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# Hormonal contraception does not increase women's HIV acquisition risk in Zambian discordant couples, 1994–2012

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## Abstract

**Objective—**To determine the impact of hormonal contraceptive methods on risk of HIV acquisition among HIV-negative women cohabiting with HIV-positive male partners.

**Study design—**From 1994–2012, HIV discordant couples recruited from a couples' voluntary HIV counseling and testing center in Lusaka, Zambia were followed longitudinally. HIV-negative partners were tested quarterly. This analysis is restricted to couples in which the man was HIV-positive and the woman was HIV-negative at enrollment and the man was not on antiretroviral treatment. Multivariate Cox models evaluated associations between time-varying contraceptive methods and HIV acquisition among women. Sensitivity analyses explored exposure misclassification and time-varying confounder mediation.

**Results—**Among 1393 couples, 252 incident infections occurred in women over 2842 couple-years (8.9 infections per 100 couple-years; 95% CI, 7.8–10.0). Multivariate Cox models indicated that neither injectable [adjusted hazard ratio (aHR)=1.2; 95% CI, 0.8–1.7], oral contraceptive pill (OCP, aHR=1.3; 95% CI, 0.9–1.8), or implant (aHR=1.1; 95% CI, 0.5–2.2) use was significantly



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associated with HIV acquisition relative to non-hormonal contraception controlling for woman's age, literacy and time-varying measures of genital ulceration/inflammation. This remained true when only looking at the subset of infections acquired from the spouse (82% of infections) and additionally controlling for baseline HIV viral load of the male partner, pregnancy status, and time-varying measures of sperm on a vaginal swab wet prep and self-reported unprotected sex. OCP and injectable users reported more unprotected sex (p<.001), and OCP users were more likely to have sperm on vaginal swab (p=.1) than nonhormonal method users.

**Conclusions—**We found no association between hormonal contraception and HIV acquisition risk in women. Condom use and reinforced condom counseling should always be recommended for HIV discordant couples. HIV testing of sex partners together is critical to establish HIV risk, ascertain couple fertility intentions and counsel appropriately.

**Implications—**These findings add to a controversial literature and uniquely address several common design and analytic challenges faced by previous studies. After controlling for confounders, we found no association between hormonal contraception and HIV acquisition risk in women. We support promoting condoms for HIV prevention and increasing the contraceptive method mix to decrease unintended pregnancy.

### Keywords

Discordant couples; HIV risk; Hormonal contraception; Longitudinal cohort; Women; Zambia

## 1. Introduction

Hormonal contraception (HC), including injectable depot medroxyprogesterone acetate (DMPA) and oral contraceptive pills (OCPs), prevents unintended pregnancy [1] and is widely used in high HIV prevalence areas [2]. After reviewing the evidence, a 2014 World Health Organization meeting recommended that no restrictions (Medical Eligibility Criteria Category 1) be placed on HC use by women at risk for HIV and that “women and couples at high risk of HIV acquisition considering progestogen-only injectables should also be informed about and have access to HIV preventive measures, including male and female condoms” [1].

However, extant evidence is conflicting and highly debated [1,3–7]. In a recent systematic review, one out of eight studies deemed “informative but with important limitations” found OCP use significantly increased HIV acquisition risk in women. In that same review, four out of nine studies deemed “informative but with important limitations” found injectable contraception significantly increased HIV acquisition risk in women (notably, one found increased risk in marginal structural models but not Cox models) [8]. In a meta-analysis of observational studies of hormonal contraceptive method use and risk of HIV acquisition among women published in 2015, ten of twelve studies that met inclusion criteria indicated moderate increased risk of HIV acquisition among women using DMPA; none of the 10 studies that met inclusion criteria indicated increased risk among women using OCPs [9]. Finally, in another meta-analysis also published in 2015, DMPA use was associated with HIV acquisition relative to non-hormonal method use after pooling 18 studies, but this association became non-significant when looking at studies deemed to be at lower risk for methodological bias [10]. Limited data exist evaluating the association between HIV acquisition risk and contraceptive implants [8].

Various analytic design and methodological challenges faced by previous studies have made findings difficult to synthesize. As a result, recommendations were recently developed for more rigorous and consistent analytic methods [11]. The methodological design of the present study allowed for comprehensive consideration of these recommendations. Our objective was to determine the impact of HC, including injectable DMPA, OCPs and implants, on risk of HIV acquisition among women in HIV discordant couples.

## 2. Methods

### 2.1. Participants and ethics

From 1994–2012, married or cohabiting HIV sero-discordant (one partner HIV-1 infected and one uninfected) couples living in Lusaka, Zambia were enrolled in a prospective study. Discordant couples were identified from couples' voluntary HIV counseling and testing (CVCT) services offered by the Rwanda Zambia HIV Research Group (RZHRG). RZHRG CVCT promotions, recruitment [12,13], enrollment, retention [14], testing, counseling [14,15] and cohort demographics [16] have been described previously. Briefly, CVCT includes group counseling, rapid HIV testing, and joint post-test couple counseling. This analysis is restricted to couples in which the man was HIV-positive and the woman was HIV-negative (M+F−) at enrollment, the man was not on antiretroviral treatment, and the couple had at least one follow-up visit. This study was approved by the Office for Human Research Protections-registered Institutional Review Boards at Emory University and in Zambia. Written informed consent was obtained from participants.

### 2.2. Exposure

Contraceptive methods [categorized as no method/condoms alone, combined OCPs (progesterone-only typically prescribed to breastfeeding women until children were 6 months old), DMPA injectables (150 mg IM dosage), copper intrauterine device (IUD), contraceptive implant (Norplant, Jadelle), or permanent methods (hysterectomy/tubal ligation/vasectomy)] were provided at the research site at baseline and at three-monthly follow-up visits. In our primary analysis, contraceptive methods were categorized as implant, injectable, or OCP versus non-HC control (which includes couples using no method/condoms alone, copper IUD, or who had a hysterectomy/tubal ligation/vasectomy).

### 2.3. Baseline covariates

At enrollment, baseline demographic data were collected including age, years cohabiting, monthly income, and Nyanja literacy (the most commonly used local language in Lusaka). Behavioral risk factors included number of previous pregnancies, current pregnancy, fertility intentions and number of lifetime sexual partners. Clinical characteristics of HIV-positive men partners included viral load (VL) categorized as ≥100,000 copies/mL, ≥10,000 to <100,000 copies/mL, or <10,000 copies/mL [17].

### 2.4. Time-varying covariates

Data collected at scheduled three-monthly follow-up visits included prior three month: incident pregnancy, prevalent pregnancy, self-reported number of protected and unprotected sex acts, any self-reported sex with the study partner with and without a condom and presence of sperm on a vaginal swab wet prep. Composite variables for genital ulceration were created from time-varying measures of chronic/recurrent or acute genital or perianal ulcers (whether diagnosed/treated at the research clinic or reported by the client); ulceration upon physical examination (including erosion or friability of the cervix or vagina in women); or newly positive rapid plasma reagin serology for syphilis [18]. Composite variables for genital inflammation were created from time-varying measures of genital inflammation, genital discharge and trichomoniasis, gonorrhea, chlamydia, candida or bacterial vaginosis [19].

### 2.5. Outcomes

This analysis considers the association between time-varying HC method use and two outcomes of interest: (1) any incident HIV infection among women partners and (2) incident HIV infection genetically linked to the cohabiting male partner. HIV testing using rapid serologic tests was conducted at three-monthly visits [15]. By comparing conserved PCR-amplified nucleotide sequences from each partner, we determined whether incident infections were genetically linked to the study partner or were unlinked (acquired from outside the study couple) [20]. Eleven couples with unknown linkage were classified as linked [20,21].

### 2.6. Longitudinal data collection

Data collection varied by type and frequency over 17 years of follow-up. Plasma banking for VL testing was available beginning in 1999. From 1994 to 2002, both partners were seen quarterly, had physical and genital exams, and received laboratory screening for sexually transmitted infections (STIs). Routine p24 antigen screening began in 2003. From 2002 to 2011, fertility goals were recorded. Physical exams and STI laboratory diagnoses were performed at baseline and thereafter given signs and symptoms of STI. In 2007, HIV-negative women were seen at visit months 0, 1, 2 and 3 and completed a sexual exposure risk assessment at quarterly visits. Couples with at least one exposure (unprotected sex, sperm or trichomonas on a wet prep, incident pregnancy or incident STI) received monthly HIV testing until the next quarterly visit, at which time the risk assessment was repeated. From 2008 to 2011, HIV-negative partners were tested monthly.

### 2.7. Data analysis

Analyses were conducted with SAS v9.3 (Cary, NC, USA). Baseline demographic, behavioral and clinical data are described by HIV transmission status using counts and percentages (for categorical variables) or means and standard deviations (for continuous variables). Index HIV-positive male partner characteristics are only described for genetically linked infections.

Infection rates were calculated as the number of incident infections per couple-year of follow-up, stratified by contraceptive method type. Hormonal method-specific seroincidence rates were compared to a non-HC reference group using univariate Cox models. Couples were censored if either partner died, the couple separated, the positive partner started antiretroviral therapy or if either partner was lost to follow-up.

Bivariate associations between covariates and outcomes of interest were evaluated via crude hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate Cox models estimated the effect of time-varying contraceptive method type on incident HIV acquisition. Effect-measure modification was considered for genital ulceration, inflammation, VL of the HIV-positive partner at baseline, fertility intentions, and woman's age. Covariates significantly ($p<.05$) associated with the exposure and outcome of interest in univariate analyses were considered as potential confounders. Multi-collinearity was assessed; if any two variables were found to be collinear, the variable with the weakest association with the outcome was removed. The proportional hazards assumption was confirmed for time-independent covariates.

## 2.8. Sensitivity analyses

Sensitivity analyses explored the effects of different contraceptive method exposure categorizations and control groups, misclassification of unprotected sex, controlling for pregnancy, and potential bias due to time-varying confounders simultaneously acting as mediators. To address the first issue, we considered all methods disaggregated versus none/condom control group; cumulative injectable exposure (calculated as the time-varying cumulative sum of intervals reporting injectable use) versus non-HC control; and cumulative OCP exposure versus non-HC control. To assess misclassification of self-reported unprotected sex, we evaluated the association between this measure and sperm on wet prep in the past three months, incident pregnancy, HIV acquisition, and genital ulceration/inflammation using Chi-square tests. Models of incident linked seroconversion were run using a composite measure of self-reported unprotected sex (i.e., using an indicator of any self-reported unprotected sex, sperm on vaginal swab wet prep, incident pregnancy, or incident STI). We estimated our results both controlling and not controlling for pregnancy. Marginal structural models estimated through inverse probability weighting were used to adjust for time-varying confounders which may simultaneously act as mediators. Finally, we conducted our analyses among a subset of couples with no indication of condomless sex (using an indicator of any self-reported unprotected sex, sperm on vaginal swab wet prep, incident pregnancy, or incident STI) since the last study interval.

## 2.9. Unprotected sex, contraceptive method use, and pregnancy

We explored differences in contraceptive method use by measures of unprotected sex using Chi-square tests for categorical variables and t-tests (unequal variance) for continuous variables. We also explored differences in pregnancy status (categorized as pregnant, up to six months post-partum, or not pregnant/post-partum) by measures of protected and unprotected sex using chi-square tests for categorical variables and *t* tests (unequal variance) for continuous variables.

## 3. Results

### 3.1. Baseline demographics and bivariate analyses (Tables 1–2)

Eighty-two percent of couples were non-seroconverters (*n*=1141), 15% acquired genetically linked infections (*n*= 207), and 3% acquired genetically unlinked infections (*n*=45). Couples were followed for a median of 440 days (IQR=756).

Baseline risk factors significantly associated with incident HIV infection included younger age of the woman, fewer years cohabiting, illiteracy in Nyanja, fewer previous pregnancies, and the woman desiring more children. Additional baseline risk factors significantly associated with incident genetically linked HIV infection included younger age of the man, pregnancy, the man desiring more children, and higher VL of the man (Table 1).

Time-varying covariates significantly associated with incident genetically linked HIV infection included self-reported unprotected sex with the study partner, sperm on a wet prep (Table 2). Time-varying measures of genital inflammation or ulceration in either partner in the past three months were significantly associated with any incident infection and genetically linked infections (data not shown).

### 3.2. Seroconversion rates by contraceptive method (Table 3)

Of 1393 couples, 252 seroconversions occurred over 2841.9 couple-years (CY) of follow-up. Women using OCPs or injectables since the previous follow-up visit had higher rates of seroconversion relative to women using non-HC methods since the previous follow-up visit; these differences were not statistically significant.

### 3.3. Multivariate analyses (Table 4)

HC use was not associated in multivariate analyses with any incident HIV infection or the subset of genetically linked infections. No effect-measure modification by genital ulceration, genital inflammation, VL, fertility intentions, or woman's age was observed. Collinear variables included: man and woman age, number of prior pregnancies, and years cohabiting (woman age retained).

Among all infections, use of implant, injectables, or OCPs was not associated with HIV acquisition relative to non-hormonal methods when controlling for woman's age (per year increase), literacy in Nyanja, time-varying measures of genital ulceration and inflammation in the woman partner in the past three months, and time interval since enrollment.

Among linked infections, use of implant, injectables, or OCPs was not associated with HIV acquisition relative to non-hormonal methods controlling for the above factors, baseline pregnancy, sperm present on a vaginal swab wet prep, couples' self-reported unprotected sex in the last three months, time-varying measures of genital ulceration and inflammation of the man in the past three months, and man's baseline log VL.

### 3.4. Sensitivity analyses

Analyzing different exposure categorizations, controlling for time-varying pregnancy, removing IUD users from the control group, and controlling for fertility intentions did not yield different conclusions. In almost two-thirds of intervals during which incident HIV was detected, women reported no unprotected sex in the prior three months. Women reported no unprotected sex in almost 40% of intervals during which an incident pregnancy was detected. Using a composite measure to indicate unprotected sex did not yield different results. Marginal structural models did not yield different results (i.e., marginal structural models also did not indicate any association between hormonal contraceptive method use and HIV acquisition risk). Finally, performing these analyses among couples with no indication of condomless sex did not yield different results, and these non-significant findings were of the same magnitude as those for the entire cohort.

### 3.5. Unprotected sex, contraceptive method use, and pregnancy (Tables 5–6)

OCP users reported a higher number of unprotected sex acts with the study partner in the past three months and had sperm on a wet prep more often than nonhormonal method users. Injectable users reported more unprotected sex than nonhormonal method users. Implant users reported a lower number of unprotected sex acts with the study partner in the past three months, reported less unprotected sex, and had sperm on a wet prep less often than nonhormonal method users (Table 5).

Pregnant women reported a higher average number of protected sex acts relative to post-partum women and a higher average number of unprotected sex acts relative to post-partum or non-pregnant/non-post-partum women. Pregnant women were more likely to report sex without a condom (Table 6).

## 4. Discussion

Use of oral or injectable HC was not associated with increased risk of HIV acquisition among Zambian women in HIV discordant couples after adjustment for behavioral and biological risk factors. This investigation, both in design and analysis, overcomes several challenges faced by previous studies [11]. We measured various self-reported and biological fixed and time-varying measures of unprotected sex over 17 years of prospective follow-up. We estimated HIV acquisition risk related to contraceptive implants. Contraception was provided at the research site and was measured frequently to capture high rates of stopping and switching; in our cohorts, we have observed that about 25% of women switch methods during follow-up, with most discontinuation/switching observed among injectable (34%) and IUD (33%) users [13,22]. This is one of few studies to differentiate between genetically linked versus unlinked infections, important when modeling index partner covariates. Discordant couples have relatively little within-sample variation in HIV exposure risk. Finally, we corroborated our findings with marginal structural models and rigorous sensitivity analyses.

The relationships between measures of unprotected sex and HC use, pregnancy, and post-partum periods were of particular interest. The reproductive lifetime of most women in Africa cycles through these three stages, each of which involves endogenous and/or exogenous hormonal influences. We found the high rates of biological and self-reported measures of unprotected sex during OCP use, injectable use, and pregnancy surprising. This illustrates the complexity of the relationships between behavioral and biological risk factors for HIV transmission and indicates that counseling must emphasize maintaining consistent condom use regardless of pregnancy status or other contraceptive method use.

Hormonal implant use was associated with less unprotected sex and fewer pregnancies relative to other methods and had a reduced adjusted hazard ratio for seroconversion. Further research is warranted to assess the role of this effective and cost-effective contraceptive method, along with the copper IUD, in women and couples at risk of HIV. Ongoing long-acting reversible contraception (LARC) promotion and provision for those wishing to delay pregnancy is important given high rates of unprotected sex and unintended pregnancy observed among OCP users – we have previously shown that the rate of unintended pregnancy among OCP users in our discordant couple cohorts (20.7/100 CY) was not significantly lower than women reporting no method/condom use only [23].

Selection bias due to enrollment and loss to follow-up have been thoroughly explored in our cohorts: among M+F-couples, older age and current contraceptive use are predictive of enrollment, while residence far from the clinic, younger age, and women's age at first intercourse being ≤17 are predictive of attrition [14]. Our findings may therefore be most generalizable to relatively older, contraception experienced couples. Additionally, our study was underpowered to rule out a type II error in conclusions drawn from the univariate associations between seroincidence rates in implant versus non-HC control users.

Based on our findings, we support efforts to increase: 1) the contraceptive method mix to decrease unintended pregnancy, in particular access to LARC methods which are not currently available to many African women, 2) reinforced condom counseling for all persons at risk of HIV, and 3) couple's HIV testing to ascertain the most immediate source of HIV risk of negative adults and support couple-level fertility intentions.

Pragmatically, the latter can be achieved by integrating HIV and family planning services with a focus on couples. Finally, when weighing the current body of published evidence, the effectiveness of HC, especially hormonal LARC methods, to decrease unintended pregnancy, maternal and child mortality, and vertical HIV transmission must be considered when making policy recommendations.

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## Table 1

Descriptive analyses and unadjusted associations between covariates and time to HIV seroconversion (N=1393 M+F- couples)

| | Non-seroconverters (N=1141) | | Linked and unlinked infections (N=252) | | | | | | Linked infections (N=207) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | HR | 95% CI | | p (2-tailed) | N | % | HR | 95% CI | | p (2-tailed) |
| Man age (mean, S.D.; HR per year increase) | 35.5 | 7.7 | | | | | | | 33.5 | 7.5 | 0.97 | 0.95 | 0.99 | <.001 |
| Woman age (mean, S.D.; HR per year increase) | 28.8 | 7.0 | 26.2 | 6.3 | 0.96 | 0.94 | 0.98 | < .0001 | 26.3 | 6.3 | 0.96 | 0.94 | 0.98 | <.001 |
| Years cohabiting (mean, S.D.; HR per year increase) | 8.3 | 6.7 | 6.5 | 5.6 | 0.96 | 0.94 | 0.98 | < .001 | 6.7 | 5.7 | 0.96 | 0.94 | 0.99 | .002 |
| Monthly family income (mean, S.D.; HR per US dollar increase) | 94.0 | 118.8 | 62.9 | 70.4 | 0.998 | 0.996 | 1.000 | .088 | 65.4 | 74.9 | 1.00 | 1.00 | 1.00 | .351 |
| Woman reads Nyanja | | | | | | | | | | | | | | |
| Yes, easily | 272 | 24% | 40 | 16% | ref | | | | 35 | 17% | ref | | | |
| With difficulty/not at all | 857 | 76% | 203 | 84% | 1.50 | 1.07 | 2.11 | .019 | 167 | 83% | 1.45 | 1.01 | 2.09 | .047 |
| Number of previous pregnancies (mean, S.D.; HR per pregnancy increase) | 3.7 | 2.5 | 3.1 | 2.0 | 0.89 | 0.84 | 0.94 | <.0001 | 3.1 | 2.1 | 0.90 | 0.85 | 0.96 | .001 |
| Pregnant at baseline | | | | | | | | | | | | | | |
| Yes | 155 | 14% | 47 | 19% | 1.31 | 0.96 | 1.80 | .094 | 41 | 20% | 1.43 | 1.02 | 2.01 | .041 |
| No | 986 | 86% | 205 | 81% | ref | | | | 166 | 80% | ref | | | |
| Fertility intentions of man | | | | | | | | | | | | | | |
| Yes, next year | 44 | 12% | | | | | | | 18 | 26% | 3.02 | 1.63 | 5.61 | <.001 |
| Yes, but not next year | 107 | 29% | | | | | | | 27 | 40% | 2.04 | 1.17 | 3.57 | .012 |
| Don't know/No | 216 | 59% | | | | | | | 23 | 34% | ref | | | |
| Fertility intentions of woman | | | | | | | | | | | | | | |
| Yes, next year | 87 | 19% | 24 | 28% | 2.36 | 1.41 | 3.96 | .001 | 20 | 29% | 2.72 | 1.53 | 4.86 | .001 |
| Yes, but not next year | 88 | 19% | 26 | 30% | 1.99 | 1.21 | 3.30 | .007 | 21 | 31% | 2.22 | 1.26 | 3.94 | .006 |
| Don't know/No | 278 | 61% | 37 | 43% | ref | | | | 27 | 40% | ref | | | |
| Man lifetime sex partners (mean, S.D.; HR per partner increase) | 11.6 | 16.0 | | | | | | | 10.4 | 11.5 | 1.00 | 0.98 | 1.01 | .378 |
| Man last year sex partners (mean, S.D.; HR per partner increase) | 1.8 | 1.7 | | | | | | | 1.8 | 1.3 | 0.98 | 0.91 | 1.06 | .654 |
| Woman lifetime sex partners (per partner increase) | 2.8 | 3.4 | 2.7 | 2.6 | 1.01 | 0.97 | 1.05 | .659 | 2.7 | 2.6 | 1.00 | 0.96 | 1.05 | .935 |
| Woman last year sex partners (mean, S.D.; HR per partner increase) | 1.0 | 0.4 | 1.1 | 0.5 | 1.24 | 0.99 | 1.55 | .060 | 1.1 | 0.3 | 1.07 | 0.76 | 1.51 | .710 |
| Log viral load of positive partner, log10 copies/mL (mean, S.D.; HR per unit increase) | 4.6 | 1.0 | | | | | | | 5.1 | 0.7 | 1.66 | 1.36 | 2.04 | <.0001 |

Fertility intentions collected from 2002 to 2011; VL collected from 1999.

## Table 2

Unadjusted associations between time-varying covariates and time to HIV seroconversion (N=1393 M+F – couples)

| | All couples | | Linked and unlinked infections | | | | | | Linked infections | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N intervals** | **%** | **N intervals** | **%** | **HR** | **95% CI** | | **p (2-tailed)** | **N intervals** | **%** | **HR** | **95% CI** | | **p (2-tailed)** |
| Contraceptive method used at visit | | | | | | | | | | | | | | |
| Non-hormonal* | 9060 | 65% | 153 | 61% | ref | | | | 133 | 64% | ref | | | |
| Implant | 1000 | 7% | 9 | 4% | 1.16 | 0.57 | 2.35 | .678 | 6 | 3% | 1.01 | 0.43 | 2.36 | .991 |
| Injectables | 1899 | 14% | 41 | 16% | 1.21 | 0.85 | 1.73 | .296 | 33 | 16% | 1.15 | 0.77 | 1.70 | .505 |
| OCPs | 1921 | 14% | 49 | 19% | 1.31 | 0.94 | 1.82 | .114 | 35 | 17% | 1.10 | 0.75 | 1.62 | .612 |
| Pregnant during interval | | | | | | | | | | | | | | |
| Yes | 1130 | 9% | 29 | 12% | 1.27 | 0.86 | 1.88 | .225 | 27 | 14% | 1.41 | 0.94 | 2.12 | .097 |
| No | 11168 | 91% | 213 | 88% | ref | | | | 171 | 86% | ref | | | |
| No. times sex with study partner *with* a condom in the last 3 months (mean, S.D.) | 18.9 | 19.4 | 19.4 | 25.2 | 1.00 | 0.99 | 1.01 | .921 | 19.9 | 26.5 | 1.001 | 1.00 | 1.01 | .789 |
| No. times sex with study partner *without* a condom in the last 3 months (mean, S.D.) | 2.4 | 8.5 | 3.6 | 10.7 | 1.00 | 0.99 | 1.01 | .987 | 3.7 | 10.3 | 1.00 | 0.99 | 1.01 | .890 |
| Sex *with* study partner with a condom in past 3 months | | | | | | | | | | | | | | |
| Yes | 11606 | 86% | | | | | | | 176 | 85% | 1.20 | 0.81 | 1.77 | 0.360 |
| No | 1913 | 14% | | | | | | | 30 | 15% | ref | | | |
| Sex with study partner *without* a condom in past 3 months | | | | | | | | | | | | | | |
| Yes | 4087 | 30% | | | | | | | 87 | 42% | 1.39 | 1.04 | 1.84 | 0.024 |
| No | 9433 | 70% | | | | | | | 119 | 58% | ref | | | |
| Sperm present on wet prep | | | | | | | | | | | | | | |
| Yes | 831 | 6% | 26 | 11% | 1.50 | 0.97 | 2.32 | .066 | 25 | 13% | 1.74 | 1.11 | 2.73 | .016 |
| No | 12209 | 94% | 208 | 89% | ref | | | | 165 | 87% | ref | | | |

* IUD, none/condoms alone, permanent method.

## Table 3

Seroconversion rates among HIV-negative women in discordant relationships by method of contraception (N=1393 M+F– couples)

| | Number of seroconversions | Couple-years of follow-up time | Seroincidence per 100 couple-years | 95% CI | | p (2-tailed)* |
|---|---|---|---|---|---|---|
| Current contraceptive method used at follow-up visit | | | | | | |
| Non-hormonal^ | 153 | 1902.3 | 8.0 | 6.8 | 9.4 | ref |
| OCPs | 49 | 424.5 | 11.5 | 8.5 | 15.3 | .114 |
| Injectables | 41 | 392.3 | 10.5 | 7.5 | 14.2 | .296 |
| Implant | 9 | 122.9 | 7.3 | 3.3 | 13.9 | .678 |
| *Total* | *252* | *2841.9* | *8.9* | *7.8* | *10.0* | |

67 study intervals (accounting for 5.7 couple years) were missing contraceptive information.

^Copper intrauterine device, none/condoms alone, permanent method.

*From univariate Cox proportional hazards models.

**Table 4**

Multivariate models of hormonal contraception use and time to HIV seroconversion (N=1393 M+F – couples)

| | Linked and unlinked infections | | | | Linked infections | | | |
|---|---|---|---|---|---|---|---|---|
| | **aHR*** | **95% CI** | | **p value (2-tailed)** | **aHR**** | **95% CI** | | **p value (2-tailed)** |
| Current contraceptive method at follow-up visit | | | | | | | | |
| Non-hormonal^ | ref | | | | ref | | | |
| Implant | 1.08 | 0.53 | 2.20 | .83 | 0.96 | 0.29 | 3.14 | .947 |
| Injectables | 1.19 | 0.81 | 1.73 | .37 | 1.34 | 0.85 | 2.12 | .204 |
| OCPs | 1.29 | 0.92 | 1.80 | .15 | 1.39 | 0.90 | 2.15 | .140 |

aHR: adjusted hazard ratio.

*Controlling for woman's age (per year increase), woman's literacy in Nyanja, genital ulceration of woman in past 3 months, genital inflammation of woman in the past 3 months, and time interval since enrollment (0-3 months versus > 3 months).

**Controlling for * and baseline pregnancy, sperm present on a wet prep, couples' self-reported unprotected sex in the last 3 months, genital ulceration of man in past 3 months, genital inflammation of man in the past 3 months, and man's baseline log viral load (per log10 copies/mL increase).

^Copper intrauterine device, none/condoms alone, permanent method.

### Table 5

Measures of unprotected sex by method of contraception (N=1393 M+F – couples)

| | Non-hormonal (IUD, none/ condoms alone, permanent method) | | OCPs | | Injectable | | Implant | | p (2-tailed)* |
|---|---|---|---|---|---|---|---|---|---|
| | **N intervals** | **%** | **N intervals** | **%** | **N intervals** | **%** | **N intervals** | **%** | |
| Number of times sex with partner in project without a condom in the last 3 months reported by woman (mean, S.D.) | 2.47 | 8.78 | 2.87 | 9.10 | 2.42 | 7.96 | 1.25 | 4.88 | ^& |
| Sex with study partner without a condom in past 3 months reported by woman | | | | | | | | | ^#& |
| Yes | 2644 | 29% | 717 | 37% | 640 | 34% | 180 | 18% | |
| No | 6321 | 71% | 1198 | 63% | 1221 | 66% | 810 | 82% | |
| Sperm present on wet prep in last 3 months | | | | | | | | | |
| Yes | 570 | 7% | 151 | 8% | 113 | 6% | 23 | 2% | |
| No | 7836 | 93% | 1774 | 92% | 1805 | 94% | 986 | 98% | |

*chi-Square (or Fisher's exact) test for categorical variables; t-tests (unequal variance) for continuous variables.

^p<.1 for tests of differences between OCP versus non-hormonal contraception distributions.

#p<.001 for tests of differences between injectables versus non-hormonal contraception distributions.

&p<.001 for tests of differences between implant versus non-hormonal contraception distributions.

## Table 6

Measures of protected and unprotected sex by pregnancy status (N=1393 M+F – couples)

| | Pregnant | | Post-partum (up to 6 months past delivery) | | Not pregnant or post-partum | | p (2-tailed)* |
|---|---|---|---|---|---|---|---|
| | N intervals | % | N intervals | % | N intervals | % | |
| Number of times sex with partner in project with a condom in the last 3 months reported by woman (mean, S.D.) | 16.67 | 17.09 | 8.77 | 12.05 | 19.59 | 20.09 | ^#& |
| Number of times sex with partner in project without a condom in the last 3 months reported by woman (mean, S.D.) | 6.10 | 14.42 | 1.53 | 6.59 | 2.25 | 8.05 | ^#& |
| Sex with study partner with a condom in past 3 months reported by woman | | | | | | | ^#& |
| Yes | 959 | 84% | 322 | 63% | 9257 | 87% | |
| No | 180 | 16% | 187 | 37% | 1377 | 13% | |
| Sex with study partner without a condom in past 3 months reported by woman | | | | | | | |
| Yes | 593 | 52% | 116 | 23% | 3145 | 30% | ^#& |
| No | 546 | 48% | 393 | 77% | 7490 | 70% | |
| Sperm present on wet prep in last 3 months | | | | | | | # |
| Yes | 95 | 9% | 32 | 6% | 690 | 7% | |
| No | 966 | 91% | 478 | 94% | 9476 | 93% | |

[*] chi-Square (or Fisher's exact) test for categorical variables; t tests (unequal variance) for continuous variables.

[^] p<.01 for tests of differences between pregnant versus post-partum women.

[#] p<.01 for tests of differences between pregnant versus not pregnant or post-partum women.

[&] p<.01 for tests of differences between post-partum versus not pregnant or post-partum women.