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Hormonal contraception is not associated with reduced ART effectiveness among women initiating ART: evidence from longitudinal data

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Abstract

Background—To explore the association between concomitant hormonal contraceptive and antiretroviral therapy (ART) use and 1) plasma viral suppression and 2) genital HIV shedding among HIV-positive women initiating ART.

Methods—We analyzed plasma viral load and genital viral RNA shedding from 1,079 HIV-positive women initiating ART who were followed prospectively in three sub-Saharan Africa HIV prevention studies. Plasma and endocervical swab samples were collected every six months. Self-reported contraceptive use was categorized into injectable, implant, oral, or non-hormonal/no contraception. We used multivariate Cox regression to assess time to plasma viral suppression and logistic regression with generalized estimating equations to assess genital viral shedding for each contraceptive method.

Results—At the time of ART initiation, there were 211 (20%) injectable, 69 (6%) implant, 50 (5%) oral, and 749 (69%) non-hormonal or no method users. Plasma viral suppression was high

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(90% by 6 months) and hormonal contraceptives did not diminish time to plasma viral suppression as compared to non-hormonal/no methods [adjusted hazard ratios: injectables 0.89 (95% CI 0.75–1.07), implants 0.91 (0.68–1.23), and oral methods 1.33 (1.06–1.66)]. Genital viral shedding was uncommon any time after ART initiation (only 9% of samples had detectable viral shedding) and hormonal contraceptives were not associated with an increased detection of genital viral shedding [adjusted odds ratios: injectables 1.07 (0.69–1.65), implants 0.67 (0.31–1.49), and oral methods 0.56 (0.19–1.69)].

Conclusions—The hormonal contraceptives assessed were not associated with reduced ART effectiveness among HIV-positive women initiating ART. HIV-positive women should continue to be offered contraceptive options, including hormonal ones, that best meet their needs.

Keywords

hormonal contraception; antiretroviral therapy; plasma viral suppression; genital shedding

INTRODUCTION

An estimated 13 million HIV-positive women of reproductive age live in sub-Saharan Africa¹ where a marked increase in modern contraceptive prevalence has occurred in recent decades, with average prevalence ranging from 8% in the 1980s to 22% in 2010.^{2,3} Effective contraception, including hormonal contraception, prevents unintended pregnancies and reduces maternal morbidity and mortality.⁴ Family planning is also one of the pillars of preventing perinatal HIV transmission.⁵ Finally, HIV-positive women require access to effective contraception to fulfill their reproductive health rights.

The World Health Organization (WHO) currently recommends initiation of life-long antiretroviral therapy (ART) regardless of HIV/AIDS disease status, and efavirenz-containing ART is the recommended first-line regimen, including among women of reproductive age.⁶ Concomitant use of certain hormonal contraceptives and ART regimens raise concerns about drug-drug interactions with potential to reduce the effectiveness or increase the toxicity of either therapy.^{7,8} Furthermore, progestin-based contraceptive use in HIV-positive women not on ART has been implicated in potentially increasing the risk of HIV transmission to their uninfected male partners, with increased genital viral shedding in the HIV-positive women using progestin-based contraception despite having undetectable plasma viral load.⁹ Progestin-based contraception may increase viral replication, diversity, or set point viral load or decrease immune regulation in the genital tract of HIV-positive women.¹⁰ However, among women on ART, data are limited on whether concomitant use reduces ART effectiveness or increases risk of transmission.

To better understand the impact of hormonal contraception on ART effectiveness and potential for increasing HIV transmission among women on ART, as measured by plasma viral load and genital shedding, respectively, we analyzed data from three prospective studies conducted in sub-Saharan Africa.

METHODS

Study population

We used data from HIV-positive women who were enrolled in one of three studies conducted with HIV-discordant couples: the Partners in Prevention HSV/HIV Transmission Study, Couples Observational Study, and Partners PrEP Study. Women who initiated ART after study enrollment and had at least one assessment of viral load after ART initiation were included in this analysis. Study visits were scheduled every 1–3 months; detailed enrollment and follow-up procedures for these participants are described elsewhere.^{11–16} Women not eligible for ART initiation at the time of study enrollment had their clinical and immunological status monitored at study visits, and if eligible to initiate ART according to national guidelines during follow-up, they were referred to local HIV facilities for ART initiation. Women who had plasma viral suppression before reporting ART initiation—potentially because of covert ART use¹⁷—were excluded. The University of Washington Human Subjects Division and local ethic review boards at each study site approved the studies. Participants provided written informed consent.

Exposures

Contraceptive use and ART regimen were self-reported at each study visit but assessed at 3-month intervals for consistency among the three studies. We categorized contraceptive use into injectable, implant, oral, or non-hormonal/no contraception. Non-hormonal contraception included non-hormonal intrauterine devices or surgical or barrier methods. For each woman, we included her follow-up time from ART initiation to time of first change in contraceptive method use or end of study follow-up. We chose to censor women at the time of first method switch (i.e. limiting our analysis to consistent contraceptive method use) to avoid any potential misclassification, because it is unclear if hormonal contraceptive use has longstanding effects on plasma viral suppression or genital viral shedding. We defined an ART regimen as at least a three-drug combination of antiretrovirals. Date of ART initiation was estimated as the midpoint of the first interval before ART use was reported or, when available, using the self-reported number of days of ART use. For a subgroup analysis, ART regimen type was classified into efavirenz- or nevirapine-containing ART or other ART.

Outcomes

Plasma and endocervical swab samples were collected every six months, irrespective of ART initiation, and included in this analysis if they were collected after ART initiation. The samples were linked to the contraceptive method reported as being used at the sample collection visit. Plasma and genital viral detection was conducted using COBAS AmpliPrep/COBAS TaqMan Real-Time HIV-1 RNA assay (Roche Diagnostics, Indianapolis, IN) for Partners in Prevention and Couples Observational Studies and Abbott RealTime HIV-1 assay (Abbott Laboratories, Des Plains, IL) for Partners PrEP Study, as previously detailed.^{11,18} The lower limits of quantification for HIV-1 RNA assays in both undiluted plasma and endocervical samples were 40–48 copies/mL of fluid tested. Plasma viral suppression was considered <400 copies/mL and genital shedding as any detectable genital viral RNA. We defined isolated genital shedding as any detectable genital viral RNA in the setting of plasma viral suppression at the same visit.

Statistical analysis

We used Cox proportional hazards regression to estimate hazard ratios comparing time to first plasma viral suppression after ART initiation by contraceptive use categories. The Cox regression models were adjusted for age at study enrollment, plasma viral load prior to ART initiation, and study. A subgroup analysis included specific ART regimen types as an effect measure modifier. We used logistic regression with generalized estimating equations to estimate odds ratios for genital viral shedding by contraceptive categories, adjusting for time from ART initiation, acyclovir use, presence of any sexually transmitted infections (defined as endocervical or urine samples testing positive for *Neisseria gonorrhea*, *Chlamydia trachomatis*, or *Trichomonas vaginalis* via nucleic acid amplification) or genital ulcer disease (defined clinically based on physical exam) at study enrollment, time-varying plasma viral load, age at study enrollment, and study. Analyses were conducted in SAS version 9.4 (Cary, NC).

RESULTS

1,079 women across the three studies were included in this analysis. At the time of ART initiation, the median age was 30 years (IQR 25–35), median CD4 cell count 424 cells/ μ L (306–566), and 924 (86%) were at WHO clinical stage I or II. At the time of ART initiation, 211 (20%) women were using injectables, 69 (6%) implants, 50 (5%) oral, and 749 (69%) non-hormonal or no methods, which included 16 (1.5%) non-hormonal intrauterine device users. One hundred and seventy-three (16%) and 661 (61%) women initiated efavirenz- and nevirapine-containing ART, respectively.

The proportion of women virally suppressed in plasma at 6 and 12 months after ART initiation was 90% and 99%, respectively. Hormonal contraceptive use did not significantly delay time to plasma viral suppression as compared to non-hormonal or no methods. The adjusted hazard ratios (aHR) of time to plasma viral suppression among hormonal contraceptive users compared to non-hormonal or no method users were: 0.89 (95% CI 0.75–1.07) among injectable and 0.91 (0.68–1.23) among implant users. Women using oral contraceptive methods achieved plasma viral suppression at a faster rate as compared to non-hormonal or no method users (aHR 1.33 (1.06–1.66); Figure 1).

In the subgroup analysis, the associations between hormonal contraceptive use and plasma viral suppression did not significantly differ by ART regimen ($p=0.31$ for the interaction term between ART regimen and hormonal contraceptive method). When comparing by ART regimen, independent of contraceptive method use, use of efavirenz-containing ART trended achieved plasma viral suppression at a faster rate than use of nevirapine-containing ART (aHR 1.24, 95% CI 1.03–1.50, $p=0.02$).

The median number of endocervical samples analyzed per woman was 1 (IQR 1–2). One hundred and fifty-five of 1,635 (9%) endocervical samples had detectable genital HIV shedding, regardless of plasma viral suppression in the woman, and 94 of 1,238 (8%) samples had isolated genital viral shedding, in the setting of plasma viral suppression. Hormonal contraceptive use did not significantly increase the odds of detecting genital viral shedding compared to non-hormonal or no methods. The adjusted odds ratios of detecting

any genital viral shedding for hormonal contraceptive users compared to non-hormonal or no method users were: 1.07 (0.69–1.65) among injectable, 0.67 (0.31–1.49) among implant, and 0.56 (0.19–1.69) among oral users (Table 1). Similarly, there was no evidence of increased isolated genital viral shedding (i.e., in the setting of plasma viral suppression) for hormonal contraceptive users compared to non-hormonal or no method users (Table 1).

DISCUSSION

In this large, prospective analysis of HIV-positive women initiating ART from sub-Saharan Africa, the rate of plasma viral suppression after ART initiation was high and was not significantly delayed by the concomitant use of hormonal contraceptives. The concomitant use of hormonal contraceptives and ART was also not significantly associated with detection of genital viral shedding, whether in the presence or absence of detectable plasma viremia.

In the era of increasing ART use in sub-Saharan Africa, ours is the largest study to date to report on the effect of hormonal contraception on ART effectiveness as measured by plasma viral suppression. In the pre-ART era, most studies did not find that hormonal contraceptive use was associated with HIV disease progression, as measured by change in CD4 cell count, eligibility to initiate ART, occurrence of opportunistic infections, or death.¹⁹ With increasing ART use, more recently published studies consistently reported similar findings, with no reduction in HIV plasma viral suppression rates with hormonal contraceptive use.^{20–22} Interestingly in our study, time to plasma viral suppression was shorter among women consistently using oral methods of contraception compared to women using no hormonal or contraceptive methods, which may reflect prior experience taking pills and thus greater potential to also be adherent to ART. Oral contraceptives, however, have been associated with low adherence to oral pre-exposure prophylaxis in one study.²³ Regardless, oral contraceptives are less effective than longer-acting contraceptive methods in preventing pregnancy^{24,25} and should not be promoted as a strategy to enhance ART adherence or effectiveness.

The use of specific combinations of hormonal contraceptives and ART regimens may reduce contraceptive effectiveness, likely due to drug-drug interactions.⁸ Specifically, among implant users, women using efavirenz-containing ART had higher rates of pregnancy, indicating contraceptive failure, than women using nevirapine-containing ART.²⁶ However, we did not observe the reverse—i.e., we did not detect a reduction in the effectiveness of efavirenz-containing ART in achieving plasma viral suppression among women using hormonal contraception. The time to plasma viral suppression being shorter among women using efavirenz- vs. nevirapine-containing ART, independent of hormonal contraceptive use, may indicate the higher potency of efavirenz- vs. nevirapine-containing ART.²⁷

Progestin-based injectable use, particularly depot medroxyprogesterone acetate use, has been implicated in potentially increasing the risk of HIV acquisition among HIV-negative women.^{28–30} A parallel concern is the potential for progestin-based hormonal contraception to increase the risk of HIV transmission from HIV-positive women to their partners. In one analysis, women who had not yet initiated ART and used injectable or oral contraception transmitted HIV to their negative partners at twice the rate of women who did not use

hormonal contraception; these women were also more likely to have detectable genital viral shedding.⁹ These effects were strongest among women using injectable contraception. In our study, use of hormonal contraceptives, including injectables, did not alter HIV genital shedding in women initiating ART, with overall high viral suppression in plasma and the genital compartment. Other studies conducted among women on ART using various hormonal contraceptives also report no differences in genital shedding.^{31,32} Confirmed plasma viral suppression after ART initiation essentially prevents HIV transmission.³³ Plasma and genital HIV RNA levels are strongly correlated,^{34,35} though some women on ART with suppressed plasma viral load may shed genital RNA.^{32,34–38} Ultimately, it appears that effective ART overwhelms any potential negative impact of hormonal contraception on genital shedding regardless of the mechanism.

Despite analyzing data from one of the largest databases with clinical measures, our study has some limitations. First, ascertainment of the exposure categories of hormonal contraceptive and ART use were self-reported, and we did not evaluate adherence to the contraceptive method, though pregnancy rates among women using injectables and oral contraceptives in these studies are as expected.³⁹ Second, the ascertainment of the outcomes was conducted at six-month intervals, mimicking clinical care; however, these wide time intervals do not allow for more precise assessment of time to plasma viral suppression. Nonetheless, studies among women on ART with more frequently sampling have also not found any significant associations between hormonal contraception and ART effectiveness. Third, for the genital viral shedding analysis, we were unable to account for important potential confounders, such as time-varying sexually transmitted infections, including genital herpes or syphilis, or genital ulcer disease and vaginal washing practices. Fourth, when dividing the cohort by women using various hormonal contraceptive methods and ART regimen types, our sample sizes for each grouping became relatively small, preventing definitive conclusions for specific ART regimen types. Finally, our datasets did not allow for further evaluation of contraceptive exposures, such as type of injectable or implant use or whether women were using combined or progestin-only oral contraceptive pills, which may have differential effects on ART effectiveness.

Conclusion

We found no evidence of reduced ART effectiveness or increased potential of HIV transmission among HIV-positive women concomitantly using various forms of hormonal contraception and ART. As use of both hormonal contraception and ART increase globally among HIV-positive women, studies that investigate the issues with their concomitant use are urgently needed. HIV-positive women should continue to be offered contraceptive options, including hormonal ones, that best meet their needs.

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References

1. (UNAIDS) JUNPoHA. Global report: UNAIDS report on the global AIDS epidemic 2013. Geneva, Switzerland: UNAIDS; 2013.
2. Alkema L, Kantorova V, Menozzi C, Biddlecom A. National, regional, and global rates and trends in contraceptive prevalence and unmet need for family planning between 1990 and 2015: a systematic and comprehensive analysis. *Lancet*. 2013; 381(9878):1642–1652. [PubMed: 23489750]
3. Emina JB, Chirwa T, Kandala NB. Trend in the use of modern contraception in sub-Saharan Africa: Does women's education matter? *Contraception*. 2014; 90(2):154–161. [PubMed: 24835827]
4. Halperin DT, Stover J, Reynolds HW. Benefits and costs of expanding access to family planning programs to women living with HIV. *AIDS*. 2009; 23(Suppl 1):S123–S130. [PubMed: 20081384]
5. (UNAIDS) JUNPoHA. Global plan towards the elimination of new HIV infections. Geneva, Switzerland: 2011.
6. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, Switzerland: World Health Organization; 2015.

7. Robinson JA, Jamshidi R, Burke AE. Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2012; 2012:890160. [PubMed: 22927715]
8. Tseng A, Hills-Niemenen C. Drug interactions between antiretrovirals and hormonal contraceptives. *Expert Opin Drug Metab Toxicol*. 2013; 9(5):559–572. [PubMed: 23425052]
9. Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *The Lancet Infectious Diseases*. 2012; 12(1):19–26. [PubMed: 21975269]
10. Hel Z, Stringer E, Mestecky J. Sex steroid hormones, hormonal contraception, and the immunobiology of human immunodeficiency virus-1 infection. *Endocr Rev*. 2010; 31(1):79–97. [PubMed: 19903932]
11. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012; 367(5):399–410. [PubMed: 22784037]
12. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010; 362(5):427–439. [PubMed: 20089951]
13. Kahle EM, Hughes JP, Lingappa JR, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. *J Acquir Immune Defic Syndr*. 2013; 62(3):339–347. [PubMed: 23187945]
14. Lingappa JR, Baeten JM, Wald A, et al. Daily acyclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. *Lancet*. 2010; 375(9717):824–833. [PubMed: 20153888]
15. Mujugira A, Baeten JM, Donnell D, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. *PLoS One*. 2011; 6(10):e25828. [PubMed: 21998703]
16. Pyra M, Heffron R, Mugo NR, et al. Effectiveness of hormonal contraception in HIV-infected women using antiretroviral therapy. *AIDS*. 2015; 29(17):2353–2359. [PubMed: 26544706]
17. Kahle EM, Kashuba A, Baeten JM, et al. Unreported antiretroviral use by HIV-1-infected participants enrolling in a prospective research study. *J Acquir Immune Defic Syndr*. 2014; 65(2):e90–94. [PubMed: 24442233]
18. Baeten JM, Kahle E, Lingappa JR, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. *Sci Transl Med*. 2011; 3(77):77ra29.
19. Phillips SJ, Curtis KM, Polis CB. Effect of hormonal contraceptive methods on HIV disease progression: a systematic review. *AIDS*. 2013; 27(5):787–794. [PubMed: 23135169]
20. Phillips SJ, Polis CB, Curtis KM. The safety of hormonal contraceptives for women living with HIV and their sexual partners. *Contraception*. 2016; 93(1):11–16. [PubMed: 26515194]
21. Polis CB, Nakigozi G, Ssempijja V, et al. Effect of injectable contraceptive use on response to antiretroviral therapy among women in Rakai, Uganda. *Contraception*. 2012; 86(6):725–730. [PubMed: 22717186]
22. Chu JH, Gange SJ, Anastos K, et al. Hormonal contraceptive use and the effectiveness of highly active antiretroviral therapy. *Am J Epidemiol*. 2005; 161(9):881–890. [PubMed: 15840621]
23. Corneli AL, Deese J, Wang M, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. *J Acquir Immune Defic Syndr*. 2014; 66(3):324–331. [PubMed: 25157647]
24. Polis CB, Bradley SE, Bankole A, Onda T, Croft T, Singh S. Typical-use contraceptive failure rates in 43 countries with Demographic and Health Survey data: summary of a detailed report. *Contraception*. 2016; 94(1):11–17. [PubMed: 27018154]
25. Trussell J. Contraceptive failure in the United States. *Contraception*. 2011; 83(5):397–404. [PubMed: 21477680]
26. Patel RC, Onono M, Gandhi M, et al. Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study. *The Lancet HIV*. 2015; 2(11):e474–e482. [PubMed: 26520927]
27. Pillay P, Ford N, Shubber Z, Ferrand RA. Outcomes for efavirenz versus nevirapine-containing regimens for treatment of HIV-1 infection: a systematic review and meta-analysis. *PLoS One*. 2013; 8(7):e68995. [PubMed: 23894391]

28. Morrison CS, Chen PL, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. *PLoS Med*. 2015; 12(1):e1001778. [PubMed: 25612136]
29. Polis CB, Phillips SJ, Curtis KM, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. *Contraception*. 2014; 90(4):360–390. [PubMed: 25183264]
30. Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. *Lancet Infect Dis*. 2015; 15(2):181–189. [PubMed: 25578825]
31. Day S, Graham SM, Masese LN, et al. A prospective cohort study of the effect of depot medroxyprogesterone acetate on detection of plasma and cervical HIV-1 in women initiating and continuing antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2014; 66(4):452–456. [PubMed: 24798764]
32. Low AJ, Konate I, Nagot N, et al. Cervicovaginal HIV-1 shedding in women taking antiretroviral therapy in Burkina Faso: a longitudinal study. *J Acquir Immune Defic Syndr*. 2014; 65(2):237–245. [PubMed: 24226060]
33. Loutfy MR, Wu W, Letchumanan M, et al. Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy. *PLoS One*. 2013; 8(2):e55747. [PubMed: 23418455]
34. Cu-Uvin S, Caliendo AM, Reinert S, et al. Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA. *AIDS*. 2000; 14(4):415–421. [PubMed: 10770544]
35. Tanton C, Weiss HA, Le Goff J, et al. Correlates of HIV-1 genital shedding in Tanzanian women. *PLoS One*. 2011; 6(3):e17480. [PubMed: 21390251]
36. Cu-Uvin S, DeLong AK, Venkatesh KK, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. *AIDS*. 2010; 24(16):2489–2497. [PubMed: 20736815]
37. Fiore JR, Suligoi B, Saracino A, et al. Correlates of HIV-1 shedding in cervicovaginal secretions and effects of antiretroviral therapies. *AIDS*. 2003; 17(15):2169–2176. [PubMed: 14523273]
38. Sheth AN, Evans-Strickfaden T, Haaland R, et al. HIV-1 genital shedding is suppressed in the setting of high genital antiretroviral drug concentrations throughout the menstrual cycle. *J Infect Dis*. 2014; 210(5):736–744. [PubMed: 24643223]
39. Ngunjiri K, Heffron R, Muganyizi NR, et al. Contraceptive method and pregnancy incidence among women in HIV-1-serodiscordant partnerships. *AIDS*. 2012; 26(4):513–518. [PubMed: 22156966]

Figure 1.
 Hormonal contraceptive use and time to plasma HIV load suppression during consistent contraceptive method use

Table 1

Hormonal contraceptive use and genital HIV shedding

	Number of samples with detectable genital viral shedding/total number of samples (%)	Unadjusted odds ratio (OR; 95% CI)	p-value	Adjusted odds ratio (aOR; 95% CI)	p-value
Genital viral shedding					
Contraceptive use *					
Injectable	38/353 (11%)	1.10 (0.74–1.65)	0.63	1.07 (0.69–1.65)	0.77
Implant	9/106 (9%)	0.80 (0.39–1.64)	0.54	0.67 (0.31–1.49)	0.33
Oral	4/78 (5%)	0.47 (0.17–1.33)	0.16	0.56 (0.19–1.69)	0.31
Non-hormonal/no method **	104/1098 (10%)	Ref.	Ref.	Ref.	Ref.
Isolated genital viral shedding ***					
Contraceptive use ****					
Injectable	25/274 (9%)	1.26 (0.76–2.09)	0.37	1.31 (0.79–2.18)	0.29
Implant	4/79 (5%)	0.66 (0.23–1.86)	0.43	0.72 (0.25–2.06)	0.54
Oral	4/66 (6%)	0.78 (0.27–2.25)	0.65	0.86 (0.30–2.48)	0.78
Non-hormonal/no method **	61/819 (8%)	Ref.	Ref.	Ref.	Ref.

* Contraceptive method use reported at time of endocervical swab collection and adjusted for time from ART initiation, acyclovir use, any sexually transmitted infections or genital ulcer disease at enrollment, age at study enrollment (< 24 years or ≥ 24 years), log-10 transformed plasma viral load, and study

** A sensitivity analysis that excluded intrauterine device users (n=16) from this category resulted in nearly identical findings

*** Isolated genital shedding defined as any detectable genital HIV-1 RNA in the setting of plasma viral suppression (<400 copies/mL)

**** Contraceptive method use reported at time of endocervical swab collection and adjusted for time from ART initiation, acyclovir use, any sexually transmitted infections or genital ulcer disease at enrollment, age at study enrollment (< 24 years or ≥ 24 years), and study