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Contraceptive method and pregnancy incidence among African women in HIV-1 serodiscordant partnerships

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Abstract

Background—Effective contraception reduces unintended pregnancies and is a central strategy to reduce vertical HIV-1 transmission for HIV-1 infected women.

Methods—Among 2269 HIV-1 seropositive and 1085 seronegative women from 7 African countries who were members of HIV-1 serodiscordant heterosexual partnerships and who were participating in an HIV-1 prevention clinical trial, we assessed pregnancy incidence for women using various contraceptive methods using multivariate Andersen-Gill analysis.

Results—Compared with women using no contraceptive method, pregnancy incidence was significantly reduced among HIV-1 seropositive and seronegative women using injectable contraception (adjusted hazard ratio (aHR) 0.24, $p=0.001$ and aHR 0.25, $p<0.001$, respectively). Oral contraceptives significantly reduced pregnancy risk only among HIV-1 seropositive women (aHR 0.51, $p=0.004$) but not seronegative women (aHR 0.64, $p=0.3$), and, for both seropositive and seronegative women, oral contraceptive pill users were more likely to become pregnant than injectable contraceptive users (aHR 2.22, $p=0.01$ for HIV-1 seropositive women and aHR 2.65, $p=0.09$ for HIV-1 seronegative women). Condoms, when reported as being used as the primary

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Author Contributions

KN, RH, and JMB conceived the study and wrote the first draft of the manuscript. RH and JMB performed the statistical analysis. NRM, CC, CRC, JO, HR, JK, and EW contributed critical revisions to the analysis and interpretation. All authors contributed to the writing of the final draft.

contraceptive method, marginally reduced pregnancy incidence (aHR 0.85, $p=0.1$ for seropositive women and aHR 0.67, $p=0.02$ for seronegative women). There were no pregnancies among women using intrauterine devices, implantable methods or who had undergone surgical sterilization, although these methods were used relatively infrequently.

Conclusions—Family planning programs and HIV-1 prevention trials need innovative ways to motivate uptake and sustained use of longer acting, less user-dependent contraception for women who do not desire pregnancy.

Keywords

HIV-1; serodiscordant couples; contraception; Africa; women

Introduction

Pregnancy rates are high in sub-Saharan Africa [1] and almost one-quarter of pregnancies are estimated to be unintended [2]. Reducing unintended pregnancies among HIV-1 seropositive women is a core strategy to reduce vertical HIV-1 transmission [3]. Moreover, pregnancy may increase HIV-1 risk, further emphasizing the benefits of preventing unintended pregnancies [4, 5].

For clinical trials of new HIV-1 prevention strategies, such as antiretroviral pre-exposure prophylaxis (PrEP), contraceptive use minimizes protocol-required discontinuation of study products during pregnancy and fetal exposure to investigational agents [6]. Indeed, some recent HIV-1 prevention trials have required participants to use an effective contraceptive method in order to qualify for enrollment [7].

In previous studies among women from Africa, factors related to incident pregnancy have included younger age, fewer children, cohabitation with a male partner, and having frequent sex unprotected by condoms [8, 9]. Few studies have explored whether the choice of contraceptive method impacts pregnancy incidence among HIV-1 seropositive and HIV-1 seronegative African women. Among women participating in an HIV-1 prevention trial, all of whom were in an HIV-1 serodiscordant partnership (i.e. one partner was HIV-1 infected and the other was HIV-1 uninfected), we sought to determine if pregnancy incidence differed by contraceptive method.

Methods

Population and procedures

Between December 2004 and October 2008, 3408 heterosexual HIV-1 serodiscordant couples were enrolled in the Partners in Prevention HSV/HIV Transmission Study, a randomized, double-blind, placebo-controlled clinical trial of daily acyclovir herpes simplex virus type 2 (HSV-2) suppressive therapy provided to HIV-1 seropositive members of couples to reduce HIV-1 transmission risk. The study was conducted at 14 sites in 7 countries in East and Southern Africa (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia); acyclovir did not decrease HIV-1 transmission risk [10]. Couples were recruited through community outreach activities and referrals from HIV-1 testing and care organizations [11]. This report is a secondary analysis using data from this prospective study.

Eligible couples were 18 years of age, reported 3 episodes of vaginal intercourse during the three months prior to screening, and intended to remain as a couple. HIV-1 infected partners were seropositive for HSV-2, had a CD4 count ≥ 250 cells/mm³, and were not

eligible at enrolment for antiretroviral therapy (ART), according to national guidelines. Couples were followed for up to 24 months, with HIV-1 seropositive partners seen monthly and HIV-1 seronegative partners seen quarterly and were encouraged to come together during the quarterly visit for couples' risk reduction counselling. HIV-1 infected partners who became eligible for ART initiation during follow-up were actively referred to local HIV-1 care clinics.

Women were not required to use contraception, although HIV-1 seropositive women (who received study medication) could not be pregnant at study enrollment and were encouraged to delay pregnancy until after the study. Current contraceptive method, by self-report, was recorded at each study visit. Contraception was provided on-site or by referral [12]. For hormonal contraceptive methods, specific brand names were not recorded, although combined low-dose oral contraceptives and injectable depot medroxyprogesterone acetate were the most common contraceptive types used in national family planning programs at the time of the study. Urine pregnancy tests were performed quarterly for HIV-1 seropositive women; for HIV-1 seronegative women, pregnancy tests were done based on report of missed menses. HIV-1 seropositive women who became pregnant discontinued study medication for the duration of pregnancy and were referred for prevention of mother-to-child HIV-1 transmission services, and HIV-1 seronegative women who became pregnant were referred for antenatal services. All participants provided written informed consent. The institutional review boards at the University of Washington and all study sites approved the study protocol.

Statistical methods

We used multivariate Andersen-Gill modeling for recurrent events (with Efron methods for ties [13]) to assess the risk of pregnancy among women using different contraceptive methods versus women not using any contraception, analyzed as a time-dependent variable. Adjusted models included socio-demographic and clinical factors. Observations following pregnancy discovery at the study site were censored; observations following pregnancy termination remained in the dataset since women returned to being "at risk" for another pregnancy. For women experiencing multiple pregnancies, the same censoring rules were used for observations during the second or third pregnancy. For HIV-1 seronegative women, observations were censored following HIV-1 seroconversion. We tested whether the effectiveness of each contraceptive method differed between HIV-1 seropositive and seronegative women using a likelihood ratio test. Analyses were conducted using SAS 9.2.

Results

Population characteristics

After excluding 27 women who were determined ineligible for the trial based on confirmatory HIV-1 and HSV-2 testing completed after study completion and 27 women without follow-up data, 3354 women remained for analysis: 2269 (67.7%) were HIV-1 seropositive and 1085 (32.3%) were seronegative. The median age was 30 years and women had 1-2 children on average. Women reported a median of 4 [IQR 2-8] sex acts per month (Table 1).

Pregnancy rates during follow-up

Median follow-up for HIV-1 seropositive and HIV-1 seronegative women was 1.64 (IQR 1.21-1.97) and 1.68 (IQR 1.25-2.00) years, respectively. There were 500 pregnancies in 3197.2 woman-years (w-y) of follow-up among HIV-1 seropositive women and 226 pregnancies in 1542.6 w-y of follow-up among HIV-1 seronegative women (incidence rates of 15.6 and 14.8 per 100 w-y, respectively).

Contraceptive use and pregnancy during follow-up

83.3% and 80.5% of HIV-1 seropositive and seronegative women reported using condoms as contraceptive method at least once during the study, 12.6% and 9.0% ever used oral contraceptives, and 33.0% and 20.3% ever used injectable contraception. However, 67.0% of HIV-1 seropositive and 63.5% of HIV-1 seronegative women reported no contraceptive method during at least one study visit.

Among women not using contraception, pregnancy incidence was 21.0 and 26.8 per 100 w-y for HIV-1 seropositive and seronegative women (Table 2). Pregnancy rates were lower among women using condoms only (18.4 and 11.4 per 100 w-y for seropositive and seronegative women, respectively), oral contraception (15.6 and 14.4 per 100 w-y), and injectable contraception (6.8 and 6.0 per 100 w-y). There were no pregnancies observed among women using intrauterine devices (IUDs), implantable methods, or who had undergone surgical sterilization but very few women used these methods.

In multivariate analysis, both HIV-1 seropositive and seronegative women were substantially less likely to become pregnant if they used injectable contraception compared to women who used no contraception (adjusted hazard ratio [aHR]=0.25, $p<0.001$ and aHR=0.24, $p=0.001$, respectively). Condoms and oral contraceptives also reduced the incidence of pregnancy, but the effect of oral contraceptives was not statistically different from the effect of no contraception among HIV-1 seronegative women (aHR=0.64, $p=0.3$) and the effect of condoms was not statistically different from the effect of no contraception among HIV-1 seropositive women (aHR=0.85, $p=0.1$). The extent to which condoms prevented pregnancy among HIV-1 seropositive (aHR=0.85, $p=0.1$) and seronegative women (aHR=0.67, $p=0.02$) was statistically different (p -value for interaction=0.002) but the effectiveness of injectables and oral contraceptives was not different (p -value for interaction=0.15 and 0.1, respectively). When compared with those using injectable contraception, women were more likely to become pregnant if they used oral contraceptives (aHR=2.06, $p=0.01$ for HIV-1 seropositive women and aHR=2.71, $p=0.09$ for HIV-1 seronegative women) or condoms only (aHR=3.39, $p<0.001$ for HIV-1 seropositive women and aHR=2.82, $p=0.01$ for HIV-1 seronegative women).

In the multivariate models, other factors independently associated with incident pregnancy included being younger (aHR=5.08, $p<0.001$ for HIV-1 seropositive women and aHR=4.48, $p<0.001$ for HIV-1 seronegative women for those ≤ 24 years of age and aHR=3.16, $p<0.001$ and aHR=3.16, $p<0.001$ for those 25-34 years when compared to women >35 years old), having ≥ 2 children (aHR=1.96, $p<0.001$ and aHR=2.49, $p=0.001$), having a greater number of sex acts (aHR=1.81-2.32 for categories >0 /month; not statistically significant for HIV-1 seronegative women), reporting unprotected sex with the study partner (independent of condom use for contraception, aHR=2.30, $p<0.001$ and aHR=5.89, $p<0.001$), and having sex with a partner other than the study partner (aHR=2.24, $p<0.001$ and aHR=3.26, $p<0.001$). Having a curable sexually transmitted infection at the time of study enrollment and ART use by the HIV-1 seropositive member of the couple during study follow-up were not associated with pregnancy.

Discussion

In this large, prospective, multinational cohort of HIV-1 seropositive and seronegative African women in known heterosexual HIV-1 serodiscordant partnerships, women using injectable contraceptives had significantly lower pregnancy rates than oral contraceptive users. These results are consistent with previous studies reporting that injectable methods are more effective than oral methods in reducing the likelihood of pregnancy [8, 9,14]. We also observed high rates of pregnancy for both HIV-1 seropositive and HIV-1 seronegative

women (incidence 15.6 and 14.8 per 100 w-y, respectively) – similar to rates seen in other HIV-1 prevention trials in sub-Saharan Africa [8, 9, 15]. These high rates of pregnancy have the potential to compromise the power of biomedical HIV-1 prevention trials involving women, since those who become pregnant often are required to discontinue study products.

Notably, we found that no women using IUDs and implantable contraceptives experienced pregnancy, although the number using these methods was small. Previous studies have reported that IUDs are safe and effective for preventing pregnancy among women with and at risk for HIV-1 yet their use is still very low in sub-Saharan Africa [16-18]. Our data provide additional evidence of the potential for safe and effective long-acting user-independent contraceptive methods to reduce unintended pregnancies among HIV-1 seronegative and seropositive African women.

We have previously reported higher rates of condom use and lower rates of incident HIV-1 infection in this cohort (2.7 cases per 100 person-years overall) [10] compared to similar cohorts in this geographical region [19, 20]. In our cohort, condoms alone were not as effective for pregnancy prevention as injectable methods and their effectiveness differed based on HIV-1 status. Qualitative work we have done among HIV-1 serodiscordant couples has described challenges with consistent and correct condom use, with seronegative women reported more consistent condom use to prevent HIV-1 acquisition than seronegative men [21]. As family planning programs consider novel ways to increase access to and uptake of long-acting user-independent methods, it is also important to continue counseling women and men about the importance of condom use for protection against HIV-1 and sexually transmitted infections in conjunction with hormonal contraceptive use for pregnancy prevention [22, 23]. In clinical trial settings, efforts to link participants with contraceptive counseling and resources in the community will foster sustained use of contraceptive methods following study closure.

In conclusion, in this study of >3300 African women in stable heterosexual partnerships, injectable methods were the most effective contraceptive method for pregnancy prevention. Family planning programs and HIV-1 prevention trials need to develop innovative ways to motivate use of longer-acting, less user-dependent contraception for women with or at risk of HIV-1 who do not desire pregnancy and ensure that couples understand the importance of using dual methods for HIV-1 and pregnancy prevention.

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Table 1

Participant Characteristics*

	HIV-1 infected women (N=2269) N (%) or median (IQR)	HIV-1 uninfected women (N=1085) N (%) or median (IQR)
<i>Demographic characteristic</i>		
Age, yrs	30.0 (25.3 - 34.8)	30.6 (25.4 - 37.8)
Education, yrs	8.0 (6.0 - 10.0)	8.0 (6.0 - 10.0)
Married	1647 (73.7)	874 (80.6)
Partnership duration, yrs	4.8 (2.1 - 9.3)	6.7 (3.0 - 13.8)
Number of children	1.0 (0.0 - 2.0)	2.0 (1.0 - 3.0)
<i>Behavioral characteristics</i>		
Number of sex acts, past month	4.0 (2.0 - 8.0)	4.0 (2.0 - 8.0)
Any unprotected sex, past month	652 (29.2)	168 (30.8)
Any sex with an outside partner, past month	33 (1.5)	5 (0.9)
<i>Medical history</i>		
Curable sexually transmitted infection **	389 (18.9)	133 (14.1)
HSV-2 seropositive	2236 (100.0)	934 (86.1)
Circumcised (male partners)	1228 (54.9)	366 (33.8)
Ever pregnant during study (women)	474 (21.2)	293 (27.0)
Plasma HIV-1 RNA, (log ₁₀ copies/mL)	3.95 (3.2 - 4.5)	N/A
CD4 count (cells/mm ³)	480.5 (354.0 - 663.0)	N/A
<i>Contraceptive method</i>		
No contraception	725 (32.4)	394 (36.3)
Oral contraception	92 (4.1)	46 (4.2)
Injectable contraception	319 (14.3)	122 (11.2)
IUD	14 (0.6)	19 (1.8)
Implantable contraception	19 (0.9)	9 (0.8)
Hysterectomy/tubal ligation	87 (3.9)	38 (3.5)
Condoms	980 (43.8)	457 (42.1)

* All data are from the time of enrolment except the number / proportion who became pregnant during the study.

** *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*;

Table 2
Pregnancy incidence, by contraceptive method, for HIV-1 seropositive and seronegative women in African heterosexual HIV-1 serodiscordant partnerships

Contraceptive Method	HIV-1 Seropositive Women			HIV-1 Seronegative Women		
	# Pregnancies /follow-up time	Pregnancy incidence* (95% CI)	aHR** (95% CI) p-value	# Pregnancies/ follow-up time	Pregnancy incidence (95% CI)*	aHR** (95% CI) p-value
All women	500/3197.2	15.6 (14.4-16.9)		226/1524.6	14.8 (13.0-16.6)	
None	173/882.4	21.0 (18.3-23.8)	1.00	118/440.0	26.8 (22.7-31.0)	1.00
Oral contraceptives	24/153.5	15.6 (9.9-21.4)	0.51 (0.32-0.81) p=0.004	7/48.8	14.4 (4.5-24.2)	0.64 (0.26-1.56) p=0.3
Injectables	39/570.3	6.8 (4.8-8.9)	0.25 (0.17-0.37) p<0.001	8/132.4	6.0 (2.0-10.1)	0.24 (0.10-0.54) p=0.001
IUD	0/22.8	0.0 (0-13.1)	N/A	0/16.1	0.0 (0-18.6)	N/A
Contraceptive implant	0/42.9	0.0 (0-7.0)	N/A	0/17.1	0.0 (0-17.6)	N/A
Hysterectomy	0/149.2	0.0 (0-2.0)	N/A	0/53.5	0.0 (0-5.6)	N/A
Condoms	264/1436.1	18.4 (16.4-20.4)	0.85 (0.68-1.06) p=0.1	93/816.8	11.4 (9.2-13.6)	0.67 (0.47-0.94) p=0.02

* per 100 woman-years

** Multivariate Andersen-Gill proportional hazards analysis, adjusted for age (24, 25-34, 35 years), number of children with study partner (0, 1, 2), partnership duration (<1, 1-3, 4-10, >10 years), number of sex acts (0, 1-5, 6-10, > 10 per month), any unprotected sex with study partner (any versus none, per month), any sex with additional partners (any versus none, per month), having a sexually transmitted infection at study enrolment (any of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* in either partner), and antiretroviral therapy use by the HIV-1 seropositive member of the couple.