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Hormonal contraceptive use and HIV disease progression among women in Uganda and Zimbabwe

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Abstract

Background—HIV-infected women need highly effective contraception to reduce unintended pregnancies and mother-to-child HIV transmission. Previous studies report conflicting results regarding the effect of hormonal contraception (HC) on HIV disease progression.

Methods—HIV-infected women in Uganda and Zimbabwe were recruited immediately after seroconversion; CD4 testing and clinical exams were conducted quarterly. The study endpoint was time to AIDS (two successive CD4 ≤ 200 cells/mm³ or WHO advanced stage 3 or stage 4 disease). We used marginal structural Cox survival models to estimate the effect of cumulative exposure to depot-medroxyprogesterone acetate (DMPA) and oral contraceptives (OC) on time to AIDS.

Results—303 HIV-infected women contributed 1,408 person-years (py). 111 women (37%) developed AIDS. Cumulative probability of AIDS was 50% at 7 years and did not vary by country. AIDS incidence was 6.6, 9.3 and 8.8 per 100py for DMPA, OC and non-hormonal users. Neither DMPA (adjusted hazard ratio (AHR) = 0.90; 95% CI 0.76-1.08) nor OCs (AHR = 1.07; 95% CI 0.89-1.29) were associated with HIV disease progression. Alternative exposure definitions of HC use during the year prior to AIDS or at time of HIV infection produced similar results. STI symptoms were associated with faster progression while young age at HIV infection (18-24 years) was associated with slower progression. Adding baseline CD4 level and setpoint viral load to models did not change the HC results but subtype D infection became associated with disease progression.

Conclusion—Hormonal contraceptive use was not associated with more rapid HIV disease progression but older age, STI symptoms and subtype D infection were.

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Keywords

HIV; disease progression; hormonal contraception; family planning; women

Introduction

Worldwide, almost 16 million women are HIV-infected and most are of reproductive age and live in resource-limited settings¹. Access to effective contraception is a critical component of reproductive healthcare for HIV-infected women for a number of reasons. First, a high proportion of HIV-infected women do not want to become pregnant²⁻⁴. Second, access to effective contraception for HIV-infected women not wanting to become pregnant has been identified by the WHO as an important strategy for the prevention of mother-to-child HIV transmission⁵; this approach is as cost-effective as the provision of antiretroviral drugs to pregnant women^{6,7}. Use of effective contraception by HIV-infected women not wishing to become pregnant also reduces the number of HIV-related orphans. Third, pregnancy may increase the likelihood of HIV transmission from an infected woman to her uninfected male partner⁸. Finally, use of highly effective contraception preserves the health of HIV-infected women by eliminating the mortality and morbidity associated with pregnancy and childbirth.

The choice of appropriate contraception can be difficult for HIV-infected women. Health care providers may put strong emphasis on condom use when counseling HIV-infected women and less emphasis on highly effective contraceptive methods. Providers may also be reluctant to prescribe hormonal contraceptives to women using HAART because of concerns about potential interactions between hormonal contraception with antiretroviral drugs that can theoretically result in lower contraceptive or antiretroviral efficacy⁹.

Several studies, including a trial in Zambia of women randomized to either hormonal contraception or intrauterine devices, have raised the concern that hormonal contraception (particularly DMPA and OCs) might accelerate HIV disease progression^{10,11,12}. However, other studies have found no increase in viral loads or decrease in CD4 levels^{13,14} and no increased risk in time to AIDS, death or ART initiation among OC or injectable users compared to women not using these methods¹⁵⁻¹⁸.

We evaluated whether women using DMPA and OCs had more rapid progression from time of HIV infection to AIDS than women not using hormonal contraception among women attending reproductive health clinics in Uganda and Zimbabwe. This cohort was uniquely suited to examine this question because of accurate measurement of HIV infection timing, short visit windows (every 12 weeks), long follow-up with high retention rates and accurate measurement of contraceptive use, CD4 counts and clinical outcomes.

Methods

The research was approved by the institutional review boards of collaborating institutions. All study participants provided written informed consent.

Study Population and Procedures

The study population were women who became HIV-infected while participating in the 'Hormonal Contraception and Risk of HIV Acquisition (HC-HIV) Study' and a subsequent serosurveillance phase during 2001-2009. The 303 study participants were HIV-infected, ages 18-45 years, and used either DMPA (150 mg depot-medroxyprogesterone acetate

administered quarterly), OCs (low-dose pills containing 30 mcg ethinyl estradiol and 150 mcg of levonorgestrel) or no hormonal method.

Study procedures have been described in detail previously¹⁹. Briefly, we notified HC-HIV study participants who became HIV-infected about their infection status and scheduled interested women for enrollment into the 'Hormonal Contraception and HIV Genital Shedding and Disease Progression (GS) Study' as soon as possible. After conducting informed consent procedures, we interviewed participants to collect sexual behavior, reproductive health and contraceptive history data. We provided contraceptive, HIV risk reduction and condom use counseling and free contraceptives and condoms. Study clinicians conducted a standardized physical (including pelvic) exam and collected specimens for reproductive tract infections (RTIs), pregnancy testing, Pap smears, lymphocyte phenotyping and plasma and cervical viral loads. We tested for RTIs and pregnancy as previously described²⁰. We treated participants onsite for vaginal infections and recalled women diagnosed with asymptomatic chlamydia, gonorrhea or syphilis infections for treatment. HIV subtype determination was performed as previously described using the C2-V3 region of the *env* gene¹⁹.

We conducted follow-up visits at 4, 8 and 12 weeks following enrollment and at 12-week intervals thereafter for up to 9.3 years. Follow-up procedures were similar to those at enrolment and included testing for RTIs and pregnancy.

Beginning in 2003, we offered highly active antiretroviral therapy and trimethoprim-sulfamethoxazole to women who developed severe symptoms of HIV infection (WHO clinical stage 4 or severe stage 3 disease), or who had successive CD4 lymphocyte counts of ≤ 200 cells/mm³.

Analysis Population and Variable Definition

The analysis population included 303 Ugandan and Zimbabwean women contributing 5,300 regular study visits and 1,408 years of follow-up.

HIV polymerase chain reaction (PCR, Cobas AMPLICOR, Roche, USA) was performed on samples from visits prior to HIV seroconversion to establish timing of initial infection²⁰. For women whose seroconversion visit was also their first PCR+ visit, HIV-1 infection dates were estimated as the midpoint between this and the previous visit. Because HIV testing was conducted every 12 weeks in the HC-HIV Study, estimated infection date was usually within a 6-week window of the actual infection date. We estimated acute HIV infections (serologically negative but HIV PCR+) to have occurred 15 days prior to the first PCR+ visit.

We defined contraceptive exposure for our primary analysis as the cumulative (time-varying) number of months of DMPA and OC exposure from the estimated date of HIV infection up to each study visit. We performed two sensitivity analyses using time-fixed contraceptive exposures. First, we defined contraceptive exposure as the total cumulative number of months of DMPA and OC exposure during the year prior to AIDS. Second, we used the contraceptive exposure at the estimated time of HIV infection. The contraceptive exposure definitions are similar to those proposed to assess the effect of contraceptive use on HIV-1 disease progression in the literature²¹. We used a wash-out period of 120 days from last injection when women switched from DMPA to the non-hormonal (NH) group.

We defined two analysis endpoints. Our primary endpoint was an AIDS diagnosis which we defined as two successive study visits (or two visits within 6 months) with a CD4 count ≤ 200 cells/mm³ or WHO clinical stage 4 disease or severe stage 3 disease (≥ 3 stage 3

criteria) (whichever occurred first). Participants not reaching the AIDS endpoint were censored at the time of HAART initiation or their last follow-up visit. We conducted sensitivity analyses of different HC exposure definitions and analyses of the time to AIDS, HAART initiation or death (the secondary endpoint) using the same approaches as for the primary analysis.

Statistical Methods

Participant characteristics at the HIV seroconversion visit were summarized and compared by contraceptive group using Cochran-Mantel-Haenszel tests for categorical variables and the Kruskal-Wallis test for continuous variables.

We used Cox proportional hazard regressions and logistic regressions adjusted for repeated observations to evaluate bivariable associations between baseline and time-varying characteristics and AIDS diagnosis, and to assess potential confounding factors. Time-independent variables were defined as confounders if the hazard ratio for the association between HC exposure and an AIDS diagnosis changed by at least 10% when the variable was added to the primary model and were retained in final multivariate models. This covariate selection process was applied to all data analyses. In addition, for time-varying cumulative contraceptive exposure, if a time-dependent covariate was associated ($p < 0.05$) with an AIDS diagnosis and predicted HC exposure and was predicted by past HC exposure, it was considered a time-dependent confounder²². Since the effects of cumulative HC exposure on AIDS diagnosis could be biased by time-dependent confounding, we used a marginal structural Cox survival model with the stabilized inverse-probability-treatment weighting approach as the primary analysis method to provide consistent estimates of the cumulative HC exposure effect on time to AIDS adjusted by baseline confounders and variables considered a priori to be important (site, age, HIV subtype)²³. Because it was possible that contraceptive exposure at the time of HIV infection could influence the initial CD4 and setpoint viral load measurements (and thus be intermediary variables in a contraceptive exposure – HIV disease progression pathway), we did not control for these variables in our primary analysis, but instead, included these variables in sensitivity analyses. We calculated 95% confidence intervals for estimated hazard ratios using the robust sandwich estimate of the covariance matrix²⁴. We further used conventional Cox proportional hazards models to evaluate covariate association with time to AIDS.

Because all Zimbabwean participants with completed subtyping ($n=96$) are subtype C, we assumed that all the remaining 80 Zimbabwean participants also had subtype C HIV infections. Additionally, 3 Ugandan participants with subtype C infections and 5 Ugandan participants with missing subtype information were excluded from multivariate modeling.

Data analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

From a total of 333 seroconverters in the HC-HIV Study (213 seroconverters) and a follow-on serosurveillance phase (120 seroconverters), 306 women joined the GS Study. Three study participants did not contribute sufficient follow-up time and were excluded from this analysis. Of the remaining 303 participants, 127 (42%) were Ugandan and 176 (58%) were from Zimbabwe. Women were retained for 95% of their expected follow-up time in the study (Uganda 94%, Zimbabwe 96%).

Participant Characteristics at Time of HIV Seroconversion

At the HIV seroconversion visit the median age and education was 26 and 10 years, respectively (Table 1). Almost two-thirds of women used hormonal contraception including

DMPA (36%) and OCs (27%). Only 7% of women were currently pregnant and 11% were breastfeeding. Few women reported multiple partners (6%) or commercial sex (1%). Only 29% of women at HIV seroconversion reported either consistent condom use or not having sex in the previous three months. RTI prevalence was high including 18 women (6%) with chlamydia, 30 women (10%) with gonorrhea, 16 women (6%) with trichomoniasis, 80 women (27%) with bacterial vaginosis and 244 women (82%) infected with herpes simplex virus-2 (HSV-2). Subtype C HIV infection was most common (59%) while 28% of women had subtype A and 11% had subtype D infections.

At HIV seroconversion, women in the non-hormonal (NH) group as compared to the hormonal groups were slightly older, more likely Ugandan and pregnant, more likely to have risky sexual behavior, more likely to use condoms but to have sex less often, and more likely to have HIV subtypes A and D infections (Table 1). No difference existed between groups in cohabitation or educational status, primary partner risk or in the prevalence of RTIs.

Analyses of AIDS Incidence

There were 255, 213 and 171 study participants who contributed at least 1, 3 and 5 years, respectively, of follow-up data. The median follow-up time of study participants was 58 months. During the study 111 women received an AIDS diagnosis (median of 47.3 months) while 192 women did not (median follow-up 63.1 months). The AIDS incidence rate (IR) was 7.9 per 100 women years overall. The AIDS IR was 6.6, 9.3, and 8.8 per 100py for DMPA, OC and non-hormonal users, respectively (Table 2). AIDS IR was higher for Uganda subtype D than for Uganda subtype A or Zimbabwe subtype C (11.0, 6.9, and 7.9 per 100wy, respectively). AIDS incidence and was also higher for older (≥ 25 years) than for younger women (9.1 vs. 6.1 per 100wy).

The cumulative probability of AIDS was 5.6% at 2 years (7.1% for ZM, 3.5% for UG), 29.4% at 5 years (29.7% for ZM, 29.1% for UG), and 49.5% at 7 years (49.0% for ZM, 50.7% for UG). There were no differences in the cumulative probability of AIDS by country ($p=0.87$).

Cumulative Hormonal Contraceptive Exposure and Time to AIDS

Cumulative exposure to DMPA and OCs was not associated with time from HIV infection to AIDS in marginal structural modeling. The adjusted hazard ratio (AHR) for DMPA and OCs per year of use was 0.90 (95% CI 0.76-1.08) and 1.07 (95% CI 0.89-1.29), respectively (Table 3). When baseline CD4 and setpoint viral load were added to the marginal structural Cox model, the AHRs for DMPA and OC use (compared with no hormonal use) remained very similar.

We also calculated the association of covariates with HIV progression to AIDS from a conventional Cox proportional hazards model including baseline CD4 and setpoint viral load. Younger age (18-24 years) (AHR=0.60, 95% CI 0.40-0.91) and higher baseline CD4 (per 100 cell increase) (AHR= 0.76, 95% CI 0.67-0.86) were associated with slower progression to AIDS while setpoint viral load (per log₁₀ unit increase)(AHR=1.40, 95% CI 1.07-1.83) was associated with more rapid disease progression (Table 4). Uganda/subtype D (AHR=1.91, 95% CI 1.00-3.68) infection was also marginally associated with more rapid disease progression.

We also assessed the secondary (combined) endpoint of time to AIDS, death or HAART initiation. Out of the 303 women in this analysis, 116 women (38%) used ART at some point during the study. Mean CD4 cell count at ART initiation was 175 cells/mm³ and sixteen participants initiated ART or died prior to an AIDS diagnosis. One hundred twenty-

seven (49 Ugandan, 78 Zimbabwean) women reached the combined endpoint (IR: 9.0 per 100 women years). The IR for AIDS, HAART initiation or death was 10.0, 7.3 and 10.8 per 100py for OC, DMPA and non-hormonal users, respectively. Cumulative exposure to DMPA and OCs was not associated with this endpoint; the AHR for DMPA and OCs per year of contraceptive use was 0.90 (95% CI 0.77-1.06) and 1.02 (95% CI 0.86-1.22), respectively (Table 3). Relationships of other covariates (age, STI symptoms, unprotected sex acts) with the secondary endpoint were similar to those for the primary endpoint (Table 4).

The Effect of Hormonal Contraceptive Use during the Year Prior to AIDS

We hypothesized that cumulative hormonal contraceptive use during the year prior to AIDS might influence whether a woman reached an AIDS endpoint. Therefore, we conducted analyses of hormonal contraceptive use during the year prior to AIDS (or censoring). Neither cumulative DMPA (AHR=0.82 95% CI 0.50-1.36) nor OC use (AHR=1.29 95% CI 0.69-2.44) during the year prior to AIDS was associated with time to AIDS (Table 3). When we considered the effect of hormonal contraception in the year prior to AIDS, HAART initiation or death, we again found no association between either DMPA (AHR=0.81 95% CI 0.51-1.31) or OC use (AHR=1.26 95% CI 0.69-2.29) and this outcome (Table 3).

The Effect of Contraceptive Exposure at Time of HIV Infection

Finally, we considered the effect of hormonal contraceptive exposure at the time of HIV infection on time to AIDS. Neither DMPA (AHR=1.14 95% CI 0.73-1.79) nor OC use (AHR=0.93 95% CI 0.56-1.55) at the time of infection was associated with disease progression (Table 3). The results were largely the same for DMPA (AHR=1.23 95% CI 0.81-1.87) and OC (AHR=0.85 95% CI 0.52-1.39) use at the time of HIV infection when we considered the secondary endpoint of time to AIDS, death, or HAART initiation.

Discussion

In this study of women with accurately timed HIV infection dates, we found that neither time-varying cumulative DMPA nor OC use was associated with time from HIV infection until AIDS. This result did not change when we examined the alternative study endpoint of time from HIV infection to AIDS, HAART initiation or death. We also found no association of DMPA and OC use with time to AIDS when we considered definitions of hormonal contraceptive use during the year prior to AIDS or at the time of HIV infection.

The cumulative probability of AIDS among women in our study population was 50% by 7 years. This estimate did not vary by country. While adding baseline CD4 and setpoint viral load to the prediction model did not change the hormonal contraception results, Uganda subtype D infection became associated with faster HIV disease progression.

The results of our study agree with some but not all previous studies as well as a recent review²⁵ of the literature examining the relationship between hormonal contraceptive use and HIV disease progression. On the one hand, our results agree with the results of several prevalent HIV cohort studies¹⁵⁻¹⁷ and one incident HIV cohort study¹⁸ that found no increase in HIV disease progression among women using as compared to women not using hormonal contraception. These results also confirm our earlier finding of no difference in viral setpoint levels (as an indicator of future disease progression) between women using DMPA and OCs compared with women not using hormonal contraception at the time of HIV infection¹⁹. On the other hand our results conflict with the findings of a trial in which women with prevalent HIV infection randomized to DMPA and OC use experienced more rapid HIV disease progression compared to those randomized to a copper IUD^{11, 12}. Our

results also conflict with the finding that sex workers in Mombasa Kenya who used DMPA at the time of HIV infection had higher HIV viral setpoints than women not using hormonal contraception at the time of HIV infection¹⁰. As emphasized by the study design, our study results were robust to different definitions of hormonal contraceptive exposure prior to and throughout HIV disease. For example, we did not observe an association between hormonal contraceptive use during the year prior to AIDS (when switches in co-receptor usage can lead to accelerated CD4 decline²⁶ and HIV disease progression). Likewise, we found no association between hormonal contraceptive exposure at the time of HIV infection and subsequent disease progression. Past research had suggested that hormonal contraceptive use might influence the diversity of the infecting virus and result in an increased viral setpoint^{10, 27}.

We found several variables that were associated with time from HIV infection to AIDS. In accordance with a previous report we found that younger age was associated with less rapid HIV disease progression²⁸. As would be expected, we also found that higher baseline CD4 was also associated with slower disease progression and higher setpoint viral load was associated with faster disease progression. Controlling for the lower baseline CD4 levels we found among Zimbabwean than Ugandan women²⁹, Uganda subtype D infection was associated with faster disease progression than Uganda subtype A infection. This has also been reported previously³⁰⁻³³.

Our study has a number of important strengths. The study was prospective with both CD4 cell levels and physical exams (including WHO HIV clinical staging) conducted every 12 weeks. Clinical staging done by local clinicians was carefully reviewed by the study co-investigator (RS). We had high retention levels in both countries and we followed women from time of HIV infection to AIDS (up to 9 years). We accurately timed HIV infection by conducting HIV PCR testing on serial samples before women HIV seroconverted. Hormonal contraception was supplied to women by the study and we measured exposure carefully using contraceptive calendars and checked data against clinic records. We also carefully measured a number of reproductive tract infections and pregnancy. We considered several different hormonal exposure definitions and thus assessed the robustness of our analyses. Finally, we enrolled women seeking family planning services in two sub-Saharan countries. This allows for greater generalizability of study results than a study population drawn from a selected high-risk group (e.g. sex workers) in one locale.

Our study also had limitations. We do not have plasma viral load measurements from all visits and thus were unable to consider time-varying viral load as a potential mediating factor. The study was observational and it is possible that residual confounding remains despite using marginal structural models to properly adjust for time-dependent confounding. In addition, the issue of pregnancy in our analyses is complex and although we adjusted for time-varying pregnancy status, analytic issues remain. Finally, we only sequenced the C2-V3 region of the HIV *env* and thus cannot fully explore the issue of recombinant viruses on HIV disease progression.

In summary, we found that hormonal contraception, including DMPA and OC use was not associated with either time from HIV infection to AIDS or to AIDS, HAART initiation or death. We also found that the cumulative probability of AIDS was 50% at 7 years from HIV infection and did not vary by country. These results suggest that HIV-infected women who do not want to become pregnant can safely use DMPA and OCs without putting themselves at greater risk of AIDS. Additionally, HIV prevention and family planning programs can make provision of these hormonal contraceptives to HIV-infected women not wanting to become pregnant an important strategy in the prevention of mother-to-child and heterosexual HIV transmission.

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C.S.M. is the study principal investigator and directed the design and implementation of the study and wrote the manuscript draft; I.N. and B.V.D.P. planned, supervised, conducted (I.N.), and did quality assurance (B.V.D.P.) for the lab work; P.C. and Y.M. designed and conducted the statistical analysis; A.R. monitored the study sites and performed data management; T.C., R.M., and M.D. are site principal investigators and supervised the study teams in Zimbabwe and Uganda; E.A. is the laboratory co-investigator and designed, tested and supervised the virology assays; R.A.S. is the study co-principal investigator and as study clinical consultant confirmed all WHO clinical stage 3 and 4 outcomes; all authors contributed to drafts of the manuscript and approved the final manuscript.

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Table 1
Participant characteristics at the HIV infection visit¹ by contraceptive exposure group²

Characteristic	OC (n=82) n (%) or median (Q1-Q3)	DMPA (n=108) n (%) or median Q1-Q3	NH (n=113) n (%) or median (Q1-Q3)	Total (n=303) n (%) or median (Q1-Q3)	p-value ³
Sociodemographic					
Study Site					
Uganda	31 (37.8)	38 (35.19)	58 (51.33)	127 (41.91)	0.036
Zimbabwe	51 (62.2)	70 (64.81)	55 (48.67)	176 (58.09)	
Age at HIV seroconversion visit ¹	25 (23-28)	25 (23-29)	28 (24-31)	26 (23-30)	<0.001
Living with partner	56 (68.29)	73 (67.59)	69 (61.06)	198 (65.35)	0.480
Number of years in school ⁴	10 (7-11)	9.5 (7.5-11)	9 (7-11)	10 (7-11)	0.633
Health history					
Number of lifetime pregnancies	2 (1-3)	2 (2-3)	2 (2-3)	2 (1-3)	0.062
Current pregnancy	4 (4.88)	1 (0.93)	16 (14.16)	21 (6.93)	<0.001
Current breastfeeding	5 (6.1)	11 (10.19)	18 (15.93)	34 (11.22)	0.091
STI symptoms ^{5,6}	26 (31.71)	47 (43.52)	52 (46.02)	125 (41.25)	0.113
Current smoking	0	0	0	0	N/A
Current alcohol use	14 (17.07)	18 (16.67)	27 (23.89)	59 (19.47)	0.326
Participant sexual behavior with all partners					
≥2 sex partners ⁵	2 (2.44)	8 (7.41)	9 (7.96)	19 (6.27)	0.234
High participant behavioral risk ^{5,7}	2 (2.44)	11 (10.19)	14 (12.39)	27 (8.91)	0.031
Coital frequency ⁸					
0 – 14	49 (59.76)	78 (72.22)	86 (76.11)	213 (70.3)	0.040
15 – 29	25 (30.49)	24 (22.22)	21 (18.58)	70 (23.1)	
30+	8 (9.76)	6 (5.56)	6 (5.31)	20 (6.6)	
Consistent condom use ⁹	13 (15.85)	28 (25.93)	46 (40.71)	87 (28.71)	<0.001
Partner spent nights away from home (last 30 days)	0.5 (0-14)	1 (0-21)	2 (0-20)	1 (0-18)	0.744
High primary partner risk ⁹	61 (74.39)	85 (78.7)	79 (69.91)	225 (74.26)	0.328
Clinical/Laboratory Data					
Prevalent Chlamydia	8 (9.88)	6 (5.56)	4 (3.85)	18 (6.14)	0.254

Characteristic	OC (n=82) n (%) or median (Q1-Q3)	DMPA (n=108) n (%) or median (Q1-Q3)	NH (n=113) n (%) or median (Q1-Q3)	Total (n=303) n (%) or median (Q1-Q3)	p-value ³
Prevalent Gonorrhea	9 (11.25)	11 (10.19)	10 (9.71)	30 (10.31)	0.943
Positive Trichomonas	5 (6.17)	4 (3.81)	7 (6.73)	16 (5.52)	0.619
Non viral STI infection ¹⁰	17 (21.25)	17 (16.19)	19 (18.81)	53 (18.53)	0.679
Positive HSV-2	63 (79.75)	87 (82.08)	94 (84.68)	244 (82.43)	0.674
Positive BV	18 (22.22)	30 (27.78)	32 (29.63)	80 (26.94)	0.510
GUD	2 (2.47)	0 (0)	1 (0.91)	3 (1)	0.275
HIV-1 subtype					
A	21 (25.61)	26 (24.07)	38 (33.63)	85 (28.05)	0.084
C	53 (64.63)	71 (65.74)	55 (48.67)	179 (59.08)	
D	7 (8.54)	11 (10.19)	16 (14.16)	34 (11.22)	
Unknown	1 (1.22)	0(0)	4 (3.54)	5 (1.65)	

¹ For women seroconverting during the HC-HIV study, data are from the HC-HIV seroconversion visit; for women seroconverting during the serosurveillance phase, data are taken from GS 1.0 visit

² Based on the actual contraceptive use reported at time of estimated HIV infection

³ For categorical variables, Exact test was used for any cell number < 5 and Mantel-Haenszel tests was be used for all cells ≥ 5; for continuous variables, Kruskal-Wallis tests was used

⁴ At HC screening visit

⁵ In the last 3 months

⁶ Includes: abnormal vaginal discharge, genital itching, lower abdominal pain, pain during sex, bleeding between periods

⁷ Includes: having multiple partners or new sex partner or engaged in commercial sex work or had concurrent sex partners in the last 3 months

⁸ In a typical month during the last 3 months

⁹ Includes: partner HIV+ or abnormal discharge from penis or weight loss or partner had commercial sex or partner spent nights away from home

¹⁰ Includes: positive chlamydial, gonococcal or trichomonas infection

Table 2
Crude AIDS incidence estimates using cumulative duration of contraceptive use by site, HIV-1 subtype and age

Characteristic	OC N ¹ /wy ² (incidence rate per 100 wy)	DMPA N ¹ /wy ² (incidence rate per 100 wy)	Non-Hormonal N ¹ /wy ² (incidence rate per 100 wy)	Total N ¹ /wy ² (incidence rate per 100 wy)
Study site/Subtype				
Uganda				
Subtype A	5 / 60 (8.3)	12 / 172 (7)	11 / 175 (6.3)	28 / 408 (6.9)
Subtype D	2 / 17 (11.9)	6 / 59 (10.2)	8 / 70 (11.4)	16 / 146 (11)
Subtype C	0 / 1 (0)	0 / 7 (0)	1 / 4 (28.4)	1 / 12 (8.6)
Zimbabwe				
Subtype C	18 / 191 (9.4)	25 / 407 (6.1)	23 / 238 (9.7)	66 / 836 (7.9)
Total ³	25 / 269 (9.3)	43 / 648 (6.6)	43 / 491 (8.8)	111 / 1408 (7.9)
Age at estimated infection date				
< 25 years	3 / 102 (2.9)	14 / 270 (5.2)	19 / 216 (8.8)	36 / 588 (6.1)
≥ 25 years	22 / 167 (13.1)	29 / 378 (7.7)	24 / 275 (8.7)	75 / 820 (9.1)
Total	25 / 269 (9.3)	43 / 648 (6.6)	43 / 491 (8.8)	111 / 1408 (7.9)

¹ Number of incident outcomes occurring within a time interval when the contraceptive method was used

² Cumulative duration of a given contraceptive method use for women; rounded to closest integer

³ Total includes 0 outcomes and 7 women years for 5 women with unknown HIV-1 subtypes

Table 3
Adjusted hazard ratios (AHR) for hormonal contraceptive use on HIV disease progression

Exposure definition/Contraceptive group	Time to AIDS	Time to AIDS, death or HAART Initiation
	AHR (95% CI)	AHR (95% CI)
Cumulative contraceptive use throughout study¹		
Non-hormonal	Ref	Ref
DMPA	0.90 (0.76 – 1.08)	0.90 (0.77 – 1.06)
OCs	1.07 (0.89 – 1.29)	1.02 (0.86 – 1.22)
Contraceptive use in year prior to AIDS²		
Non-hormonal	Ref	Ref
DMPA	0.82 (0.50 – 1.36)	0.81 (0.51 – 1.31)
OCs	1.29 (0.69 – 2.44)	1.26 (0.69 – 2.29)
Contraceptive use at time of HIV infection³		
Non-hormonal	Ref	Ref
DMPA	1.14 (0.73 – 1.79)	1.23 (0.81-1.87)
OCs	0.93 (0.56 – 1.55)	0.85 (0.52-1.39)

¹From a marginal structural Cox survival model adjusted for enrolment age, country/HIV subtype, baseline (BL) cohabitation, education, BL participant behavioral risk, BL breastfeeding, BLSTI symptoms, BL unprotected sex acts, BL primary partner risk, and BL GUD. Includes 102 primary (AIDS) and 116 secondary outcomes. Weights computing including for enrolment age, country/HIV subtype, BL cohabitation, education, BL participant behavioral risk, BL breastfeeding, time-varying (TV) pregnancy status, TV STI symptoms, TV unprotected sex acts, TV primary partner risk, and TV GUD; The mean (median) of the estimated inverse-probability-treatment weights is 0.93 (0.98) and its range is 4.15.

²From a Cox proportional hazard model adjusted for enrolment age, country/HIV subtype, cohabitation, TV pregnancy status, TV STI history, TV unprotected sex acts, TV primary partner risk, TV GUD, and TV smoking. Includes 108 primary outcomes (AIDS) and 123 secondary outcomes.

³From a Cox proportional hazard model adjusted for enrolment age, country/HIV subtype, cohabitation, TV pregnancy status, TV STI history, TV unprotected sex acts, TV primary partner risk, and TV GUD. Includes 108 primary outcomes (AIDS) and 123 secondary outcomes.

Table 4
Estimated adjusted hazard ratios (AHR) of HIV disease progression using Cox proportional hazards modeling

	Time to AIDS AHR (95% CI) (108 events)	Time to AIDS, death or HAART Initiation AHR (95% CI) (123 events)
Cumulative contraceptive use throughout study¹		
Non-hormonal	Ref	Ref
DMPA	0.94 (0.82 – 1.09)	0.96 (0.85 – 1.10)
OCs	1.00 (0.85 – 1.17)	0.98 (0.85 – 1.13)
Uganda: Subtype A	Ref	Ref
Subtype D	1.91 (1.00 – 3.68)	1.80 (0.94 – 3.43)
Zimbabwe: Subtype C	0.72 (0.44 – 1.20)	0.81 (0.50 – 1.30)
Age: 18-24	0.60 (0.40 – 0.91)	0.62 (0.41 – 0.92)
25+	Ref	Ref
Living with partner	0.93 (0.62 – 1.41)	1.01 (0.69 – 1.49)
≤ 9 years in school	0.85 (0.56 – 1.30)	0.84 (0.56 – 1.25)
Current breastfeeding at baseline	1.50 (0.79 – 2.82)	2.12 (1.24 – 3.62)
CD4 count at enrollment (per 100 cell increase)	0.76 (0.67 – 0.86)	0.76 (0.67 – 0.85)
Setpoint viral load (per log ₁₀ unit increase)	1.40 (1.07 – 1.83)	1.33 (1.04 – 1.71)
<u>Time-varying covariates</u>		
Participant behavioral risk	1.32 (0.46 – 3.77)	1.29 (0.46 – 3.66)
Currently pregnant	0.19 (0.03 – 1.33)	1.06 (0.46 – 2.45)
STI symptoms	1.43 (0.95 – 2.14)	1.40 (0.96 – 2.05)
Number of unprotected sex acts	0.96 (0.92 – 1.01)	0.96 (0.92 – 1.00)
Primary partner risk	0.77 (0.51 – 1.16)	0.77 (0.53 – 1.14)
GUD	1.80 (0.94 – 3.44)	1.66 (0.90 – 3.08)