] of 2476 HIV-1

seropositive women). However, among 1321 women who ever used hormonal contraception during the study, 634 (48%; 448 [48%] of 945 HIV-1 seropositive women and 186 [49%] of 376 HIV-1 seronegative women) were not using such methods at some point during follow-up.

Median follow-up for HIV-1 seronegative women was 18.0 (IQR 12.6-24.2) and for HIV-1 seronegative men was 18.7 months (IQR 12.8-24.2). Retention at 12 months was 93% (1153 of 1238 women) and for HIV-1 seronegative men was 90% (2098 of 2331 men). Retention at 24 months for HIV-1 seronegative women was 87% (423 of 484 women) and for seronegative men was 84% (812 of 970 men). HIV-1 seronegative partners accrued 5157.9 person-years of follow-up for assessment of HIV-1 seroincidence, during which 167 HIV-1 seroconversions occurred. Of the 73 infections in women, 62 (85%) were determined by viral sequencing to be genetically linked within the partnership, and of the 93 infections in men, 59 (63%) were linked.

During follow-up, hormonal contraceptives were used more frequently by couples with younger HIV-1 uninfected partners and couples who did not experience pregnancy (Table 8). Sexual behaviors did not differ for HIV-1 uninfected women during periods when they were using versus not using hormonal contraception. Unprotected sex was more likely and sex with an external partner was less likely for HIV-1 uninfected men, during periods when their female partner was using hormonal contraception than it was when their partner was not taking hormonal contraception. Concentrations of plasma HIV-1 RNA and CD4 counts were similar for hormonal contraception exposed versus unexposed periods.

Rates of HIV-1 acquisition rates were higher in women using hormonal contraception than in those who were not (Table 9). In multivariate Cox proportional hazards analysis adjusted for age, pregnancy, unprotected sex and plasma HIV-1 levels in the HIV-1 infected partner, hormonal contraceptive use was associated with a 2 times increased risk of HIV-1 acquisition

(adjusted hazard ratio 1.98, 95% CI 1.06-3.68). Increased risk was reported for both injectable (adjusted hazard ratio 2.05, 95% CI 1.04-4.04) and oral contraceptive use (adjusted hazard ratio 1.80, 95% CI 0.55-5.82), although the oral contraceptive use analysis included only 50.5 person-years and did not achieve statistical significance. The results from the marginal structural models were generally in agreement with the Cox regression models. No evidence showed that the effect of hormonal contraception on HIV-1 risk was different for HSV-2 seronegative (195 [15%] of 1283) versus seropositive women (adjusted hazard ratio 1.56 versus 2.00, interaction p=0.82) or for women <25 (321 [24%] of 1314) versus ≥25 years of age (adjusted hazard ratio 1.96 versus 2.21, interaction p=0.82).

The rate of HIV-1 transmission from women using hormonal contraceptives to their male partners was higher than the rate of transmission from women who did not use hormonal contraceptives (Table 10). In multivariate analysis adjusted for age, pregnancy, unprotected sex and plasma HIV-1 levels in the HIV-1 infected partner, men's HIV-1 risk was increased 2 times when their partners were using hormonal contraception (adjusted hazard ratio 1.97, 95% CI 1.12-3.45). Both injectable and oral contraceptive use by female partners were associated with increased HIV-1 risk for men, although the effect was statistically significant only for injectable contraception. The marginal structural model analyses generated similar results to the Cox proportional hazards regression.

To account for the potential persistent biologic effects of hormonal contraception on HIV-1 risk when women switched contraceptive methods, we assessed the effect of extending the exposure window for 3 months after last hormonal contraceptive use (thus, women could be exposed to >1 method during one study visit window). This affected 32.1 (2%) of the 1782.8 person-years and one seroconversion event for the HIV-1 acquisition analysis and 70.9 (2%) of the 3375.1 person-years and one event for the female-to-male transmission analysis. The

results of these analyses were not substantially different than those presented in Tables 9 and 10 (data not shown). When we limited the analysis of HIV-1 acquisition by women to those 62 outcomes that were genetically-linked to their male study partners, the effect estimates were not substantially changed (for any hormonal contraceptive use, Cox regression adjusted hazard ratio 2.06, 95% CI 1.05-4.03 and marginal structural model odds ratio 2.01, 95% CI 1.02-3.95). In a third sensitivity analysis, we censored observations during pregnancy and adjusted our Cox model for age, unprotected sex and plasma HIV-1 levels in the HIV-1 infected partner. We did not see substantial differences in the effect estimates (Cox regression adjusted hazard ratio 1.84, 95% CI 0.97-3.49 for the association of hormonal contraception and HIV-1 acquisition among women and adjusted hazard ratio 1.86, 95% CI 1.04-3.32 for the association of hormonal contraception and HIV-1 transmission to men) for this approach compared with our primary study models.

We measured endocervical HIV-1 RNA concentrations from a single time-point in 1691 HIV-1 infected women (Table 11). Women using injectable contraception at the time of endocervical sample collection were more likely to have genital HIV-1 RNA detected than those not using hormonal contraception. Concentrations of genital HIV-1 RNA were also higher in those using injectable contraception, by an average of 0.19 $\log_{10}$ copies/swab, after adjusting for plasma HIV-1 levels and CD4 count. No association was identified between contraception and concentrations of plasma HIV-1 RNA collected at the same time as the endocervical sample (median 3.91 versus 4.03 $\log_{10}$ copies/mL for injectable users versus non-users, p=0.10), suggesting a localized effect of hormonal contraception on increased levels of HIV-1 in the female genital tract.

Discussion

Use of hormonal contraceptives was associated with a two-times increase in the risk of HIV-1 acquisition by women and HIV-1 transmission from women to men. Injectable methods were the most common form of hormonal contraception used by our study population and subgroup analyses showed significant increased HIV-1 risk associated with injectable use. Few women used oral contraceptives in our study; oral contraceptive use was associated with a non-significant increase in HIV-1 risk and our results are insufficient for drawing definitive conclusions about oral contraceptive use and HIV-1 risk. Our results were robust when we adjusted for multiple potential confounding factors, undertook different analytic approaches, and did sensitivity analyses.

Previous studies of HIV-1 acquisition risk related to contraceptive use have had inconsistent results, partly because of variable methodologic quality.[5] As a result, public health policies – targeted risk-reduction counseling and strategies to promote alternative contraceptive methods for women with or at risk of HIV-1 – have not been implemented. Our findings provide new data that show that contraception might increase a woman's risk of acquiring HIV-1, and they are consistent with longitudinal studies of sex workers in Kenya and family planning attendees from Uganda and Zimbabwe.[17, 18] Moreover, to our knowledge, ours is the first prospective study to show increased HIV-1 risk in male partners of HIV-1 infected women using hormonal contraception. We noted raised concentrations of HIV-1 RNA in endocervical secretions from HIV-1 infected women using injectable methods, suggesting a potential mechanism for increased HIV-1 transmission risk. Studies of HIV-1 transmission from women to men are urgently needed to confirm or refute our findings.

Hormonal contraceptives might have physiologic actions beyond pregnancy prevention, including possible risks of bone density loss, cervical cancer and *Chlamydia trachomatis*.[75-77] Clinical and laboratory studies have suggested possible mechanisms by which hormonal

contraception could influence HIV-1 susceptibility and infectiousness including changes to vaginal structure, cytokine regulation, CCR5 expression, and cervicovaginal HIV-1 shedding.[78]

Our analyses controlled for age, pregnancy, condom use, and HIV-1 concentrations in the infected partner; controlling for additional demographic, clinical, and behavioral factors did not alter our results. Only a clinical trial with random assignment of women to effective hormonal contraception versus non-hormonal contraception could definitively assess HIV-1 risk from different contraceptive methods with certainty that bias in contraceptive choice and due to unmeasured confounding did not influence the results. Such a study might be difficult to implement because of women's preferences for different contraceptive methods and the likelihood of contraceptive switching that could undermine randomization.

Limitations of our study were that contraceptive use was determined by self-report – we did not gather data on adherence to contraception, and we did not record the specific brand of contraception and thus cannot comment on HIV-1 risks from specific exogenous hormones. During the study period, low-dose combination hormonal oral contraceptives and long-acting injectable depot medroxyprogesterone acetate (DMPA) were the most commonly used methods in national family planning programs; few studies have assessed HIV-1 risk from other injectable methods (e.g., norethisterone enanthate).[63] Most participants in our study were participating in an HIV-1 prevention randomized clinical trial and were recruited broadly from HIV-1 testing and care centers. Nearly all HIV-1 infected partners were co-infected with HSV-2; however, HSV-2 seroprevalence is >80% among HIV-1 infected persons in sub-Saharan Africa.[79] Thus, these factors are unlikely to limit the generality of our findings. We censored follow-up for those couples in which the HIV-1 infected partner initiated ART. Future studies with long post-ART

follow-up should assess whether increased risk of HIV-1 acquisition and transmission occurs in the context of ART use.

Several observational studies have shown increased HIV-1 risk for women using hormonal contraceptives; our findings suggest that male partners of HIV-1 infected women using hormonal contraception also face heightened HIV-1 risk. The benefits of effective hormonal contraceptive methods are unequivocal and must be balanced with the risk for HIV-1 infection. Our findings argue for policies to counsel women about the potential for increased HIV-1 risk with hormonal contraceptive use, particularly injectable DMPA use, and the importance of dual protection with condoms to decrease HIV-1 risk (panel).

Our data do not provide estimates of HIV-1 risk related to other hormonal contraceptives, such as implants, patches, or combination injectables. Data on HIV-1 risk associated with these methods and non-hormonal contraceptive methods, such as intrauterine devices, are urgently needed, and strategies to improve the accessibility and uptake of these lower-dose and non-hormonal methods should be prioritized. Contraceptive counseling should be combined with HIV-1 counseling and testing, with joint scale-up of both essential for optimization of reproductive health and HIV-1 prevention choices for women and couples. Additionally, as national HIV-1 prevention programs begin to incorporate antiretroviral pre-exposure prophylaxis,[11, 80, 81] this new HIV-1 prevention method could be offered to women using contraceptives or their partners.

Panel: Research in Context

Systematic review

We searched PubMed up to July 2011 to identify studies relating use of hormonal contraceptives to HIV-1 risk, with the search terms “hormonal contraception,” “hormonal contraceptive”, “HIV-1,” and “HIV-1 acquisition or transmission” in different combinations. Additionally, systematic reviews and one meta-analysis that have been published on this topic were reviewed.

Interpretation

Several studies show – with similar magnitude of their effect estimates – the potential for hormonal contraception to increase a woman’s risk for acquiring HIV-1, even after controlling for sexual behavior. Our study is the first with adequate power to assess and show the potential for hormonal contraceptive use by HIV-1 seropositive women to increase risk of transmitting the virus to their male partners. These findings have important implications for family planning and HIV-1 prevention programs, especially in settings with high HIV-1 prevalence.

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Johannesburg, South Africa).

Author contributions

RH, DD, JMB designed the study and RH and DD did the analysis. RH and JMB wrote the initial draft. All authors contributed to data collection and writing of the report and all approved the final draft.

Table 7. Participant characteristics, prospective study of 3790 African heterosexual HIV-1 serodiscordant couples

	Median (interquartile range) or number (%)			
	Analysis of HIV-1 acquisition by women N=1314 couples		Analysis of HIV-1 transmission from women to men N=2476 couples	
	HIV-1 uninfected women	*HIV-1 infected men*	*HIV-1 uninfected men*	*HIV-1 infected women*
Demographic characteristics				
Age, years	30•2 (25•0-37•2)	37•0 (31•8-44•1)	35•0 (29•5-42•0)	29•9 (25•1-34•6)
Education, years	8•0 (6•0-10•0)	8•0 (6•0-11•0)	9•0 (7•0-12•0)	8•0 (6•0-11•0)
Couple characteristics				
Married	1081 (82•3)		1846 (74•6)	
Partnership duration, years	6•5 (2•7-13•4)		4•9 (2•1-9•4)	
Number of children	2•0 (1•0-4•0)	3•0 (2•0-5•0)	2•0 (1•0-4•0)	2•0 (1•0-3•0)
Number of children with study partner	2•0 (0•0-3•0)		1•0 (0•0-2•0)	
Sexual behavior, month prior to enrollment				
Number of sex acts	3•0 (2•0-6•0)		4•0 (2•0-8•0)	
Any unprotected sex	312 (23•7)		727 (29•4)	
Any sex with an outside partner	8 (1•0)	98 (7•5)	119/1293 (9•2)	34 (1•4)
Medical characteristics				
Sexually transmitted infection*	160 (14•5)	85 (6•6)	230/2411 (9•5)	429/2231 (19•2)
HSV-2 seropositive	1088/1283 (84•8)	1249/1280 (97•6)	1441/2393 (60•2)	2440 (99•0)
Circumcised (men)		427 (32•5)	1332 (53•8)	
Ever pregnant during study (women)	390 (29•7)			571 (23•1)
HIV-1 characteristics				
Plasma HIV-1 RNA, (log_{10} copies/mL) at enrollment		4•37 (3•71-4•94)		3•97 (3•24-4•56)
CD4 count (cells/mm^3) at enrollment		417 (323-562)		478 (348-663)
Ever used ART during study		173 (13•3)		235 (9•6)
Contraceptive use (women)				
Any hormonal contraceptive use at enrollment	194 (14•76)			430 (17•37)
Any injectable use at enrollment	142 (10•81)			335 (13•53)
Any oral use at enrollment	52 (3•96)			95 (3•84)
Any hormonal contraceptive use during follow up	275 (21•20)			815 (33•28)
Any injectable contraceptive use during follow up	208 (16•04)			656 (26•79)
Any oral contraceptive use during follow up	87 (6•71)			219 (8•94)

**N. gonorrhoeae, C. trachomatis,* or *T. vaginalis;* 72.3% of participants with a sexually transmitted infections were infected with *T. vaginalis* only, <5% of participants had *N. gonorrhoeae* or *C. trachomatis*.
HSV-2: herpes simplex virus type-2; ART: antiretroviral therapy

Table 8. Participant characteristics during quarterly follow up intervals with and without hormonal contraceptive use

	Follow-up intervals for analysis of HIV-1 acquisition by women (N=1314 HIV-1 seronegative women)			Follow-up intervals for analysis of HIV-1 transmission from women to men (N=2476 HIV-1 seropositive women)		
	n/N (%) or median (IQR)		p-value*	n/N (%) or median (IQR)		p-value*
	Any hormonal contraception	No hormonal contraception		Any hormonal contraception	No hormonal contraception	
Demographic characteristics						
Age of HIV-1 seronegative partner, years	30•0 (26•0-35•4)	30•5 (25•0-37•8)	0•02	34•0 (29•7-39•9)	35•6 (30•0-43•0)	<0•001
Children within the partnership	2•0 (1•0-3•0)	2•0 (0•0-3•0)	0•9	1•0 (1•0-2•0)	1•0 (0•0-2•0)	0•03
Sexual behavior, HIV-1 uninfected partner						
Any unprotected sex with study partner, past month	77/896 (8•6)	460/6125 (7•6)	0•4	389/3006 (12•9)	1011/9998 (10•1)	0•009
Any sex with an outside partner, past month	29/897 (3•2)	160/6024 (2•7)	0•5	294/3006 (9•8)	1221/10000 (12•2)	0•01
Medical characteristics						
CD4 count (cells/mm^3) in the HIV-1 infected partner	402 (286-601)	405 (298-562)	0•7	467 (343-656)	452 (324-631)	0•04
Plasma HIV-1 level (log_{10} copies/mL) in the HIV-1 infected partner	4•3 (3•3-4•9)	4•4 (3•6-5•0)	0•2	3•9 (3•2-4•5)	4•0 (3•2-4•7)	0•1
Pregnant, female partner**	47/898 (5•2)	967/6027 (16•0)	<0•001	146/2876 (5•1)	1288/9675 (13•3)	<0•001

* Comparisons among contraceptive exposure groups are adjusted for correlation by multiple measures from the same woman using generalized estimating equations. The number of data points considered for each cell is total number of visits with each covariate characteristic during study follow-up.

** Contraceptive use during pregnancy intervals was either contraceptive failures documented at the time of pregnancy detection or contraceptive uptake during the early postpartum period.

Table 9. Hormonal contraceptive use and risk of HIV-1 acquisition in women

			Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis*		Adjusted marginal structural models analysis**	
	# HIV-1 seroconversions / person-years	**Incidence per 100 person-years**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
All women	73/1782•8	4•09						
No hormonal contraception	60/1586•2	3•78	Reference		Reference		Reference	
Any hormonal contraception	13/196•6	6•61	1•73 (0•95-3•15)	0•07	1•98 (1•06-3•68)	0•03	1•84 (0•98-3•47)	0•06
Injectable	10/146•1	6•85	1•80 (0•92-3•52)	0•08	2•05 (1•04-4•04)	0•04	2•19 (1•01-4•74)	0•05
Oral	3/50•5	5•94	1•53 (0•48-4•90)	0•47	1•80 (0•55-5•82)	0•33	1•63 (0•47-5•66)	0•44

* Multivariate Cox proportional hazard regression model, adjusted for age, plasma HIV-1 levels in the HIV-1 infected partner, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings.

** Weighted marginal structural model is adjusted for age, region, number of children, plasma HIV-1 RNA concentration in the HIV-1 infected partner, and visit month (5-knot cubic spline with knots at the 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles) and contraceptive history; weights are truncated at the 1^{st} and 99^{th} percentiles.

Table 10. Hormonal contraceptive use and risk of HIV-1 transmission from women to men

			Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis*		Adjusted marginal structural models analysis**	
	# genetically linked HIV-1 seroconversions / person years	Incidence per 100 person-years	HR (95% CI)	p-value	HR (95% CI)	p-value	OR (95% CI)	p-value
All men	59/3375•1	1•75						
No hormonal contraception	40/2647•9	1•51	Reference		Reference		Reference	
Any hormonal contraception	19/727•2	2•61	1•76 (1•02-3•05)	0•04	1•97 (1•12-3•45)	0•02	2•05 (1•12-3•74)	0•02
Injectable	15/567•3	2•64	1•79 (0•99-3•22)	0•05	1•95 (1•06-3•58)	0•03	3•01 (1•47-6•16)	0•003
Oral	4/159•9	2•50	1•70 (0•60-4•81)	0•31	2•09 (0•75-5•84)	0•16	2•35 (0•79-6•95)	0•12

* Multivariate Cox proportional hazard regression model, adjusted for age, plasma HIV-1 levels in the HIV-1 infected partner, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings.

** Weighted marginal structural model is adjusted for age, region, number of children, plasma HIV-1 RNA concentration in the HIV-1 infected partner, and visit month (5-knot cubic spline with knots at the 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles) and contraceptive history; weights are truncated at the 1^{st} and 99^{th} percentiles.

Table 11. Endocervical HIV-1 RNA concentrations in HIV-1 seropositive women (n=1691), by contraceptive method

	Detection of any genital HIV-1 RNA			Quantity of genital HIV-1 RNA detected (log_{10} copies/swab)		
	n/N (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	Median (IQR)	Regression coefficient (average difference in HIV-1 RNA concentration) (95% CI)	Adjusted regression coefficient* (95% CI)
All HIV-1 seropositive women	1011/1691 (59•9)			3•18 (2•08-3•85)		
No hormonal contraception	782/1333 (58•7)	Reference	Reference	3•14 (2•08-3•91)	Reference	Reference
Any hormonal contraception	230/358 (64•3)	1•27 (0•99-1•61) *p-value=0•06*	1•51 (1•13-2•01) *p-value < 0•01*	3•29 (2•08-3•91)	+0•10 (-0•01, +0•21) *p-value=0•08*	+0•14 (+0•04, +0•23) *p-value<0•01*
Injectable	180/272 (66•2)	1•38 (1•05-1•81) *p-value=0•05*	1•67 (1•21-2•31) *p-value=0•02*	3•38 (2•08-4•02)	+0•15 (+0•03, +0•28) *p-value=0•02*	+0•19 (+0•08, +0•30) *p-value<0•01*
Oral	50/86 (58•1)	0•98 (0•63-1•52) *p-value=0•43*	1•06 (0•62-1•84) *p-value=0•49*	2•96 (2•08-3•65)	-0•07 (-0•28, +0•14) *p-value=0•53*	-0•05 (-0•24, +0•14) *p-value=0•60*

* Adjusted for plasma HIV-1 RNA concentration and CD4 count

CHAPTER 4: Willingness of Kenyan HIV-1 serodiscordant couples to use antiretroviral based HIV-1 prevention strategies

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BRIEF REPORT

Willingness of Kenyan HIV-1 serodiscordant couples to use antiretroviral based HIV-1 prevention strategies

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Abstract

Background: Antiretroviral treatment (ART) and pre-exposure prophylaxis (PrEP) have demonstrated efficacy as new HIV-1 prevention approaches for HIV-1 serodiscordant couples.

Methods: Among Kenyan HIV-1 serodiscordant heterosexual couples participating in a clinical trial of PrEP, we conducted a cross-sectional study of willingness to use antiretrovirals for HIV-1 prevention. The study was conducted prior to July 2011, when studies among heterosexual populations reported that ART and PrEP reduced HIV-1 risk.

Results: For 181 couples in which the HIV-1 infected partner had a CD4 count ≥350 cells/μL and had not yet initiated ART (and thus did not qualify for ART under Kenyan guidelines), 60.2% of HIV-1 infected partners (69.4% of men and 57.9% of women) were willing to use early ART (at CD4 ≥350 cells/μL) for HIV-1 prevention. Among HIV-1 uninfected partners, 92.7% (93.8% of men and 86.1% of women) reported willingness to use PrEP. When given a hypothetical choice of early ART or PrEP for HIV-1 prevention, 52.5% of HIV-1 infected participants would prefer to initiate ART early and 56.9% of HIV-1 uninfected participants would prefer to use PrEP.

Conclusions: Nearly 40% of Kenyan HIV-1 infected individuals in known HIV-1 serodiscordant partnerships reported reservations about early ART initiation for HIV-1 prevention. PrEP interest in this PrEP-experienced population was high. Strategies to achieve high uptake and sustained adherence to ART and PrEP for HIV-1 prevention in HIV-1 serodiscordant couples will require responding to couples' preferences for prevention strategies.

Key words: HIV prevention, antiretrovirals, pre-exposure prophylaxis, Africa, couples

Background

Antiretroviral-based HIV-1 prevention strategies – specifically, antiretroviral treatment (ART) to reduce the infectiousness of HIV-1 infected persons (including when initiated at CD4 counts at or above current WHO guidelines) and pre-exposure prophylaxis (PrEP) to protect HIV-1 uninfected persons from HIV-1 acquisition – are among the most promising new approaches for decreasing HIV-1 spread.[82] Stable HIV-1 serodiscordant couples are central to the African HIV-1 epidemic and could be a prime target population for antiretroviral-based HIV-1 prevention; results of landmark clinical trials have recently demonstrated substantial efficacy for these strategies to reduce HIV-1 risk in this population.[10, 11] To limit costs, policies for ART and PrEP in couples could recommend staged use – e.g., PrEP until the HIV-1 infected partner initiates ART – rather than concurrent use of both strategies in the same couple.[83] Thus, understanding couples' preferences for and concerns about antiretrovirals for HIV-1 prevention is important to inform guidelines for the use of early ART and PrEP.

Methods

We conducted a cross-sectional study among a convenience sample of HIV-1 heterosexual serodiscordant couples to determine preferences for and willingness to use antiretrovirals for HIV-1 prevention. Eligible couples were participants from the Thika, Kenya site in the Partners PrEP Study, a randomized clinical trial of daily oral tenofovir (TDF) and combination emtricitabine (FTC)/TDF PrEP to prevent HIV-1 acquisition by HIV-1 uninfected members of heterosexual HIV-1 serodiscordant couples. Study procedures have been described elsewhere.[84] At an interim review in July 2011, the Partners PrEP Study independent Data and Safety Monitoring Board recommended that the placebo arm of the trial be discontinued early due to clear demonstration of PrEP efficacy for HIV-1 prevention.[11]

Data for this cross-sectional study were collected between March and July 2011, prior to the announcement of PrEP efficacy in heterosexual populations.[85, 86] During this time, the HPTN 052 trial demonstrated that early ART (initiated at CD4 counts of 350-550 cells/μL) reduced HIV-1 risk by 96% in HIV-1 serodiscordant couples and the FEM-PrEP study closed early due to an inability to demonstrate efficacy for FTC/TDF to prevent HIV-1 acquisition.[10, 87] Participants were informed and counseled about results from each of these studies. For the present study, participants were individually invited by study staff during a routine quarterly clinical trial visit to answer questions about HIV-1 prevention; some participants attended the study visit with their study partner while others attended separately due to conflicting work constraints or partnership dissolution. Couples were eligible if the HIV-1 uninfected partner had not seroconverted to HIV-1 prior to the study visit (i.e., the couple was still HIV-1 serodiscordant). Written informed consent for this study was obtained and interviews were conducted with each member of the couple separately. The study protocol was approved by the University of Washington and Kenyatta National Hospital institutional review boards.

The primary analysis group was couples for which both members completed the interviewer-administered questionnaire (to enable analysis of agreement within couples), both indicated that they were still a couple, and the HIV-1 infected partner had a CD4 count ≥350 cells/μL (and was therefore ineligible for ART under current Kenyan policies and WHO guidelines) and had not initiated ART. Thus, this primary analysis group could potentially be a target for early ART and/or PrEP for HIV-1 prevention. Analyses were also conducted for all participants who completed the questionnaire.

To assess participant's long term willingness to use PrEP, HIV-1 uninfected participants were asked "if we find that PrEP works to keep people free from HIV, would you be willing to take PrEP tablets every day for the next five years." To assess willingness to initiate ART for HIV-1 prevention purposes, HIV-1 infected partners were asked "would you be willing to start antiretrovirals before your CD4 count reaches 350 if it would lower your chance of giving HIV to

your partner?" In open-ended questions, participants were asked to describe their top concerns about early ART or PrEP. All participants were also asked to declare a preference for early ART or PrEP.

We used descriptive methods to analyze couple's preferences and willingness to use antiretroviral-based HIV-1 prevention and logistic regression to determine if any demographic, behavioral or clinical characteristics were associated with willingness to initiate antiretroviral-based HIV-1 prevention. Data were analyzed using SAS version 9.2.

Results

Participant characteristics. 367 HIV-1 infected and 405 HIV-1 uninfected participants completed the questionnaire (Table 12). Couples completing the questionnaire had been partners for a median of 5.6 years (IQR 2.1-11.0) and enrolled in the Partners PrEP Study for about 21 months (IQR 15-27). Less than 20% of participants no longer considered themselves a couple with their study partner and 20.6% of HIV-1 infected participants had already initiated ART due to clinical or immunologic (CD4) indicators. In total, 181 couples were included in our primary analysis group because both partners completed the questionnaire and indicated their continuing partnership and the HIV-1 infected partner had a CD4 count ≥350 cells/μL and had not yet initiated ART.

Willingness and preferences for antiretroviral-based HIV-1 prevention. Among 181 couples in the primary analysis group, 69.4% and 57.9% of HIV-1 infected men and women indicated willingness to initiate ART before their CD4 count reached 350 cells/μL and 93.8% and 86.1% of HIV-1 uninfected men and women would be willing to use PrEP (Table 13). Willingness was similarly high among all participants who completed the questionnaire. Willingness to use antiretrovirals for HIV-1 prevention before versus after May 2011 (when results from the HPTN 052 trial were publically announced) was similar (p=0.7, Cochran-Armitage trend test).

In the primary analysis population, 61.1% of HIV-1 infected male participants indicated a preference for themselves to initiate ART early. HIV-1 infected women were split between preferring to initiate early ART themselves (50.3%) and having their partner use PrEP (49.7%). HIV-1 uninfected participants slightly preferred PrEP use for themselves over ART use for prevention by their HIV-1 infected partner (57.2% of men and 55.6% of women). In 26.0% of couples, both members preferred to have the HIV-1 uninfected partner use PrEP and in 21.5% of couples, both members preferred to have the HIV-1 infected partner initiate ART.

Participant concerns about antiretroviral-based HIV-1 prevention. Among HIV-1 infected participants who were unwilling to initiate early ART for HIV-1 prevention (n=72), the primary concerns were side effects (a concern of 51.4% of those unwilling), stigma (20.8%), pill burden (19.4%) and the potential for earlier development of antiretroviral resistance (18.1%). Men and women had similar concerns. Among HIV-1 uninfected participants, 14 (7.7%) were unwilling to use PrEP and their primary concerns were that 5 years would be too long (6/14 of those unwilling), people should not take drugs unless they are sick (3/14 of those unwilling), side effects (3/14 of those unwilling), and drug fatigue (2/14 of those unwilling). Logistic regression did not identify any characteristics that were significantly associated with willingness to use early ART or PrEP, including gender, sexual behavior, fertility desires, contraceptive use, risk perception of acquiring/transmitting HIV-1, and, for HIV-1 infected partners, CD4 count and WHO stage (data not shown).

Discussion

In this cohort of Kenyan HIV-1 serodiscordant couples that received regular counseling about HIV-1 prevention, including counseling about the importance of ART for treatment and prevention, 40% of HIV-1 infected individuals were unwilling to consider initiating ART early for

HIV-1 prevention purposes. Similar to prior work on ART acceptability in Africa, side effects were a top concern for participants.[33-35] This population was experienced with and well-informed about PrEP and 90% of HIV-1 uninfected participants said they would be willing to use PrEP on a long-term basis. When given a hypothetical choice of ART or PrEP for HIV-1 prevention, participants tended to choose the prevention option that they would control themselves (HIV-1 uninfected participants chose PrEP and HIV-1 infected participants chose ART).

Numerous studies from diverse settings have identified structural and social challenges leading to lower than expected rates of ART initiation among adults meeting eligibility criteria. While structural challenges, such as accessing HIV-1 testing, enrolling in HIV-1 care programs, and receiving CD4 test results [88], are being addressed through programs to strengthen health systems, concerns about side effects, stigma, and perceptions that ART is only for sick people may prevent individuals' from accessing ART and need to be addressed through counseling and community sensitization.[89] Early ART implementation, even among HIV-1 serodiscordant couples who recognize their own HIV-1 risk, will need to address the perceptions couples have of ART use, including its risks and benefits.

A possible HIV-1 prevention strategy for serodiscordant couples that will utilize both ART and PrEP is for the HIV-1 uninfected partner to use PrEP until the HIV-1 infected partner is willing and able to initiate ART.[83] Such a strategy may be cost-effective, provide HIV-1 infected partners an opportunity to decide when to start ART, and may allow a "bridge period" for a few months after the infected partner starts ART, when transmission risk may still be high because viral load is not yet suppressed.

Our study was conducted among HIV-1 serodiscordant couples who were very aware of the potential benefits of PrEP and ART. Similar studies should be conducted among couples who are just learning of their HIV-1 serodiscordant status and are less familiar with HIV-1 prevention strategies. Future studies of this question will also benefit from following couples to

identify trends in willingness, uptake of antiretrovirals, and the inclusion of qualitative methods to gain a deeper understanding of individuals' and dyadic preferences of these novel prevention methods.

Successful implementation of antiretroviral-based HIV-1 prevention for HIV-1 serodiscordant couples will need to be targeted to couples at highest risk for transmission who are also willing to initiate and adhere to daily antiretrovirals. In our study, not all couples would be willing to use ART prior to the HIV-1 infected partner having clinical symptoms and a perceived need for initiation; PrEP could be a suitable alternative for these couples. As antiretroviral-based HIV-1 prevention strategies are incorporated into prevention policies and programs, it will be important to understand and accommodate couples' preferences and willingness to use antiretroviral-based HIV-1 prevention.

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Author contributions

All authors contributed to the design of the study. RH wrote the first draft of the manuscript and all authors provided feedback and approved the final manuscript draft.

Table 12. Participant characteristics

	Couples with HIV-1 uninfected men		Couples with HIV-1 uninfected women	
	HIV-1 uninfected men	**HIV-1 infected women**	**HIV-1 uninfected women**	**HIV-1 infected men**
Eligible to participate	379	377	112	111
Enrolled prior to July 2011 (N, % of eligible)**	285 (75.2%)	312 (82.8%)	82 (73.2%)	93 (83.8%)
Months since enrollment in Partners PrEP Study (median, IQR)	21 (15 - 27)	21 (15 - 27)	21 (12 - 24)	21 (15 - 27)
Still a couple with study partner (N, %)	243 (85.3%)	253 (82.1%)	67 (81.7%)	72 (80.0%)
Age, years (median, IQR)	34.5 (29.8 - 40.8)	29.5 (25.1 - 34.4)	33.0 (27.1 - 39.8)	38.2 (34.2 - 44.6)
Children with study partner (median, IQR)	2 (0 - 3)		2 (0 - 3)	
Partnership duration, years (median, IQR)	4.4 (1.8 - 9.9)		10.0 (4.2 - 19.7)	
On ART at the time of data collection (N, %)		59 (18.9)		24 (25.8)
Not on ART and not eligible for ART*** (N, %)		203 (65.1)		54 (58.1)

*Couples were offered enrollment separately – 323 couples (250 with HIV-1 uninfected men and 73 with HIV-1 uninfected women) had participation from both members.

**Data analysis included only couples who enrolled prior to the placebo arm discontinuation of the Partners PrEP Study in July 2011.

***Under current Kenyan ART guidelines.

Table 13. Willingness and preferences for ART-based HIV-1 prevention

	Couples with HIV-1 uninfected men		Couples with HIV-1 uninfected women	
	HIV-1 uninfected men	HIV-1 infected women	HIV-1 uninfected women	HIV-1 infected men
Primary analysis group*				
Number of participants	145	145	36	36
Willing to use early ART		84 (57.9)		25 (69.4)
Willing to use PrEP	136 (93.8)		31 (86.1)	
Prefers early ART initiation	62 (42.8)	73 (50.3)	16 (44.4)	22 (61.1)
Prefers PrEP	83 (57.2)	72 (49.7)	20 (55.6)	14 (38.9)
All enrolled				
Number of participants	285	312	82	93
Willing to use early ART		205 (66.6)		67 (75.3)
Willing to use PrEP	257 (90.2)		68 (82.9)	
Prefers early ART initiation	128 (44.9)	190 (61.7)	38 (46.3)	65 (73.0)
Prefers PrEP	157 (55.1)	118 (38.3)	44 (53.7)	24 (27.0)

*The primary analysis group was defined as participants for which both members of the couple completed the questionnaire, both considered themselves still in a partnership with each other, and the HIV-1 infected partner had a CD4 count >350 cells/μL and had not yet initiated ART.

CHAPTER 4 ADDENDUM: Fertility intentions and HIV-1 risk perceptions of Kenyan HIV-1 serodiscordant couples

Background

Past studies have found that fertility intentions among African HIV-1 seropositive men and women are influenced by cultural expectations, social stigma, fears of poor pregnancy outcomes and the potential for HIV-1 transmission to the uninfected partner.[90-97] With the current availability of antiretroviral therapy and effective programs for averting vertical HIV-1 transmission, there have been recent reports of restored fertility and fertility desire among HIV-1 seropositive women.[91] In an effort to better understand the decision-making process that serodiscordant couples undergo when deciding whether to use contraception, we assessed couples' fertility intentions, specifically whether couples desiring fertility balance this desire with their perceived risk for HIV-1 and couples' preferences for using antiretroviral-based HIV-1 prevention during peri-conception periods.

Methods

Using the cross sectional data collected from Partners PrEP Study participants as described in Chapter 4, we used descriptive methods to summarize fertility intentions, the perception of HIV-1 risk and their interaction and logistic regression to examine characteristics of men and women with future fertility desires. Any characteristics significant at the $p<0.05$ level in univariate analysis were included in multivariate logistic regression models. For this analysis, we included only participants who indicated they were still in a partnership with their study partner.

Results

Fertility intentions. Nearly half of all participants indicated that they would like to have more children in the future (45.3% of women and 49.3% of men, 44.0% of HIV-1 infected participants and 50.3% of HIV-1 uninfected participants). Among women and men with fertility intentions, 88.9% and 100% respectively, said they were trying to get pregnant the last time they had sex. When asked about the preferred timing of future children, 10.0% of participants with fertility

intentions were already pregnant, 21.1% desire another child within 1 year, 21.7% within 1-3 years, 28.1% in 3 or more years and 19.1% stated they did not know when they would like to have their next child (these did not differ by gender X^2 p=0.3). 55.6% of women and 66.7% of men knew about timing unprotected sex to the most fertile days as a method to reduce harm during peri-conception periods. 61.5% of women and 40.0% of men knew about waiting for the HIV-1 infected partner to have a low viral load or high CD4 count before attempting conception as a possible harm reduction strategy.

Antiretroviral-based HIV-1 prevention with fertility intentions. Among HIV-1 uninfected participants, 88.2% with fertility desires would be willing to use PrEP (X^2 p=0.87). Among HIV-1 infected participants with fertility desires, 71.5% would be willing to initiate antiretrovirals early for HIV-1 prevention purposes (X^2 p=0.28). Women tended to prefer early antiretroviral therapy for HIV-1 prevention (59.0%) while men were more evenly split between preferring early antiretroviral therapy and PrEP (48.8% preferred early antiretroviral therapy and 52.1% preferred PrEP).

HIV-1 risk perception. Most participants felt they had low or no risk of HIV-1 transmission (87.4% of HIV-1 uninfected and 85.8% of HIV-1 infected participants). Men with a high or moderate level of risk perception were more likely to have future fertility desires than men with no risk perception (OR = 2.57, p=0.04, Table 14). Risk perception was not associated with fertility desires for women or within subgroups of HIV-1 infected or uninfected participants (data not shown).

Characteristics of participants with fertility desires. In multivariate analysis, women and men with more children (adjusted OR=0.64, 95% CI: 0.51-0.81 for women and adjusted OR=0.63 95% CI: 0.47 – 0.85 for men) and longer partnership durations with their study partner (adjusted

OR=0.94, 95% CI: 0.89-1.00 for women and adjusted OR=0.88, 95% CI: 0.82-0.95 for men) were less likely to desire more children in the future (Table 14). They were also less likely to report that they would use effective contraceptive methods in the future. In addition, older women were less likely to have future fertility desires (adjusted OR=0.91, 95% CI 0.87-0.95).

Conclusion

Consistent with previous studies of fertility intentions among HIV-1 infected populations, we found that nearly half of our population men and women in of HIV-1 serodiscordant couples desire more children in the future. More than half of participants with fertility desires were either already pregnant or would like to have another child within the next 3 years. Participants were largely willing to use ARV-based HIV-1 prevention and some were aware of harm reduction strategies during peri-conception periods such as limiting unprotected to peak fertile periods and waiting for the HIV-1 infected partner's CD4 count to be high or viral load to be suppressed. Interestingly, HIV-1 risk perception was only correlated with fertility desire among men and men with higher risk perception were more likely to desire more children in the future. Not surprisingly, older participants with more children were less likely to want more children in the future, indicating that they have already satisfied their fertility desires. Men and women desiring fertility were less likely to postulate that they would use effective contraceptive methods in the future.

The peri-conception period, when condoms are not used and coital frequency increases, is a time of very high risk for HIV-1 transmission among HIV-1 serodiscordant couples. Despite the risk for horizontal and vertical HIV-1 transmission facing these couples, pregnancy rates remain high at 10-20% per year.[7-9] Currently, there is very little research testing whether proposed strategies for safer conception, such as PrEP or early ART use, are feasible and acceptable for HIV-1 serodiscordant couples in resource-limited settings.[98] A small, retrospectively compiled dataset from European couples demonstrated that natural conception

without HIV-1 transmission can be achieved when the HIV-1 infected partner is using antiretrovirals and HIV-1 levels are suppressed.[99] PrEP used in conjunction with timed unprotected sex has also been recently tested in a small cohort of European HIV-1 serodiscordant couples: 70% of 46 couples became pregnant within 12 months and none of the HIV-1 uninfected partners acquired HIV-1 during 2 years of follow up.[100]

Men and women in HIV-1 serodiscordant partnerships with fertility desires were willing to use antiretroviral-based HIV-1 prevention to reduce the risk of HIV-1 transmission. Research to design and test harm reduction strategies to reduce HIV-1 transmission risk during peri-conception periods is urgently needed in resource-limited settings. Young men and women with few children and in new partnerships should be targeted by reproductive health and HIV-1 prevention programs to receive peri-conception harm reduction interventions.

Table 14. Correlates of fertility desire among men and women in HIV-1 serodiscordant partnerships in Thika, Kenya

	Women				Men			
	OR (95% CI)	**p-value**	**aOR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Demographic characteristics								
Age	0.89 (0.86-0.92)	<0.001	0.91 (0.87-0.95)	<0.001	0.90 (0.88-0.93)	<0.001	0.97 (0.92-1.02)	0.31
Number of children with study partner	0.48 (0.40-0.58)	<0.001	0.64 (0.51-0.81)	<0.001	1.06 (1.01-1.11)	0.013	0.63 (0.47-0.85)	0.002
Partnership duration	0.86 (0.82-0.89)	<0.001	0.94 (0.89-1.00)	0.06	0.85 (0.81-0.89)	<0.001	0.88 (0.82-0.95)	<0.001
Medical characteristics, risk behavior & perception								
HIV-1 infected	0.95 (0.62-1.46)	0.82			0.57 (0.35-0.92)	0.02	0.70 (0.32-1.54)	0.38
Coital frequency	1.03 (0.99-1.06)	0.12			1.06 (1.01-1.11)	0.013	1.03 (0.96-1.11)	0.4
Used condom at last sex	0.62 (0.34-1.14)	0.12			0.85 (0.39-1.85)	0.68		
Some condom use last month (vs. none)	0.62 (0.22-1.74)	0.57			4.82 (1.03-22.57)	0.022	1.96 (0.23-16.48)	0.54
100% condom use last month (vs. none)	0.62 (0.29-1.33)	0.41			1.02 (0.40-2.60)	0.065	0.61 (0.13-2.90)	0.54
Sex with an additional partner last month	1.07 (0.35-3.24)	0.91			0.82 (0.38-1.77)	0.62		
Having high or moderate HIV-1 risk perception (vs. none)	0.94 (0.48-1.83)	0.85			2.57 (1.05-6.31)	0.04	0.50 (0.16-1.62)	0.25
Having low HIV-1 risk perception (vs. none)	1.37 (0.86-2.16)	0.18			0.94 (0.57-1.54)	0.81	0.64 (0.32-1.26)	0.19
Prevention choice (among 181 couples who would be eligible for either PrEP or early antiretroviral therapy)*								
Early antiretroviral therapy (vs. PrEP)*	0.99 (0.55-1.77)	0.98			0.57 (0.31-1.05)	0.07		
Current contraceptive use (vs. none)								
Oral	0.39 (0.20-0.75)	0.005						
IUD	0.35 (0.14-0.89)	0.03						
Injectables	0.41 (0.25-0.67)	0.001						
Implant	0.57 (0.25-1.16)	0.12						
Other	0.99 (0.41-2.38)	0.97						
Future contraceptive use (vs. none)								
Oral	0.29 (0.14-0.62)	0.001	0.31 (0.12-0.77)	0.01	0.43 (0.20-0.94)	0.03	0.25 (0.06-1.06)	0.06
IUD	0.24 (0.10-0.59)	0.002	0.26 (0.08-0.86)	0.03	0.28 (0.09-0.86)	0.03	0.16 (0.03-0.98)	0.05
Injectables	0.32 (0.17-0.60)	<0.001	0.30 (0.13-0.68)	0.004	0.36 (0.18-0.73)	0.005	0.15 (0.04-0.62)	0.009
Implant	0.33 (0.15-0.71)	0.005	0.32 (0.12-0.85)	0.02	0.23 (0.09-0.59)	0.002	0.05 (0.01-0.28)	<0.001
Other	0.14 (0.01-1.47)	0.10	0.70 (0.01-91.77)	0.89	0.33 (0.09-1.25)	0.10	0.17 (0.01-2.79)	0.22
Condoms only	0.43 (0.20-0.95)	0.04	1.00 (0.36-2.74)	0.99	0.39 (0.18-0.84)	0.02	0.18 (0.04-0.78)	0.02

CHAPTER 5: Conclusion

The data presented in this dissertation contribute to understanding HIV-1 serodiscordant couples' contraceptive practices, HIV-1 risk associated with hormonal contraceptive use, and willingness to use antiretroviral-based HIV-1 prevention strategies. By integrating approaches from the HIV-1 prevention and reproductive health fields, the studies conducted present potential solutions to improve the health of HIV-1 serodiscordant couples.

CHAPTER 2 INTERPRETATIONS

Among women with or at high-risk of HIV-1, effective contraceptive use is surprisingly low: less than 30% of over 3400 HIV-1 infected and uninfected women in our Chapter 2 study reported using an effective contraceptive method after two years of couples counseling. Among HIV-1 infected women who were taking study drug and intensely counseled to avoid pregnancy, use of injectable and oral contraceptives increased significantly during the study and the coordinated approach used by one study site to improve contraceptive uptake has been carefully detailed and could be replicated in HIV-1 prevention trials and primary care facilities.[66] Injectable contraceptives were the most preferred method and hormonal contraceptive use was associated with having at least one child and a reduction in condom use. This study highlighted the lack of dual contraceptive use among women with and at-risk for HIV-1 and the need for novel counseling messages to promote its use.

CHAPTER 3 INTERPRETATIONS

In Chapter 3, we demonstrated that relative to women not using hormonal contraception, women who used injectable contraceptives had a greater risk of acquiring HIV-1 or transmitting HIV-1 to male partners even after accounting for sexual behaviors and HIV-1 viral levels. The methods employed for this study were very strong resulting in immediate widespread international attention from HIV-1 prevention and family planning groups. More than 6 months since the study was first published online, the public health community remains very engaged to

seek a more definitive answer to whether injectable contraceptives induce a biologic reaction that increases HIV-1 susceptibility and/or infectiousness.

INTERNATIONAL REACTION TO OUR CHAPTER 3 RESULTS

Balancing the potential HIV-1 risk from injectable contraceptives and the importance of preventing unintended pregnancy is complex. When the study of hormonal contraception and HIV-1 risk (Chapter 3) was published online in *The Lancet Infectious Diseases* and chronicled on the front page of the *New York Times* in early October 2011, family planning and HIV-1 prevention communities were alarmed and responded with a variety of loud reactions – questioning the validity of the data and calling out exaggerated media headlines, reprimanding the family planning community for ignoring decades of biologic and human data demonstrating increased HIV-1 risk with exogenous progesterone use and calling for a randomized controlled trial to provide a definitive answer.[27, 101, 102] These reactions highlight the ongoing importance of integrating HIV-1 prevention and reproductive health programs and the diversity of experience and expertise that researchers and implementers from these fields possess.

The WHO responded to the "Heffron et al." study by initiating a systematic review and convening a consultation of 75 experts to determine whether changes to the *Medical Eligibility*

Figure 5. Title page from the WHO response to the "Heffron et al" study published in *The Lancet Infectious Diseases*, October 2011.

Criteria, 4th edition 2009 (MEC) for contraceptives were warranted (Figure 6).[28] In the systematic review, the majority of highest quality studies (including the one presented in this dissertation and 2 published rapidly prior to the WHO technical consultation) of oral contraceptives and HIV-1 risk demonstrated no increase in risk but the evidence on injectable DMPA and HIV-1 risk was mixed with risk increases ranging from 48% to 100%. In February 2012, the WHO technical consultation report concluded with the following statement that reflects the careful and arduous deliberation:

> *"Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition, other studies do not show this association. A WHO expert group reviewed all the available evidence and agreed that the data were not sufficiently conclusive to change current guidance. However, because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other HIV preventive measures. Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential. These recommendations will be continually reviewed in light of new evidence."*

While experts agreed that the epidemiologic and biologic evidence is inconsistent and insufficient to recommend modification currently, the MEC will now include a note to highlight the importance of dual contraceptive use by women using progestogen-only injectables and the evidence will continue to be reviewed.

The WHO statement also highlights the need to expand the contraceptive method mix. If there were ever to be a recommendation for women in high HIV-1 risk settings to avoid using DMPA-containing injectable contraceptives, alternative methods are not widely accessible or accepted. Thus a recommendation against DMPA injectable use would likely result in hormonal contraceptive discontinuation for some women and an increase in unintended pregnancy and its consequences would follow. If alternative methods, such as IUD or implants, were more readily available and women were comfortable using them, method switching would ensue, rather than hormonal contraceptive discontinuation. It is important to note, however, that recommendations for alternative methods are not evidence-based. As with our study, data are lacking on most

alternative effective contraceptives. Our study and one other of high quality indicate that oral contraceptives may potentially elevate HIV-1 risk.[17] Data are urgently needed to test whether other contraceptive methods are associated with adverse outcomes, including HIV-1 infection risk.

STRENGTHS AND LIMITATIONS OF OUR CHAPTER 3 STUDY

Data from HIV-1 serodiscordant couples may have fewer limitations than other cohorts of women. HIV-1 uninfected partners in mutually disclosed HIV-1 serodiscordant partnerships know that they are at risk of HIV-1 infection each time they have unprotected sex with their partner. This is a unique advantage of our dataset because each woman has a known risk of HIV-1 infection. Women with HIV-1 seronegative partners or partners with unknown HIV-1 serostatus, the types of women included in all other observational analyses of hormonal contraception and HIV-1 risk, have different degrees of risk and risk perception. Indeed, during the course of a study, many women will not have sex with HIV-1 infected partners and not have any risk for becoming HIV-1 infected. Another advantage of following HIV-1 serodiscordant couples is the ability to collect clinical and behavioral data from the HIV-1 infected partner. The strongest predictor of HIV-1 transmission is HIV-1 viral load.[73] In our analysis, we were able to control for this factor because it has been collected from HIV-1 infected partners at enrollment and during follow up. Future studies designed to address questions about HIV-1 transmission would benefit greatly from having at least one measure of HIV-1 RNA levels from sexual partners.

Our primary analytic findings were robust to multiple statistical techniques. As explained in the Introduction, marginal structural models are a theoretically stronger statistical approach for handling time dependent confounding than Cox proportional hazards regression. It is important to note, however, that this method has only recently gained attention and the methods for describing its use in observational analyses is not yet standardized. Marginal structural

modeling requires building at least two different statistical models. The first model predicts the probability of exposure based on past exposure history as well as known correlates of the exposure and these probabilities are used in the calculation of standardized weights. The second model is the final weighted model that gives the final results. Additional models can be built to estimate the probability of censoring and incorporated into weight calculations. Recently published manuscripts that have employed marginal structural models are often lacking details describing the parameterization of each variable in each model, especially the parameterization of past exposure history. This may be due to word count limitations imposed by journals and time limits required for conference presentations. For observational analyses, control of confounding is imperative and careful description of statistical model construction is necessary to allow comparisons of one study to another and to explore reasons for inconsistent results. Future observational analyses of hormonal contraception and HIV-1 risk should employ marginal structural models and carefully describe variable selection and the parameterization of each variable in the final models.

The effect of injectable contraception on HIV-1 acquisition risk for women that we observed persists in additional post hoc sensitivity analyses conducted to explore the robustness of our findings. Using our primary Cox proportional hazards regression model with adjustment for age, plasma viral load, pregnancy and unprotected sex, we ran additional models to 1) adjust for additional or alternative covariates to account for sexual behavior, 2) restrict to follow-up periods when unprotected sex was reported, 3) censor visits after a woman switched her contraceptive method (to minimize the effect of changing methods on risk), and 4) restrict to consistent injectable users outside of South Africa (with access to only injectable DMPA). In all models, the approximately 2-fold increase in HIV-1 acquisition risk persisted (Table 15). Some analyses had p-values >0.05 due to reduced statistical power but the magnitude of association continued to be as strong as that seen in our primary analytic model. In fact, when only consistent, presumed DMPA users were retained (i.e. South Africans excluded), injectable

contraception was associated with a nearly 4-fold increased HIV-1 risk (aHR=3.93, p=0.01). Such consistent findings from multiple sensitivity analyses strongly support the internal validity

Table 15. Hormonal contraception and HIV-1 Risk: results from sensitivity analyses

Analysis description	Contraceptive method	Adjusted hazard ratio for HIV-1 acquisition by women
Adjustment for male report of unprotected sex (instead of female report)	Any HC Injectable Oral	2.03 (1.03-4.01) p=0.04 2.03 (0.95-4.32) p=0.07 2.06 (0.62-6.90) p=0.24
Additional adjustment for coital frequency	Any HC Injectable Oral	2.01 (1.08-3.76) p=0.03 2.06 (1.04-4.07) p=0.04 1.88 (0.57-6.22) p=0.30
In the strata of women who report some or none of sex acts protected by a condom	Any HC Injectable Oral	2.18 (0.74-6.45) p=0.16 2.29 (0.70-7.53) p=0.17 1.97 (0.28-13.80) p=0.50
Censoring visits after a woman switch her contraceptive method (either to initiate HC, discontinue HC or switch HC method)	Any HC Injectable Oral	2.88 (1.22-6.93) p=0.02 2.62 (0.93-7.33) p=0.07 3.64 (0.83-15.99) p=0.09
Excluding women from South Africa and using only women who were consistently on DMPA versus women who were consistently not using and hormonal contraceptive during study follow up	DMPA	3.93 (1.38-11.22) p=0.01
HC: hormonal contraception; DMPA: depot medroxyprogesterone acetate		

of our findings from this dataset.

Hormonal contraceptive users and non-users may have inaccurately reported their condom use – and potentially by a differential degree. A limitation of our study was that contraceptive use and sexual behavior data were collected via self-report and were not verified through pharmacy records. Hormonal contraceptives reduced pregnancy incidence and women and men reporting unprotected sex were 2-3 times more likely to acquire HIV-1, enhancing confidence in the validity of this self-reported data.[103] Non-differential misclassification would result in a spuriously high effect estimate and differential misclassification could result in bias in either direction. Arguments can be made to speculate about differential misclassification in either direction (i.e. that hormonal contraceptive users were more likely to misreport or vice versa) but it is not possible to retrospectively assess whether this occurred. Laboratory analysis

of stored genital samples and data collection via daily coital diaries can be built into future studies to validate reporting accuracy. Reports of unprotected sex were relatively rare in this cohort but frequent condom use would be expected among mutually disclosed HIV-1 serodiscordant couples undergoing quarterly couples HIV-1 prevention counseling. Furthermore, the per-contact transmission rate from the overall cohort and the HIV-1 risk reduction associated with self-reported condom use is similar to that found in other HIV-1 serodiscordant couple studies, suggesting that the couples in our study practiced sexual behaviors similar to those in other cohorts. [104, 105] Statistical control of confounding factors is essential in observational analyses to provide the least biased estimate of the amount of risk attributable to a specific exposure. Deciphering whether behavioral or biological factors are responsible for the increase in risk is important to determine if structural interventions are warranted. But from a public health perspective, women using hormonal contraceptives are at an increased risk for HIV-1 whether it is due to their behaviors, a biologic effect of exogenous hormones, or other factors, and this message is important for women worldwide.

Considering the potential impact of injectable contraception to increase HIV-1 risk is important in settings with high HIV-1 incidence and where injectable contraception is commonly used. Mathematical modeling has demonstrated that the impact of a policy change to restrict the use of injectable contraceptives in these regions (i.e. South Africa) would substantially impact the annual number of births and maternal and HIV-1 related deaths (Figure 7).[106] However, most geographic locations in the world do not have such a risk for HIV-1 and the consequences of unintended pregnancy (which would increase if policy recommendations restrict injectable contraceptive use) are a greater concern. If injectable hormonal contraception truly doubles HIV-1 acquisition risk, in locations with high HIV-1 incidence and prevalence of injectable contraceptive use, cessation of injectable contraceptive use would result in fewer

deaths among women overall (Figure 8).

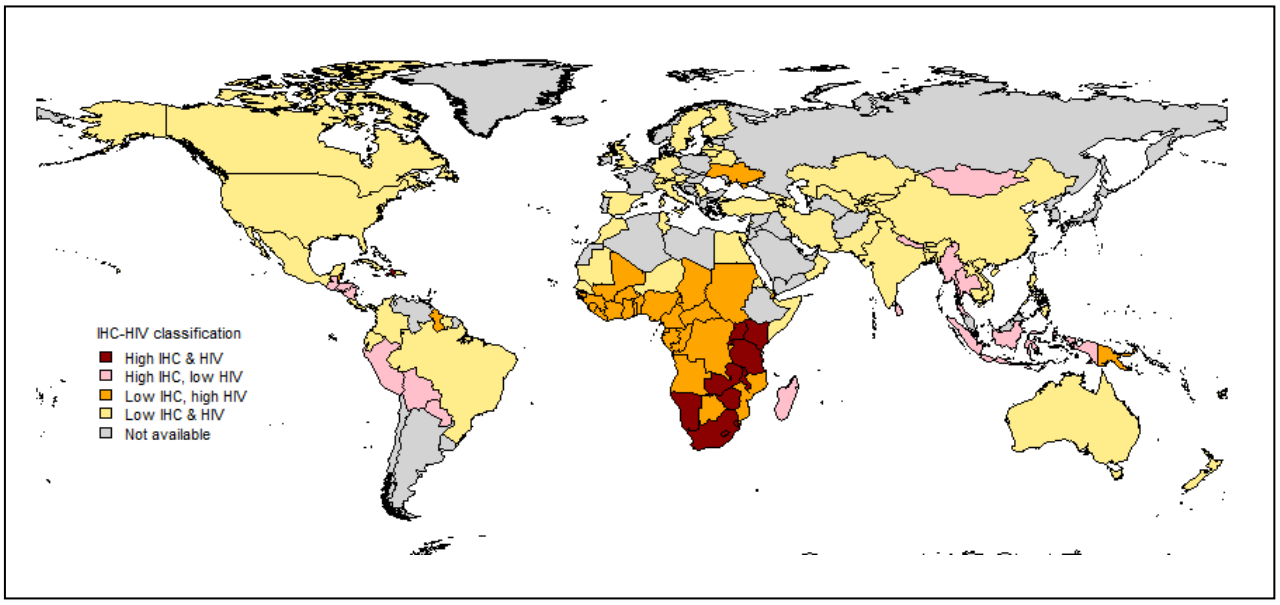

Figure 6. The overlap between use of injectables and HIV prevalence [106]

If the risk level were more moderate (e.g. increasing risk by only 20%), cessation of injectable contraceptive use could result in a greater number of deaths among women, as depicted for Malawi in Figure 8. If there was truly no increased HIV-1 risk from injectable contraceptives and injectables were discontinued, there would be a net increase in maternal death regardless of the HIV-1 incidence rate. This modeling work has been very helpful to put recent data in perspective for program and policy guidelines.

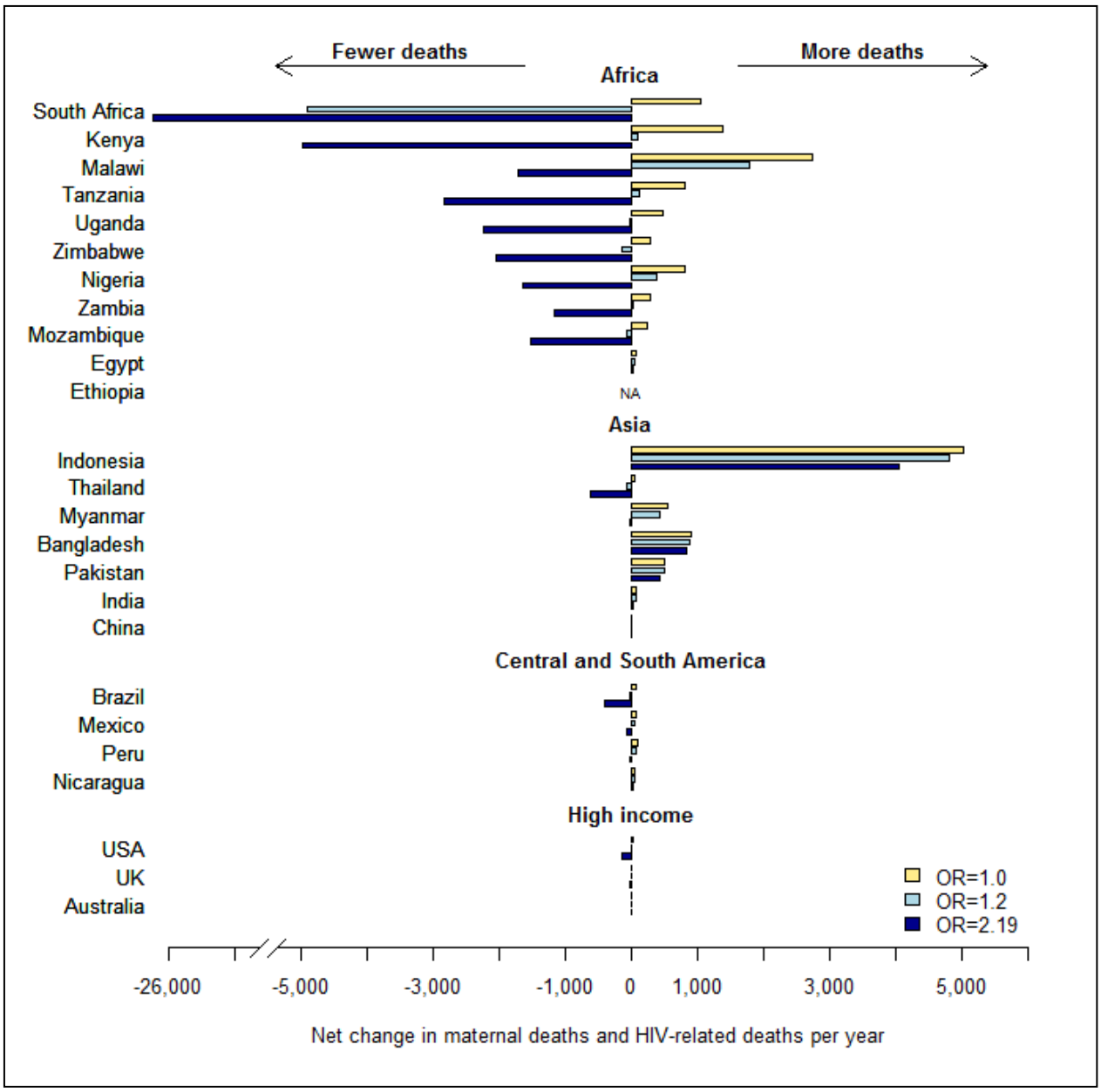

Figure 7. Absolute change in the net maternal and HIV-related deaths following cessation of injectable contraceptive use [106]

A well-conducted randomized trial could provide a definitive answer to the question of whether DMPA increases HIV-1 acquisition risk.[101] However, such a trial could only be ethically justified if the study were designed to establish whether a particular contraceptive method is more protective against HIV-1 infection than DMPA, rather than to establish that DMPA is harmful. Designing and conducting such a trial – with minimal loss to follow up and

contraceptive method switching, two factors that would undermine randomization – would be very difficult. [107] During the study design phase, a program for retaining participants could be laid out to minimize loss to follow up. This program could include gathering detailed locator information for each participant, scheduling frequent study visits (monthly or quarterly) to reduce the amount of time prior to discovering that a woman was lost to follow up, active tracing of lost participants until located and obtaining consent to conduct in-home study visits when participants fail to attend their scheduled study visit at the study clinic (Table 16).

Table 16. Potential limitations and methods to minimize limitations of a randomized controlled trial of DMPA and HIV-1 risk

Limitation of RCT	Method to minimize limitation
Loss to follow up	Short intervals between study visits, careful pre-study planning to locate missing participants, ability to conduct in-home study visits
Switching contraceptive method during study follow up	Use of long-acting user independent methods, such as injectables or implants
Alternative methods to DMPA are not readily available in Africa	Focus on multiple injectables that are available: DMPA and Net-En
Ethical obligation to provide antiretroviral PrEP to women enrolled in the study	Recruitment of high risk women, potentially using a risk score to incorporate factors most predictive of HIV acquisition [Kahle et al. CROI 2012]

Additionally, it is unclear what contraceptive methods should be used by women in the comparison arm (or arms) of a potential randomized trial. It would be unethical to randomize women desiring pregnancy prevention to use condoms only because this method requires partner participation that is not always forthcoming. Using a copper IUD, a very effective non-hormonal contraceptive, has been suggested but little human data exist on whether a copper IUD affects HIV-1 risk and biological studies suggest that a copper IUD may reduce HIV-1 risk due to the microbicidal effect of copper ions. Alternative progesterone-based injectables (i.e. Net-En) or implants may be most comparable to injectable DMPA but the study would then test whether DMPA increases risk relative to these methods, a different question than the one tested by studies to date. Furthermore, if either of these methods was found to be less risky than DMPA, the lack of acceptance and use of these methods currently in Africa would limit the

practical application of the results. In the absence of a randomized study, observational analyses using high quality, previously collected HIV-1 prevention trial data can contribute to the body of knowledge if appropriate statistical methods are used to carefully account for confounding factors.[108]

CHAPTER 4 INTERPRETATIONS

Antiretroviral-based HIV-1 prevention strategies may mitigate the potentially increased HIV-1 risk incurred by injectable contraceptive use. But in Chapter 4, we have learned that incorporating antiretroviral-based strategies into HIV-1 prevention programs for HIV-1 serodiscordant couples will need to consider individual preferences and offer alternatives to couples who are not ready to use and adhere to these methods. Forty percent of HIV-1 infected men and women in our study reported that they would not be willing to use antiretrovirals for HIV-1 prevention prior to their clinical needs. Information from future studies of antiretroviral willingness among public health clinic attendees will be the key to determine if our conclusions are generalizable to a population that is less familiar with HIV-1 prevention strategies. Most HIV-1 uninfected participants in our study in Thika, Kenya indicated a willingness to use PrEP on a long-term basis to reduce their susceptibility to HIV-1 infection. Targeted PrEP use prior to an HIV-1 infected partner's willingness to use and adhere to a full regimen of antiretrovirals could be a cost effective strategy.[83]

Delivery of antiretroviral-based HIV-1 prevention strategies should promote high adherence. Combining antiretroviral HIV-1 prevention delivery with contraceptive provision is one strategy that could improve women's adherence to antiretrovirals, especially PrEP. In the FEM-PrEP clinical trial of PrEP among high risk HIV-1 uninfected women, drug level testing revealed that <40% of women had sufficient blood levels of tenofovir to benefit from protection by PrEP. Whether this lack of adherence is due to low HIV-1 risk perception, convenience, or other factors may be better understood with ongoing qualitative work from this trial and

others.[109] Pregnancy prevention is often a greater priority for women than HIV-1 prevention and offering HIV-1 prevention services in conjunction with routine family planning services may increase convenience for women and take advantage of routine clinic visits for HIV-1 testing and PrEP provision. A similar model has been established with HIV-1 testing in antenatal settings to identify infected women and link them with services to prevent mother-to-child HIV-1 transmission.

Table 17. Quotes about potential antiretroviral use during peri-conception periods from members of HIV-1 serodiscordant couples in Thika, Kenya, who recently experienced a pregnancy

"It [to become HIV-1 infected] needs just only once so if there can be some medications…" *– HIV-1 uninfected male*
"It [getting a child] could be risky if there is nothing you are using like drugs or anything else." *–HIV-1 infected male*
"About the issue of another way [besides the use of medication and artificial insemination], there is no other way." *– HIV-1 uninfected male*
"We wanted to have another child after the approval of Truvada and Tenofovir." *–HIV-1 infected female*

Antiretroviral-based HIV-1 preventions strategies may be appropriate for couples during peri-conception periods. An important yet unmet need for HIV-1 serodiscordant couples is the knowledge and ability to practice strategies to reduce their HIV-1 risk while allowing them to conceive a child. In the Chapter 4 Addendum, nearly half of the participants had future fertility desires and of those, half were either currently pregnant or planning to have a child within the next 3 years. In our study, only half of participants were aware of strategies to reduce HIV-1 transmission while attempting to conceive a child, such as timed unprotected sex and antiretroviral use to achieve viral suppression. These findings are similar to findings in a study of men and women attending family planning clinics in South Africa, where participants lacked knowledge about harm reduction approaches to reduce HIV-1 transmission risk while allowing for conception. [39] In qualitative interviews with HIV-1 serodiscordant couples participating in the Partners PrEP Study in Thika, Kenya, couples who recently experienced pregnancy have indicated that they have little information that there are methods available to reduce their HIV-1 risk when they desire to conceive again in the future. But they have also indicated that they would be very willing to employ strategies to reduce HIV-1 risk, particularly antiretrovirals, if they were

counseled and were able to access them (Heffron, Ngure, Mugo, Baeten, Celum, unpublished, Table 17). In European couples, safer conception programs encouraging antiretroviral use and PrEP provision are underway; [100, 110] these strategies need to be tested in an African setting. Antiretrovirals could be the cornerstone in safer conception interventions for African HIV-1 serodiscordant couples and implementation research will be important to establish whether couples will use antiretrovirals during peri-conception periods.

FUTURE DIRECTIONS

Future directions for this work include research into the specific question of whether hormonal contraceptives are associated with an increased risk of HIV-1 and broader questions that bridge the fields of HIV-1 prevention and reproductive health. To continue to understand if there is an effect of hormonal contraception (particularly injectable DMPA) on HIV-1 susceptibility and infectiousness beyond sexual behavior, observational analyses will be conducted using data from the Partners PrEP Study. Compared to the study presented in Chapter 3, there are more women using hormonal contraceptives and <24 years old yet fewer HIV-1 endpoints in the Partners PrEP Study dataset. Thus power may be sub-optimal for some subgroup analyses but we intend to look for a differential effect of hormonal contraception on HIV-1 risk among younger women, which has been seen in one prior study.[14, 18, 84] With this dataset, we will also be able to determine if PrEP efficacy differs among women using and not using hormonal contraception and if PrEP reduces the efficacy of hormonal contraception to prevent pregnancy. There may also be an opportunity to conduct Y chromosome testing to validate self-reported condom use data.[111] These are timely and important questions that reproductive health and HIV-1 prevention practitioners need answers to.

A study of hormonal contraceptive use and cytokine levels is planned to explore one hypothesized biological mechanism. Previous studies on animal models and in cell culture and have indicated that progesterone may inhibit cytokine production. [20-22] Using data from the

Partners in Prevention HSV/HIV Transmission Study, we will examine the association of hormonal contraceptive use and serum cytokine levels among initially HIV-1 uninfected women (with matched samples from seroconverting and non-seroconverting women) using a mixed model and controlling for confounding factors. The panel of quantified analytes includes RANTES and IFN-α, which have been correlated with DMPA use in other studies and have been demonstrated to be associated with HIV-1 risk.[22, 112, 113]

Results from a meta-analysis encompassing data from multiple HIV-1 prevention trials to determine the association of hormonal contraception and HIV-1 risk will also provide insight. FHI360, a leader in the effort to find a definitive answer to the question of hormonal contraception and HIV-1 risk, is gathering data from 16 studies (including our data used in Chapter 3) to include in a meta-analysis. The principal investigators plan to conduct a longitudinal analysis among >26,000 women experiencing >1,300 HIV-1 seroconversions with careful control for behavioral covariates. This study should have sufficient numbers of DMPA, Net-En and oral contraceptive users, young women (<age 24) and HSV-2 infected and uninfected women to conduct subgroup analyses that have not always been adequately powered in the individual studies. Despite its size, this study will only be as methodologically sound as the datasets that contribute to it and it will be limited by self-reported contraceptive use and sexual behavior data, varying time intervals between HIV-1 testing, and heterogeneity in the HIV-1 risk of women (including members of serodiscordant couples, sex workers, and family planning clinic attendees). There is likely to be good precision in the risk estimate due to the large sample size and it will be important for the investigators to summarize the findings in light of these limitations.

Research into the best practices for implementing antiretroviral-based HIV-1 prevention to ensure high levels of coverage and adherence is essential. Now that PrEP and early ART efficacy has been demonstrated by multiple trials, PrEP demonstration projects are being conducted to determine “real world” acceptability, uptake and adherence to guide program

policy. New WHO guidelines recommend antiretrovirals for HIV-1 infected members of HIV-1 serodiscordant couples, regardless of CD4 count, to reduce transmission to the uninfected partner and many African countries are anticipated to adopt these guidelines.[30] An advisory committee to the U.S. Food and Drug Administration recently voted to approve a formal label indication for Truvada for HIV-1 prevention which would increase its acceptability and availability in some locations.[114] Long acting delivery systems for PrEP are also being studied, including two Phase III safety and effectiveness trials among >5000 African women of a dapivirine-containing vaginal ring to protect against HIV-1 infection.[115] Pharmaceutical companies and nonprofit organizations are also beginning to formulate and test multipurpose prevention technologies to deliver an antiretroviral and a contraceptive through one delivery mechanism (i.e. an injection or ring).[116] All of these strategies to incorporate antiretrovirals – as prophylaxis or treatment – into multi-component HIV-1 prevention programs will eventually provide individuals with a range of risk reduction options.

CONCLUSION

This dissertation has contributed landmark findings to the fields of HIV-1 prevention and reproductive health and provided insight into the best approaches to implement novel HIV-1 prevention strategies using antiretrovirals. Much work remains to control the African HIV-1 epidemic but the promise of HIV-1 prevention programs that incorporate antiretrovirals and are integrated with reproductive health services are fueling policy makers, researchers and providers to ensure these programs are successfully implemented with high quality to achieve the greatest impact.

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116. International Partnership for Microbicides. IPM Receives Award from USAID to Advance Dual-Purpose Prevention Ring. Accessed at: http://www.ipmglobal.org/publications/ipm-receives-award-usaid-advance-dual-purpose-prevention-ring on 3/30/2012. In; 2011.

CURRICULUM VITAE

Renee Annette Johnson Heffron, MPH, PhD

1. Education

Boston University, BA in Biological Anthropology, August 1996 – May 2000

- Completed undergraduate coursework requirements for the anthropology major degree and African studies minor

Tulane University, MPH in International Health and Development, August 2003-December 2004

- Completed graduate coursework and fieldwork requirements with an emphasis on HIV monitoring and evaluation in developing countries

University of Washington, PhD, Department of Epidemiology, September 20908-June 2012

- Infectious disease focus; research interests include HIV prevention and transmission and reproductive health decision-making among HIV discordant couples in Africa
- Funded through the Center for AIDS and STDs predoctoral fellowship training grant

2. Professional positions

Research Assistant – University of Washington, Dept of Global Health International Clinical Research Center
September 2008 – 2012

- Conduct routine monitoring of ongoing HIV-1 prevention clinical trial to ensure timely progression of study enrollment and high quality data collection
- Conduct longitudinal data analysis of various exposure and disease associations among HIV-1 serodiscordant couples in sub-Saharan Africa

Teaching Assistant, Epidemiologic Methods I & II – University of Washington, Dept of Epidemiology
September 2009-March 2010

- Conducted weekly in-class discussions of student homework assignments, graded student homework problems, and held weekly office hours to assist students to better understand core epidemiologic methods

Teaching Assistant, Introduction to Epidemiology, Executive degree program– University of Washington
June –July 2010 and September-December 2011

- Conduct sessions to review student homework assignments and key concepts presented during class lectures (2011 sessions conducted via Webinar); design and write additional practice problems for students; grade student homework problems and assist professor to grade student exams; respond to student e-mails concerning difficulties completing homework and understanding epidemiological concepts.

Epidemiology & Surveillance Associate – US Centers for Disease Control & Prevention, Zambia, Association of Schools of Public Health
February 2007 – June 2008

- Responsible for protocol development, submission to and regular correspondence with local and US IRB, supervised all field operations for data collection and staff training, conducted data analysis and manuscript preparation for prospective cohort study of risk factors for prevalent and incident HIV-1 among migrant farm workers
- Assisted with conduct of feasibility assessment for a study of HIV prevalence and risk factors for HIV infection among men who have sex with men in Zambia; participated in full study protocol development, held regular discussions with local stakeholders and oversaw preparation for data collection; developed audio computer-assisted self interview (ACASI) data collection tool
- Provided technical assistance to Ministry of Health for bi-annual antenatal clinic sentinel surveillance survey among antenatal women in Zambia and at Zambian refugee camps

HIV Surveillance Fellow –US Centers for Disease Control & Prevention, Zambia, Association of Schools of Public Health
February 2005-February 2007

- Same responsibilities as above

Public Health Intern – Family Health International, Kinshasa, DRC
June – August 2004

- Assisted with launch of pilot HIV Biological and Behavioral Surveillance Survey among commercial sex workers in Kinshasa; participated in data entry, analysis and report preparation

Evaluation Assistant - NO/AIDS Task Force, New Orleans, LA
October 2003 – January 2005

- Conducted monitoring & evaluation activities for a CDC-funded HIV prevention program for men who have sex with men in New Orleans; participated in program planning and grant writing for funding announcements from Centers for Disease Control & Prevention
- Certified HIV Prevention & Rapid HIV-1 Antibody test counselor

Supervisory Research Assistant, Brown University, Department of Child & Family Psychiatry
September 2002 – August 2003

- Compiled and edited intervention manuals and materials for a 5-year multi-site HIV risk reduction intervention study for adolescents in outpatient mental health care funded by NIMH
- Developed audio computer-assisted self interview (ACASI) data collection tool and coordinated project implementation

Health Agent & Community Mobilizer – US Peace Corps, Burkina Faso
June 2000 – June 2002

- Collaborated with health staff and community members in a rural village in West Africa to conduct outreach activities for the promotion of: HIV/AIDS awareness and

prevention, youth and women's development, guinea worm eradication, diarrhea and malaria prevention, and polio and meningitis immunizations

3. Bibliography

Refereed research articles:

1. Ngure K, **Heffron R**, Mugo N, Irungu E, Celum C, Baeten J. Successful increase in contraceptive uptake among Kenyan HIV-1 serodiscordant couples enrolled in an HIV-1 prevention trial. AIDS 2009. 23 (suppl 1): S89-S95.

2. **Heffron R**, Were E, Celum C, Mugo N, Ngure K, Kiarie J, Baeten J. A Prospective Study of Contraceptive Use among African Women in HIV-1 Serodiscordant Partnerships. Sexually Transmitted Diseases. 2010 Oct;37(10):621-8.

3. Mujugira A, Morrow RA, Celum C, Lingappa J, Delany-Moretlwe S, Fife KH, **Heffron R**, De Bruyn G, Homawoo B, Karita E, Mugo N, Vwalika B, Baeten JM. Performance of the Focus HerpeSelect-2 enzyme immunoassay for the detection of herpes simplex virus type 2 antibodies in seven African countries. Sex Transm Infect. 2011 Apr;87(3):238-241.

4. **Heffron R**, Chao A, Mwinga A, Sinyangwe S, Sinyama A, Ginwalla R, Shields JM, Kafwembe E, Kaetano L, Mulenga C, Kasongo W, Mukonka V, Bulterys M. High Prevalent and Incident HIV-1 and Herpes Simplex Virus 2 Infection among Male Migrant and Non-migrant Sugar Farm Workers in Zambia. Sex Transm Infect. 2011 Apr.

5. Mugo N, **Heffron R**, Donnell D, Wald A, Were E, Rees H, Celum C, Kiarie J, Cohen C, Kayintekore K, Baeten J. Increased Risk of HIV-1 Transmission in Pregnancy: A prospective study among African HIV-1 serodiscordant couples. AIDS. 2011 July.

6. **Heffron R**, Donnell D, Rees H, Celum C, Mugo N, Were E*, et al.* Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis* 2012,**12**:19-26.

7. Hallett TB, Baeten JM, **Heffron R**, Barnabas R, de Bruyn G, Cremin I*, et al.* Optimal Uses of Antiretrovirals for Prevention in HIV-1 Serodiscordant Heterosexual Couples in South Africa: A Modelling Study. *PLoS Med* 2011,**8**:e1001123.

8. Ngure K, **Heffron R**, Mugo NR, Celum C, Cohen CR, Odoyo J*, et al.* Contraceptive method and pregnancy incidence among African women in HIV-1 serodiscordant partnerships. *AIDS* 2011 Dec 7.

9. **Heffron R**, Ngure K, Mugo N, Celum C, Kurth A, Curran K*, et al.* Willingness of Kenyan HIV-1 serodiscordant couples to use antiretroviral based HIV-1 prevention strategies. JAIDS. *In press.*

Manuscripts in preparation:

Heffron, R, Donnell D, Rees H, Celum C, Mugo N, Were E*, et al.* Hormonal contraceptive use and the risk of HIV-1 disease progression.

4. Conference abstracts

Oral presentations:

1. **Heffron R**, Chao A, Bulterys M, Shields M, Ginwalla R, Mwinga A, Mukonka V, Sinyangwe S. Monitoring and evaluation of HIV prevalence and associated risk factors among migrant and nonmigrant farm workers at a large sugar estate in Zambia. *Oral presentation by R Heffron at the Zambia National AIDS Committee Monitoring & Evaluation Conference, Lusaka, Zambia 2008.*

2. **Heffron R**, Mugo N, Celum C, Baeten J. Contraceptive method and pregnancy risk among African women in HIV-1 serodiscordant partnerships. *CFAR Joint Symposium on HIV Research in Women, Chicago, IL 2010.*

3. **Heffron R**, Donnell D, Rees H, Celum C, Mugo N, Were E, de Bruyn G, Nakku-Joloba E, Ngure K, Kiarie J, Coombs R, Baeten J. Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis. *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy July 2011.* Abstract #WEAX0206.

4. **Heffron R**, Donnell D, Rees H, Celum C, Mugo N, Were E, de Bruyn G, Nakku-Joloba E, Ngure K, Kiarie J, Coombs R, Baeten J. Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis. *Kenyatta National Hospital Scientific Research Conference, October 2011.* Abstract # 49/2011.

5. **Heffron, R,** Donnell D, Rees H, Celum C, Mugo N, Were E, Rees H, Kiarie J, Thomas K, Baeten JM. Hormonal contraceptive use and the risk of HIV-1 disease progression. *19th Conference on Opportunistic Infections and Retroviruses, Seattle, WA March 2012*. Abstract #21.

Poster presentations:

1. Canavera M, **Johnson R**, Millogo C. The Life Skills Program in Peace Corps/Burkina Faso. *Poster presentation at the XIIth International Conference on AIDS and STIs in Africa, Burkina Faso, 2001.*

2. Lescano C, Brown L, DiClemente R, Donenberg G, Barve C, Crosby R, Hadley W, Lang D, **Johnson R**, McBride C. Family Program for Youth with Psychiatric Disorders. *Poster presentation at the National Institute of Mental Health Conference on the Role of the Family in Preventing HIV, Washington DC, 2003.*

3. **Johnson R** and Wong F. Evaluation of a Community Mobilization HIV Prevention Program Targeting Men Who Have Sex with Men (MSM) in New Orleans. *Poster presentation at Tulane University Health Sciences Research Days, New Orleans, LA, 2004.*

4. Mansergh G, Toledo C, **Heffron R**, Mwinga A, Onjoro-Meassick E, Villar C, Mukonka V, Bulterys M. Determining the feasibility of and approach to conducting an HIV assessment of men who have sex with men in Zambia. Poster presentation at the *International AIDS Society XVII International AIDS Conference, Mexico City, 2008.*

5. Hallett T, Baeten J, **Heffron R,** De Bruyn G, Delany-Moretlwe S, Gray G, Johnson L, McIntyre J, Rees H, and Celum C. ART or PrEP for HIV Prevention in HIV Serodiscordant Partnerships: A Mathematical Modeling Comparison. *Oral presentation by T Hallett at the 18th Conference on Retroviruses and Opportunistic Infections. Boston, 2011.* Abstract #99LB.

6. **Heffron R**, Donnell D, Rees H, Celum C, Mugo N, Were E, de Bruyn G, Nakku-Joloba E, Ngure K, Kiarie J, Coombs R, Baeten J. Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis. Poster presentation at the *NIH Graduate Student Research Conference*. Bethesda, MD. October 2011.

7. **Heffron R**, Ngure K, Mugo N, Celum C, Kurth A, Curran K, Baeten JM. Willingness of Kenyan HIV-1 serodiscordant couples to use antiretroviral based HIV-1 prevention strategies. *19th Conference on Opportunistic Infections and Retroviruses, Seattle, WA March 2012*. Abstract #1065.

5. Invited oral presentations

UNAIDS Reference Group on Estimates, Modelling and Projections, Seattle, WA. October 2011. Presentation titled: "Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis." October 2011.

2011 University of Washington Department of Global Health Seminar Series "Women and Global Health", Seattle, WA. Presentation titled: "Contraceptive use and HIV risk in Women." November 2011.

2011 STD and AIDS Research Symposium, University of Washington Center for AIDS Research STD Research Conference. Presentation titled: "Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis." November 2011.

6. Honors

2011	Scholarship recipient to the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Rome, Italy
2011	Selected to attend the NIH Graduate Student Research Conference, Bethesda, MD
2011	Selected by University of Washington to apply for the NIH Director's Early Independence Award (DP-5)
2012	Young Investigator Award for the 19th Conference on Retroviruses and Opportunistic Infections in Seattle, WA