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Hormonal Contraceptive Use Among HIV-Positive Women and HIV Transmission Risk to Male Partners, Zambia, 1994–2012

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Background. Evidence on the association between female-to-male human immunodeficiency virus (HIV) transmission risk and hormonal contraception is sparse and conflicting.

Methods. Heterosexual HIV-discordant couples from Lusaka, Zambia, were followed longitudinally at 3 month-intervals from 1994 to 2012. The impact of hormonal contraception on time to HIV transmission from HIV-positive women to their HIV-negative male partners (M−F+) was evaluated.

Results. Among 1601 M−F+ couples, 171 genetically linked HIV transmissions occurred in men over 3216 couple-years (5.3 transmissions/100 couple-years; 95% confidence interval [CI], 4.5–6.2). In multivariable Cox models, neither injectable (adjusted hazard ratio [aHR], 0.6; 95% CI, .4–1.2), oral contraceptive pill (aHR, 0.8; 95% CI, .3–2.1), nor implant (aHR, 0.8; 95% CI, .5–1.4) use was associated with HIV transmission, relative to nonhormonal methods, after controlling for the man's age at baseline and time-varying measures of pregnancy, self-reported unprotected sex with the study partner, sperm present on a vaginal swab wet mount, genital inflammation of either partner, genital ulceration of the man, and first follow-up interval. Sensitivity analyses, including marginal structural modeling and controlling for viral load and fertility intentions available in a subset of couples, led to similar conclusions.

Conclusions. Our findings suggest null associations between hormonal contraception and risk of female-to-male HIV transmission. We support efforts to increase the contraceptive method mix for all women, regardless of HIV serostatus, along with reinforced condom counseling for HIV-serodiscordant couples.

Keywords. HIV discordant couples; HIV risk; hormonal contraception; longitudinal cohort; Zambia.

Hormonal contraceptive methods—oral contraceptive pills (OCPs), contraceptive implants, and injectable contraceptive agents—are mainstays of family planning and reduce unintended pregnancy (prong 2 of a 4-prong strategy developed by a World Health Organization [WHO] technical consultation for prevention of mother-to-child transmission for HIV-positive women [1, 2]), maternal-child mortality, and pregnancy-related morbidity [3, 4].

However, concern has been raised about whether hormonal contraceptive method use by human immunodeficiency virus (HIV)–positive women increases the risk of onward sexual transmission. Unfortunately, to date only 2 published studies have assessed the association between hormonal contraceptive method use and female-to-male HIV transmission, and each arrived at different conclusions, as summarized in a systematic review [5]. One study found that, among 2476 HIV-serodiscordant African couples in which the woman was HIV-positive, use of injectables increased the risk of female-to-male transmission (adjusted hazard ratio [aHR], 1.95; 95% confidence interval [CI], 1.1–3.6), relative to nonhormonal methods, in multivariable Cox models; marginal structural modeling led to similar conclusions [6]. However, another study among 159 HIV-discordant Ugandan couples in which the female was positive for HIV did not find an increased risk of HIV transmission from women using OCPs or injectables, although statistical power was limited [7].

Based on their review of the current evidence, the 2015 WHO recommendations place no restrictions on use of progestogen-only pills, progestogen-only injectables (depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate), or

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implants (levonorgestrel and etonogestrel) among HIV-positive women on the basis of HIV status alone [8]. WHO recommendations are continually updated on the basis of reviews of the literature, and additional evidence has been called for. Our study explores the association between hormonal contraceptive use (including OCPs, injectables, and implants) and the risk of female-to-male HIV transmission, while controlling for potential demographic, behavioral, and clinical confounders, in a longitudinal cohort of HIV-discordant couples in Zambia.

METHODS

Ethics

All participants provided written informed consent. This study was approved by the Office for Human Research Protections–registered institutional review boards at Emory University and in Zambia.

Study Design

From 1994 to 2012, HIV-discordant couples (married or cohabitating) identified through couples' voluntary HIV counseling and testing (CVCT) services in Lusaka, Zambia, were enrolled and followed longitudinally by the Rwanda Zambia HIV Research Group (RZHRG). We have previously reported on CVCT promotion, recruitment [9, 10], enrollment, retention [11], group pretest counseling, rapid HIV testing, counseling, couple posttest counseling [11, 12], cohort demographic characteristics [13], and the lack of association between time-varying contraceptive methods and male-to-female HIV acquisition risk [14].

Participants

This analysis is restricted to heterosexual couples residing in Lusaka in which the man was HIV negative and the woman was HIV positive (M−F+) at enrollment, the woman was not receiving antiretroviral treatment (ART), and the couple had at least 1 follow-up visit. ART became available in government clinics in 2007, and both therapeutic and prevention of mother-to-child transmission regimens and eligibility criteria changed over time. Couples were censored if either partner died, the relationship dissolved, the HIV-positive woman initiated therapeutic ART, or either partner was lost to follow-up. Couples in which the man experienced an unlinked infection (ie, an infection acquired from outside the study partnership) were excluded from the primary analysis because their female partner-level exposures cannot be assumed to have the same relationship to their outcomes and because they have different unknown confounders related to their outside partner's characteristics.

Exposures

Contraceptive methods were self-selected by the woman and categorized as OCPs, 150 mg intramuscular DMPA injectables, copper intrauterine device (IUD), Norplant or Jadelle implants, or permanent methods, including hysterectomy, vasectomy, or tubal ligation. OCPs, injectables, and implants (including placement/removal of IUDs and implants) were provided at the RZHRG research site at enrollment and at follow-up study visits that occurred every 3 months. In rare instances when women obtained these methods outside of our facilities, method use was self-reported and placement of IUDs and implants confirmed. We did not provide permanent methods (bilateral tubal ligation or hysterectomy for women or vasectomy for men) at the project site, but project physicians facilitated referrals to the University Teaching Hospital for those procedures, and notes from hospital records were transcribed into the research clinic charts. In our primary analysis, type of contraception was categorized as nonhormonal control (including condoms alone, copper IUD, and permanent methods), implant, injectable (the majority of which was DMPA), or OCP.

Collection of Baseline and Time-Varying Covariates

Baseline demographic data included age, years cohabitating, family income, Nyanja literacy, number of previous pregnancies, pregnancy status, fertility intentions, history of sexually transmitted infection (STI), herpes simplex virus type 2 (HSV-2) status, past year and lifetime number of sex partners, male circumcision status, HIV stage of the HIV-positive partner, and viral load (VL) of the HIV-positive partner. Baseline VL was collected starting in 1999, and fertility intentions were collected from 2002 to 2011.

Time-varying data collected at follow-up visits included pregnancy, self-reported number of protected and unprotected (condomless) sex acts with the study partner and acts outside of the couple, sperm on vaginal swab wet mount, composite indicators of recent genital inflammation or ulceration, and time since enrollment (dichotomized as 0–3 months vs >3 months since enrollment).

Outcome of Interest

The outcome of interest was time to genetically linked HIV transmission from HIV-positive women to their HIV-negative male partners. HIV-negative men were tested for HIV infection every 3 months, using screening and confirmatory rapid HIV serologic tests as previously described [12]. Time of infection was determined, when possible, through testing of plasma obtained from the last antibody-negative sample with p24 enzyme-linked immunosorbent assay and RNA polymerase chain reaction (PCR). Infections were classified as genetically linked after PCR-amplified comparisons of conserved nucleotide sequences from each partner [15]. Trask et al [15] examined sequence diversity in multiple regions within multiple genes in one of the most comprehensive analyses conducted to date focusing on determining linkage status based on HIV sequence variation, and led to the determination to use gp41 pair-wise distance measures and also localizing numerous gp41 sequences from many individuals on a phylogenetic tree to determine whether sequences from couples branch together. In extremely rare cases where there might be a

discrepancy between the linkage status, based on pair-wise distance measures and phylogenetic results, we repeated the analysis, using a gag region.

Data Analysis

Analyses were conducted with SAS v9.4 (Cary, North Carolina). Rates of HIV transmission were calculated as the number of incident transmissions from female-to-male partners per 100 couple-years of follow-up (couple-years are equivalent in number to person-years of observation, but "couple-years" is used to highlight our consideration of both partner's covariates). Cumulative duration of method use was calculated for each method. Average duration of follow-up, time between visits, number of visits per couple, and retention at 6 months, 1 year, and 2 years were calculated.

Descriptive analyses of baseline and time-varying measures of demographic, family planning, sexual history, and clinical characteristics were stratified by time-varying contraceptive method used and by HIV transmission status. Counts and percentages (calculated among unique couples or over all study intervals for baseline and time-varying variables, respectively) described categorical variables, while means and standard deviations described continuous variables. The significance of differences were evaluated via unadjusted Cox models, and crude HRs and 95% CIs are reported.

Variables with unadjusted associations with the outcome of interest ($P<.05$) that were also associated ($P<.05$) with method of contraception (in unadjusted Cox models, with method of contraception as a time-varying, repeated outcome; or covariates that changed the aHR for the outcome by ≥10%) were considered as confounders in the multivariable model. All time-independent variables were verified to satisfy the proportional hazards assumption using Schoenfeld residuals and graphical methods (plots of log[-log(survival probability)] vs log[time]). Multicollinearity was assessed using condition indices of 30 and variance decomposition proportions of 0.50 as cutoff criteria. Effect-measure modification was evaluated for VL, age, male circumcision status, genital inflammation, and genital ulceration. These variables were chosen on the basis of a priori hypotheses about possible differential underlying risk mechanisms. aHRs and 95% CIs are reported.

Sensitivity Analyses

Sensitivity analyses explored the effects building multivariable models: controlling for women's VL or men's fertility intentions among the subset of dates during which those variables were collected, censoring at first method switch after initial uptake, and limiting to periods with no self-reported condom use. Finally, marginal structural models (MSMs) were constructed to adjust for time-varying confounders that had the potential to simultaneously act as mediators of the association of interest. Specifically, we fit a weighted pooled logistic regression model, which may be regarded as a discrete-time analogue of the Cox proportional hazards model, with adjustment for time-varying confounders by use of stabilized weights. To build the MSMs, we used the same confounding assessment methods as for the Cox models. Loss to follow-up is captured through the censoring mechanism and modeled as a function of time-dependent and baseline risk factors, and thus the weights account for loss to follow-up [16, 17]. Further sensitivity analyses exploring the effects of building multivariable models censoring at pregnancy intervals, not controlling for pregnancy, and including couples who experienced an unlinked infection but censoring at time of unlinked infection are shown (Supplementary Table 1).

Unprotected Sex and Pregnancy Status

We explored unadjusted differences in time-varying pregnancy status (categorized as pregnant, up to 6 months after the postpartum period, or not pregnant/in the postpartum period during the interval that the behavioral or biological measures of unprotected sex were assessed) by measures of unprotected sex (as both a continuous variable and dichotomized as any vs none) and sperm presence on a vaginal swab wet mount, using χ^2 tests for categorical variables and t tests (unequal variance) for continuous variables.

Loss to Follow-up

To explore the potential for selective loss to follow-up, duration of follow-up was calculated by method of contraception, and characteristics of couples lost at 1-year of follow-up are presented stratified by method of contraception.

RESULTS

Transmission Rates and Follow-up

Of 1601 M−F+ couples, 171 linked transmissions occurred over 3216 couple-years (5.3 transmissions/100 couple-years; 95% CI, 4.5–6.2). Cumulative duration of method use was 2120 couple-years for condoms alone, 422 couple-years for OCPs, 405 couple-years for injectables, 163 couple-years for implants, 48 couple-years for IUDs, and 40 couple-years for permanent methods. Study partners were followed for a mean duration (±SD) of 734 ± 829 days. The mean time (±SD) between visits was 88 ± 50 days. The mean number of visits (±SD) per couple was 9.4 ± 9.7.

Baseline Characteristics by Contraceptive Method: Unadjusted Analyses

In unadjusted analyses, OCP users were younger, were more likely to have a male partner who wanted more children, had lower literacy, and were more likely to have sperm detected on vaginal swabs and less likely to fall pregnant during follow-up, compared with non–hormonal method users (Table 1). Injectable users had lower literacy, had more previous pregnancies, were less likely to want more children and more likely to have partners who wanted to delay the next pregnancy, self-reported more unprotected sex acts, and experienced fewer

Table 1. Descriptive Analyses of Baseline and Time-Varying Covariates, by Time-Varying Contraceptive Method Use, in Zambian Human Immunodeficiency Virus–Discordant (M−F+) Couples

Characteristic	Nonhormonal[a]	OCPs	Injectable	Implant	*P* Value[b]
Percentage of total intervals of method use	66	14	14	6	
Demographic (baseline)					
Age of man, y[c]	35.4 ± 8.7	33.6 ± 7.2	34.6 ± 7.6	35.8 ± 7.6	<.0001
Age of woman, y[c]	28.9 ± 7.0	27.5 ± 5.7	28.4 ± 5.9	29.2 ± 5.0	<.0001
Woman reads Nyanja					.01
Yes, easily	351 (28)	24 (17)	28 (21)	10 (21)	
With difficulty/not at all	903 (72)	117 (83)	107 (79)	38 (79)	
Family planning characteristics (baseline)					
Previous pregnancies, no.[c]	3.1 ± 2.3	3.1 ± 1.8	3.6 ± 2.2	3.8 ± 2.1	<.0001
Fertility intentions of man[d]					<.0001
Yes, in the next year	82 (25)	13 (14)	6 (6)	0 (0)	
Yes, but not next year	90 (28)	49 (52)	51 (50)	10 (38)	
Don't know/no	150 (47)	33 (35)	45 (44)	16 (62)	
Fertility intentions of woman[d]					<.0001
Yes, in the next year	161 (36)	22 (20)	12 (10)	1 (3)	
Yes, but not next year	87 (19)	32 (30)	39 (33)	6 (17)	
Don't know/no	200 (45)	54 (50)	69 (58)	28 (80)	
Clinical (baseline)					
VL of woman, $\log_{10}$ copies/mL[c,e]	4.5 ± 0.9	4.5 ± 0.9	4.3 ± 0.9	4.0 ± 1.0	<.0001
Circumcised male partner					.84
No	1036 (82)	122 (85)	114 (81)	42 (84)	
Yes	222 (18)	22 (15)	27 (19)	8 (16)	
Sexual behavior and family planning (time varying)					
Any unprotected sex with study partner since last visit					.03
No	5429 (64)	1110 (62)	1096 (62)	474 (67)	
Yes	3032 (36)	681 (38)	672 (38)	231 (33)	
Sperm present on vaginal swab wet mount					<.0001
No	7253 (93)	1597 (91)	1677 (94)	695 (97)	
Yes	554 (7)	159 (9)	98 (6)	24 (3)	
Pregnant					<.0001
No	6754 (90)	1594 (97)	1677 (100)	641 (100)	
Yes	782 (10)	56 (3)	5 (0)	1 (0)	

Data are no. (%) of intervals or mean value ± SD, unless otherwise indicated.

Abbreviations: OCP, oral contraceptive pill; VL, viral load.

[a] Includes couples using condoms alone, the copper intrauterine device, or permanent methods.

[b] By 2-tailed χ^2 tests for categorical variables or *t* tests (unequal variance) for continuous variables.

[c] Indicates a continuous variable.

[d] Data were collected from 2002 to 2011.

[e] Data were collected from 1999 onward.

pregnancies during follow-up, compared with nonhormonal method users. Implant users were of lower literacy, had more previous pregnancies, were less likely to want more children and to have male partners who did not want more children, self-reported fewer unprotected sex acts, had sperm on a vaginal swab wet mount less often, and experienced fewer pregnancies, compared with nonhormonal method users.

Baseline Characteristics by Transmission Status: Unadjusted Analyses

Couples experiencing a linked transmission (n = 171) versus nontransmitting couples (n = 1430) were younger, had fewer previous pregnancies, expressed increased desire for more children, had a higher VL in the female partner at baseline, and were less likely to have a circumcised male partner (Table 2). HSV-2 status for both men and women at baseline, past year and lifetime number of sex partners, couples' baseline monthly income, and baseline HIV stage of the woman were not associated with HIV transmission (data not shown).

Time-Varying Characteristics by Transmission Status: Unadjusted Analyses

Couples experiencing a linked transmission were less likely to use injectables versus a nonhormonal method and were more likely to report any unprotected sex since the last study visit, to have sperm on a vaginal swab wet mount, to be pregnant (Table 3), and to have recent genital ulceration or inflammation

Table 2. Unadjusted Descriptive Analyses of Baseline Covariates by Human Immunodeficiency Virus (HIV) Infection Outcomes Among Zambian Men in HIV-Discordant Relationships

Characteristic	Nontransmitting Couples (n = 1430)	Transmitting Couples (n = 171)	cHR (95% CI)	*P* Value[a]
Demographic				
Age of man (per year increase)[b]	35.4 ± 8.5	33.1 ± 8.0	0.97 (.95–.99)	.001
Age of woman (per year increase)[b]	29.0 ± 6.8	27.0 ± 6.2	0.97 (.94–.99)	.01
Woman reads Nyanja				
Yes, easily	379 (27)	36 (22)	Reference	
With difficulty/not at all	1037 (73)	131 (78)	1.19 (.83–1.73)	.35
Family planning				
Previous pregnancies, no.[b]	3.2 ± 2.2	3.0 ± 2.2	0.90 (.83–.98)	.02
Fertility intentions of man[c]				
Yes, in the next year	92 (19)	10 (16)	1.26 (.59–2.72)	.55
Yes, but not next year	169 (35)	33 (53)	2.08 (1.18–3.67)	.01
Don't know/no	226 (46)	19 (31)	Reference	
Fertility intentions of woman[c]				
Yes, in the next year	183 (28)	16 (24)	1.26 (.68–2.33)	.47
Yes, but not next year	144 (22)	20 (30)	1.35 (.77–2.36)	.30
Don't know/no	321 (50)	31 (46)	Reference	
Clinical				
VL of woman (per $\log_{10}$ copies/mL increase)[b,d]	4.3 ± 0.9	4.8 ± 0.7	1.45 (1.23–1.71)	<.0001
Circumcised male partner				
No	1160 (81)	159 (93)	2.69 (1.49–4.85)	.001
Yes	267 (19)	12 (7)	Reference	

Data are no. (%) of subjects or mean value ± SD.

Abbreviations: cHR, crude (unadjusted) hazard ratio; CI, confidence interval; VL, viral load.

[a] Data are 2-tailed.

[b] Indicates continuous variables.

[c] Data were collected from 2002 to 2011.

[d] Data were collected from 1999 onward.

Table 3. Unadjusted Descriptive Analyses of Time-Varying Variables, by Human Immunodeficiency Virus (HIV) Infection Outcomes Among Zambian Men in HIV-Discordant Relationships

Variable	Nontransmitting Intervals	Transmitting Intervals	cHR (95% CI)	*P* Value[a]
Contraceptive method				
Nonhormonal[b]	8419 (66)	132 (77)	Reference	
OCP	1781 (14)	21 (12)	0.77 (.48–1.23)	.27
Injectable	1786 (14)	13 (8)	0.53 (.30–.95)	.03
Implant	717 (6)	5 (3)	0.58 (.23–1.43)	.23
Sexual behavior and family planning characteristics				
Any unprotected sex with study partner since last visit				
No	8409 (64)	71 (42)	Reference	
Yes	4646 (36)	100 (58)	2.39 (1.75–3.25)	<.0001
Sperm present on vaginal swab wet mount				
No	11 153 (93)	124 (83)	Reference	
Yes	811 (7)	25 (17)	2.40 (1.50–3.85)	<.001
Pregnant				
No	10 575 (93)	135 (84)	Reference	
Yes	819 (7)	26 (16)	2.27 (1.49–3.46)	<.001

Data are no. (%) of intervals. Genital inflammation in man or woman in the past 3 months, genital ulceration of man in past 3 months, and interval of enrollment (0–3 vs >3 months) were also associated ($P < .05$) with the outcome.

Abbreviations: cHR, crude (unadjusted) hazard ratio; CI, confidence interval; OCP, oral contraceptive pill.

[a] Data are 2-tailed.

[b] Includes couples using condoms alone, the copper intrauterine device, or permanent methods.

(male or female) versus nontransmitting couples. Seroconversion was more likely between enrollment and the first follow-up visit, likely reflecting transmission that had occurred prior to joint testing and counseling, compared with subsequent follow-up intervals.

Multivariable and Sensitivity Analyses

No effect-measure modifiers (VL, age, male circumcision status, genital inflammation, or genital ulceration) were found (Table 4). Man's age, woman's age, and number of previous pregnancies were collinear; man's age was retained in the models.

The final primary analysis model controlled for man's age, pregnancy, any self-reported unprotected sex with the study partner since the last study visit, sperm on a vaginal swab wet mount, genital inflammation of either partner, genital ulceration of the male partner, and time since enrollment (0–3 months vs >3 months). The primary adjusted model models 143 of 171 outcomes (84%).

Hormonal contraception was not associated with increased risk of incident female-to-male HIV transmission in primary or sensitivity analyses (Table 4 and Supplementary Table 1).

Unprotected Sex and Pregnancy

Pregnant women reported unprotected sex more often and had a higher average number of unprotected sex acts relative to women in the postpartum period or those who were not pregnant/not in the postpartum period ($P < .05$; Table 5). Pregnant women were also more likely to have sperm on a wet mount versus women who were not pregnant/not in the postpartum period ($P < .05$).

Loss to Follow-Up

In this open cohort, overall retention was 77% at 6 months, 57% at 1 year, and 34% at 2 years. By method use, retention at 1 year was higher for hormonal method users (61% for OCP users, 69% for injectable users, and 70% for implant users) versus nonhormonal-method users (54%).

Compared with the baseline cohort, couples in which women were using injectables and were lost to follow-up by 1 year were more likely ($P < .05$) to want children within the next year, to have female partners with a lower viral load, and to have male partners who were circumcised. There were no differences in injectables users who were lost to follow-up by 1 year, compared with baseline, by couple age, sperm presence on a vaginal swab wet mount, self-reported unprotected sex, or pregnancy frequency.

Compared with the baseline cohort, OCP users lost to follow-up by 1 year were more likely ($P < .05$) to self-report unprotected sex, to not want children within the next year, and to have male partners who were uncircumcised; there were no differences in OCP users who were lost to follow-up by 1 year, compared with baseline, by couple age, sperm presence on a vaginal swab wet mount, pregnancy frequency, or female viral load.

Compared with the baseline cohort, implant users lost to follow-up by 1 year were more likely ($P < .05$) to have male partners who were circumcised and to not self-report unprotected sex; there were no differences in implant users who were lost to follow-up by 1 year, compared with baseline, by couple age, sperm presence on a vaginal swab wet mount, pregnancy frequency, female viral load, or fertility intentions.

Table 4. Multivariable Models of Time-Varying Hormonal Contraception and Time to Human Immunodeficiency Virus (HIV) Infection Among Zambian Men in HIV-Discordant Relationships

Primary Model	aHR (95% CI)	*P* Value[a]
Contraceptive method		
Nonhormonal[b]	Reference	
OCPs	0.84 (.34–2.13)	.72
Injectables	0.64 (.35–1.16)	.14
Implant	0.83 (.50–1.38)	.46
Sensitivity analyses		
Model controlling for woman's viral load[c]		
Nonhormonal[b]	Reference	
OCPs	0.99 (.38–2.57)	.98
Injectables	0.65 (.35–1.21)	.17
Implant	0.92 (.55–1.54)	.92
Model controlling for man's fertility intentions[c]		
Nonhormonal[b]	Reference	
OCPs	0.59 (.14–2.56)	.48
Injectables	0.48 (.20–1.18)	.11
Implant	0.81 (.39–1.65)	.55
Model censoring at first method switch		
Nonhormonal[b]	Reference	
OCPs	0.51 (.12–2.13)	.36
Injectables	0.67 (.34–1.33)	.26
Implant	0.87 (.47–1.60)	.65
Model limited to no self-reported condom use (only condomless sex intervals)		
Nonhormonal[b]	Reference	
OCPs	0.92 (.28–3.07)	.90
Injectables	0.68 (.31–1.46)	.32
Implant	0.76 (.37–1.59)	.47
Marginal structural models[e]		
Nonhormonal[b]	Reference	
OCPs	0.96 (.47–1.99)	.92
Injectables	0.72 (.32–1.62)	.43
Implant	1.68 (.52–5.45)	.39

Abbreviations: OCP, oral contraceptive pill; aHR, adjusted hazard ratio; CI, confidence interval; VL, viral load.

[a] Data are 2-tailed.

[b] Includes couples using condoms alone, the copper intrauterine device, or permanent methods.

[c] Models controlling for woman's viral load were run among the subset of couples tested from 1999–2012; models controlling for man's fertility intentions were run among the subset of couples tested between 2002–2011.

[d] Controlling for man's age, pregnancy, any self-reported unprotected sex with study partner in the last 3 months, sperm present on vaginal swab wet mount, genital inflammation in man or woman in the past 3 months, genital ulceration of man in past 3 months, and interval of enrollment (0–3 vs >3 months).

[e] Controlling for man's age, male circumcision status, and interval of enrollment (0–3 months vs >3 months).

DISCUSSION

In this 18-year prospective follow-up study, use of hormonal contraception (OCP, implant, or injectable) was not associated

Table 5. Time-Varying Measures of Unprotected Sex, by Time-Varying Pregnancy Status, in Zambian Human Immunodeficiency Virus–Discordant (M−F+) Couples

Variable	Pregnant	In Postpartum Period (up to 6 Mo)	Not Pregnant or in Postpartum Period	*P* Value[a]
Self-reported no. of unprotected sex acts with study partner since last visit[b]	6.8 ± 16.0	2.5 ± 10.7	3.3 ± 11.3	<.05[b,c,d]
Self-reported unprotected sex with study partner since last visit				<.05[b,c,d]
No	368 (44)	232 (73)	6537 (64)	
Yes	476 (56)	84 (27)	3687 (36)	
Sperm present on wet mount				<.05[c]
No	685 (90)	283 (92)	9120 (93)	
Yes	78 (10)	25 (8)	694 (7)	

Data are no. (%) of individuals or mean value ± SD

[a] By 2-tailed χ^2 tests for categorical variables or *t* tests (unequal variance) for continuous variables.

[b] Indicates a continuous variable, mean and standard deviation reported.

[c] *P*<.05 for tests of differences between pregnant women vs postpartum women.

[d] *P*<.05 for tests of differences between pregnant women vs women not pregnant or in postpartum period.

[e] *P*<.05 for tests of differences between postpartum women vs women not pregnant or in postpartum period.

with an increased risk of HIV transmission from HIV-positive women to their HIV-negative male partners, after adjustment for demographic, behavioral, and clinical risk factors. Our findings are in conflict with those of Heffron et al, who found injectables to be associated with an increased risk of female-to-male HIV transmission [6], and of Lutalo et al [7], who, although the power of their analysis was also limited, found a nonstatistically significant association of increased risk. However, we hesitate to overinterpret the direction of the nonsignificant association between injectables and risk of female-to-male HIV transmission in any one study but highlight the ongoing need for well-designed high-quality studies to be combined as an effort to better quantify potential trends.

The design and analysis of our investigation overcomes several common challenges in similar studies, which were recently detailed along with potential solutions in an article by Polis et al [18]. Our self-reported measures of unprotected sex could be corroborated with biological measures (including sperm presence on a wet mount, incident pregnancy, and incident STIs). Both biological and self-reported measures of unprotected sex have strengths and weaknesses. Testing for sperm on a vaginal swab wet mount has a high positive predictive value but a rather low negative predictive value (sperm can survive in the vagina for roughly 3 days). Self-reported unprotected sex is widely known to be underreported. As the 2 measures were not collinear in our data set, and since both are independently predictive of the outcome, we feel that they are both informative confounders. Contraceptive use was measured frequently (every 3 months) to accurately capture rates of use, stopping, and switching, which we know to be high in this cohort [19]. Importantly, contraceptive methods were provided primarily at the research site, and thus we did not rely on self-reported method use except for OCP adherence. We have previously validated the accuracy of self-reported contraceptive methods among the study population of interest [20], as suggested by Polis et al [18]. Our study distinguished between all incident HIV infections and those that are genetically linked to the HIV-positive female partner, whose contraceptive methods are the exposures of interest. Following serodiscordant couples minimizes the within-sample variation in risk of HIV exposure. Finally, we substantiated our findings with rigorous sensitivity analyses including marginal structural models.

We found that, similar to M+F− couples [14], pregnancy intervals are associated with the highest rates of biological and self-reported measures of unprotected sex. This finding is important given that women not using more-efficacious contraceptive methods, including injectables, implants, IUDs, or permanent methods, experience higher rates of unintended pregnancy [19] and may be at increased risk of unprotected sex during pregnancy. Reinforced condom counseling for discordant couples may be particularly important during pregnancy and among those couples not using any form of modern contraception.

ART can reduce transmission by up to 96% [21]. However, it remains important to understand these associations in ART-naive couples since, even today, roughly half of HIV-positive Zambian adults are currently not accessing ART [22]. Even among those who do access treatment, adherence and retention are low [23, 24].

As in all observational studies, unmeasured confounders may bias the results in an unknown direction. This investigation estimated total effects (ie, exposure or covariate-mediated pathways, in addition to direct effects), controlling for confounding, which may be more relevant for informing public policy rather than addressing biological plausibility. Importantly, loss to follow-up may be leading to bias and limiting generalizability. Retention is measured at the couple level (if either partner is lost to follow-up or censored for eligibility, then the couple is censored). At 6 months, retention was 77%, dropping to 54% at 1 year. In the case of injectable users, the method of most public health

concern, those lost to follow-up at 1 year were more likely to want children, which could potentially bias our results towards the null; however, these couples were more likely to have female partners with a lower viral load and to have male partners who were circumcised, which could potentially bias our results away from the null. Missing data for those retained in the study was relatively minimal and primarily concerns the confounders (not the exposure or outcomes)—due to missingness of confounders, we modeled between 75% and 85% of the outcomes. Our findings should be interpreted in light of the retention rates in this open cohort and the potential for selective loss to follow-up. Finally, although the majority of injectable use both in our study and nationwide was DMPA, we cannot quantify the frequency in which women used Net-En, possibly occurring outside of the study.

Despite these limitations, our findings add an important data point to a small, conflicting literature that is the basis for current policy recommendations. It is important to note that findings such as ours are only part of the story—any future policy changes must balance the public health goals of preventing HIV transmission and unintended pregnancy among all couples. To accomplish that, the current evidence must be weighed in the context of country-specific HIV prevalence; rates of unintended pregnancy, maternal and child mortality, and vertical HIV transmission; access and utilization of hormonal methods; and the cost-effectiveness of contraceptive methods [25].

We support efforts to increase access to the full range of contraceptive methods for all women, regardless of HIV status, to decrease unintended pregnancy and associated negative health outcomes, including maternal-child mortality and mother-to-child HIV transmission. Discordant couples who are pregnant or contemplating pregnancy merit reinforced condom counseling. Where and when affordable, ART use among HIV-positive women with negative partners and preexposure prophylaxis use by HIV-negative men with positive partners may mitigate transmission. As most discordant couples in Southern Africa do not yet know they are discordant, we urgently endorse WHO guidelines promoting couples' joint HIV testing and counseling for HIV prevention. Identification of discordant couples through couple's voluntary HIV counseling and testing provides a mechanism to counsel couples on both HIV prevention and prevention of unintended pregnancy and serves as an entry point for other prevention and treatment services.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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