HHS Public Access

Author manuscript

Contraception. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Contraception. 2016 January ; 93(1): 17–24. doi:10.1016/j.contraception.2015.07.003.

Associations of hormonal contraceptive use with measures of HIV disease progression and antiretroviral therapy effectiveness☆

Maura K. Whiteman[a,*], **Gary Jeng**[a], **Anna Samarina**[b], **Natalia Akatova**[b], **Margarita Martirosyan**[b], **Dmitry M. Kissin**[a], **Kathryn M. Curtis**[a], **Polly A. Marchbanks**[a], **Susan D. Hillis**[a], **Michele G. Mandel**[a], and **Denise J. Jamieson**[a]

[a]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

[b]St. Petersburg AIDS Center, St. Petersburg, Russia

Abstract

Objective—To examine the associations between hormonal contraceptive use and measures of HIV disease progression and antiretroviral treatment (ART) effectiveness.

Study design—A prospective cohort study of women with prevalent HIV infection in St. Petersburg, Russia, was conducted. After contraceptive counseling, participants chose to use combined oral contraceptives (COCs), depot-medroxyprogesterone acetate (DMPA), a copper intrauterine device (IUD) or male condoms for pregnancy prevention. Among participants not using ART at enrollment, we used multivariate Cox regression to assess the association between current (time-varying) contraceptive use and disease progression, measured by the primary composite outcome of CD4 decline to <350 cells/mm^3, ART initiation or death. Among participants using ART at enrollment, we used linear mixed models to estimate the predicted mean CD4 change at select time points by contraceptive method.

Results—During a total of 5233 months follow-up among participants not using ART with enrollment CD4 ≥ 350 cells/mm^3 (*n*=315), 97 experienced disease progression. Neither current use of COCs [adjusted hazard ratio (aHR) 0.91, 95% confidence interval (CI) 0.56–1.48] nor DMPA (aHR 1.28, 95% CI 0.71–2.31) was associated with a statistically significant increased risk for disease progression compared with use of nonhormonal methods (IUD or condoms). Among participants using ART at enrollment (*n*=77), we found no statistically significant differences in the predicted mean changes in CD4 cell count comparing current use of COCs (p=.1) or DMPA (p=.3) with nonhormonal methods.

Conclusion—Hormonal contraceptive use was not significantly associated with measures of HIV disease progression or ART effectiveness among women with prevalent HIV infection.

☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author. Centers for Disease Control and Prevention, 4770 Buford Highway NE, Mailstop F-74, Atlanta, GA 30341-3724, USA. acq5@cdc.gov (M.K. Whiteman)..

Implications—Hormonal contraceptive use was not significantly associated with measures of HIV disease progression or ART effectiveness among women with prevalent HIV infection.

Keywords

Antiretroviral agents/therapeutic use; CD4 lymphocyte count; Contraceptive agents; Female/administration and dosage/adverse effects; HIV seropositivity/complications/drug therapy/mortality

1. Introduction

Preventing unintended pregnancy among women with HIV reduces vertical transmission and yields additional health and social benefits for women, children and families. Hormonal contraception, including oral contraceptives (OCs) and injectable methods, are widely available in many countries with high HIV prevalence and are highly effective at preventing pregnancy when used consistently and correctly. However, there are theoretical concerns that hormonal contraception may hasten HIV disease progression by altering immunologic responses [1]. While a randomized controlled trial among postpartum HIV-infected women reported an association between hormonal contraceptive use and accelerated HIV disease progression compared with copper intrauterine device (IUD) use [2], observational studies report no evidence of an association [3,4]. All previous studies were conducted in settings where antiretroviral treatment (ART) was unavailable or recommended only for those with advanced disease [3,4]. A recent increase in ART availability as well as guidelines expanding the population for whom ART is recommended has introduced new complexity to the study of hormonal contraception and HIV disease progression [3] and suggests the need for further study.

In 2013, World Health Organization (WHO) recommended that national HIV programs provide ART to all people with HIV with CD4 ≤ 500 cells/mm^3, with priority given to those with severe disease or CD4 ≤ 350 cells/mm^3 [5]. As a result, it may be useful to reexamine the issue of hormonal contraceptive use among women with HIV in settings where ART is more widely provided than in previous studies and using different definitions of disease progression than those previously used, which included outcomes such as CD4 <200 or 250 cells/mm^3, clinical AIDS or death. These outcomes will become rarer with earlier and more wide-spread ART initiation; thus, it will be valuable to examine disease progression using outcomes more applicable to settings with increased ART availability and use. Additionally, as the number of HIV-infected women taking ART increases, it will be important to examine the effect of hormonal contraception on ART effectiveness. Currently, there is a limited body of evidence examining the association between hormonal contraception and ART effectiveness, including studies examining women on established ART [6] and initiating ART [7,8], none of which reports evidence of a detrimental effect of hormonal contraception on ART effectiveness. We sought to expand knowledge about the safety of hormonal contraception for women with HIV by examining the associations between hormonal contraception and measures of HIV disease progression and ART effectiveness among a cohort of HIV-infected women in St. Petersburg, Russia, where ART was available and recommended more broadly than in previous studies.

2. Materials and methods

2.1. Study population and procedures

Participants in this study were enrolled in a project examining the integration of family planning services into HIV clinical care in St. Petersburg, Russia [9]. Participants were recruited between October, 2007, and October, 2011, from three sites providing routine care to HIV-infected women. Eligible participants were aged 16–45 years with confirmed HIV infection; sexually active in the last year; not pregnant, breastfeeding or intending to breastfeed; and desired to avoid pregnancy for ≥ 12 months. Women were ineligible if they had a hysterectomy, were sterile or had used hormonal contraception or an IUD in the past 3 months.

Candidate participants received counseling on all approved contraceptive methods in Russia and on condom use for prevention of HIV transmission. Study contraceptive methods included combined oral contraceptives (COCs; 30 mcg ethinyl estradiol/150 mcg desogestrel), depot-medroxyprogesterone acetate (DMPA), copper IUD (copper surface area of 375 mm^2) and male condoms. If women were interested in using any study contraceptive method for pregnancy prevention (COCs, DMPA, copper IUD or male condoms alone), study clinicians assessed their medical eligibility for all study methods using WHO guidance [10]. All women were eligible to use male condoms. Women interested in participating selected a study method from among those they were medically eligible to use. Contraceptive methods were provided free of charge during the study. All participants were given male condoms. The study was approved by the institutional review boards of the Centers for Disease Control and Prevention and the collaborating institutions in Russia. All participants provided written informed consent.

After enrollment, scheduled study visits occurred at 6 weeks and every 6 months thereafter for 18–48 months. Participants were encouraged to return at any time for physical complaints or suspected pregnancy and could switch contraceptive methods at any time. At enrollment and scheduled visits, participants underwent physical exams, provided biologic specimens (to measure CD4 cell counts and plasma HIV-1 RNA) and were interviewed to collect demographic, reproductive and behavioral information (biologic specimens were routinely collected at the 6-week visit until March, 2009). Laboratory testing was conducted at the St. Petersburg City AIDS Center central laboratory. CD4 cell counts were performed using FACSCalibur (BD Biosciences, San Jose, CA). Plasma HIV-1 RNA (viral load) levels were quantified using the Abbott RealTime HIV-1 Assay (Abbott Molecular Inc., Des Plaines, IL), with 150 copies per milliliter as the lower limit of detection. Urine pregnancy tests were performed at study visits and self-reported pregnancies were verified by medical record review. Women who became pregnant were referred for care and were no longer followed. Deaths were ascertained through clinic, hospital and vital records and reports from family or friends. Two physician investigators (DMK and DJJ) blinded to participant contraceptive use classified each death as likely attributable to AIDS, non-AIDS death, indeterminate or unknown [11]. Non-AIDS deaths were not considered in our analyses.

At each follow-up visit, participants were asked about their contraceptive use since their last visit. Staff recorded the dispensing of study contraceptive methods. Participants were also

asked about ART use and responses were verified using medical records, when available. At the time of the study, government-funded antiretroviral drugs were available in Russia and ART was generally initiated in patients with CD4 <350 cells/mm^3. All analyses were conducted separately by ART use at enrollment.

2.2. Statistical analysis

2.2.1. Participants not using ART at enrollment—Participants were eligible for inclusion in analyses if they had CD4 measurements at ≥ 1 follow-up visit. We examined three composite outcome measures to assess disease progression. The first (primary) outcome was examined among participants with enrollment CD4 ≥ 350 cells/mm^3 and was defined as the first occurrence of CD4 decline to <350 cells/mm^3, ART initiation or death. The second outcome was examined among all participants eligible for analyses and was defined as the first occurrence of a CD4 decline of ≥ 20% from enrollment or death. The third outcome was examined among participants with enrollment CD4 ≥ 200 cells/mm ^{3} and was defined as the first occurrence of CD4 decline to <200 cells/mm^3 or death.

We used Cox proportional hazards models to examine the associations between contraceptive use and these HIV disease progression outcomes. Participants were censored at pregnancy (all outcomes) or at ART initiation (second and third outcomes). For our primary analysis, we examined contraceptive use as a time-varying exposure, wherein a participant who switched methods could contribute person time to multiple contraceptive groups. As method switching could be related to disease progression (e.g., if women who become more ill due to HIV discontinued hormonal contraception), we also examined contraceptive use defined as the method chosen at enrollment. Under this definition, a participant is categorized under the method they chose at enrollment, even if they switched to other methods. Because few women chose the IUD, we considered IUD use and condom use together as nonhormonal method use. Models were adjusted for enrollment CD4 count, age, postpartum status and prior hormonal contraceptive use. The addition of other enrollment variables to the model, including time since HIV diagnosis, ever use of ART, time since ART use, viral load, marital status, frequency of condom use, positive sexually transmitted disease (STD) test, parity, recent intravenous drug use or abortion history, did not appreciably change the adjusted hazard ratio (aHR) estimates. For each model, the proportional hazards assumption was confirmed for the included variables by examining interaction terms with time.

2.2.2. Participants using ART at enrollment—Participants were eligible for inclusion in analyses if they used their ART regimen at enrollment for ≥ 3 months and had CD4 measurements at ≥ 1 follow-up visit while using ART. We used linear mixed models without assuming independence of CD4 measurements in each participant to estimate the predicted mean change in CD4 count by contraceptive method at select time points. Participants were censored at the first occurrence of pregnancy, death or ART discontinuation. We assumed a linear change in CD4 count during follow-up. Models were adjusted for enrollment CD4 count, duration of ART use at enrollment, whether or not the ART regimen was highly active antiretroviral therapy (HAART) and time under observation in the study. HAART was defined as regimens including two nucleoside reverse

transcriptase inhibitors and one protease inhibitor (PI) or one nonnucleoside reverse transcriptase inhibitor (NNRTI). We examined contraceptive use defined both as current (time-varying) use and as method chosen at enrollment.

We also examined the proportion of participants who were virally suppressed on ART at enrollment who remained in that state during follow-up, by contraceptive method chosen at enrollment. Viral suppression was defined as viral load <150 copies per milliliters.

3. Results

Of 760 women eligible for the study, 709 enrolled. Three women were later discontinued from the study due to unrecognized pregnancy at enrollment. Of the remaining 706 women enrolled, 545 were not using ART at enrollment and 161 were using ART.

3.1. Participants not using ART at enrollment

Of 545 participants not using ART at enrollment, 426 (78%) had ≥ 1 follow-up CD4 measurement and were eligible for inclusion in analyses. Among these participants, median follow-up time was 19 (interquartile range, 11–30) months. At enrollment, 183 chose to use COCs, 87 chose DMPA and 156 chose a nonhormonal method (33 chose the IUD and 123 chose condoms) (Table 1). The median enrollment CD4 count was higher among those choosing DMPA and COCs than among those choosing a nonhormonal method. Compared to women choosing nonhormonal methods, a higher percentage of women choosing DMPA or COCs previously used ART, were postpartum, previously used hormonal contraception and had a positive STD test at enrollment. A higher percentage of women choosing DMPA as compared to other methods had ≥ 2 live births, while a higher percentage of those choosing nonhormonal methods reported always using condoms. Of those who reported using ART in the past month (*n*=105), all had a delivery in the past month and none reported using ART prior to their pregnancy, suggesting that previous use of ART in the study sample was primarily for the prevention of perinatal transmission. During follow-up, 103 participants switched their contraceptive method at least once and 63 participants became pregnant.

We examined the primary composite outcome of CD4 decline to <350 cells/mm^3, ART initiation or death among participants with enrollment CD4 ≥ 350 cells/mm^3 (*n*=315). Among these participants, 97 experienced at least one event: 61 experienced only a CD4 count decline, 18 experienced a CD4 count decline and initiated ART, 11 only initiated ART, 6 died as their only event and 1 experienced a CD4 count decline and died. The hazard of experiencing an event did not significantly differ among those currently using COCs [aHR 0.91, 95% confidence interval (CI) 0.56–1.48] or DMPA (aHR 1.28, 95% CI 0.71–2.31) compared to those using nonhormonal methods (Table 2). Results were similar when we defined contraceptive exposure as method selected at enrollment (Table 2).

We also examined the composite outcome of a decline of ≥ 20% from enrollment CD4 count or death. Among all women not using ART at enrollment with ≥ 1 follow-up CD4 measurement (*n*=426), 203 experienced events: 194 experienced only a CD4 count decline, 8 experienced death as their only event and 1 experienced a CD4 count and died. The hazard

of experiencing any event did not significantly differ among those currently using COCs (aHR 0.85, 95% CI 0.61–1.18) or DMPA (aHR 1.14, 95% CI 0.77–1.71) compared to those using nonhormonal methods (Table 2). Results were similar when we defined contraceptive exposure based on method selected at enrollment (Table 2).

Among women whose enrollment CD4 was ≥ 200 cells/mm^3 (*n*=402), we examined the outcome of CD4 decline to <200 cells/mm^3 or death (results not shown). Twenty-four participants experienced events; 17 experienced only a CD4 count decline and 7 experienced a CD4 count decline and death. When examining this outcome, there was no significant association with current use of COCs (aHR 0.65, 95% CI 0.25–1.70) or DMPA (aHR 0.99, 95% CI 0.31–3.20) compared to use of nonhormonal methods. Results were similar when we defined contraceptive exposure as method selected at enrollment.

For all analyses, results were similar when IUD use was excluded from the referent group. Additionally, results were similar among subgroups defined by previous use of ART, previous use of hormonal contraception and postpartum status.

3.2. Participants using ART at enrollment

Of 161 participants using ART at enrollment, 77 had at ≥ 1 follow-up CD4 measurement while using ART and had been on their regimen for ≥ 3 months and were thus eligible for inclusion in analyses. These participants contributed 308 CD4 measurements during a median follow-up of 23 (interquartile range 14–31) months. The majority of participants (90%) were on a HAART regimen. At enrollment, 24 of these participants chose to use COCs, 17 chose DMPA and 36 chose a nonhormonal method (9 chose the IUD and 27 chose condoms) (Table 3). At enrollment, a higher percentage of those choosing nonhormonal methods used ART >6 months and reported always using condoms than those choosing DMPA or COCs. During follow-up, 19 participants switched their contraceptive method at least once, 5 participants became pregnant and 2 participants died.

When adjusting for CD4 cell count at enrollment, duration of ART use at enrollment, HAART regimen and time under observation, we found no statistically significant differences in the predicted mean changes in CD4 cell count when comparing current use of COCs (p=.1) or DMPA (p=.3) with nonhormonal methods (Table 4). Similarly, when defining contraceptive exposure as the method selected at enrollment, we found no statistically significant differences in the predicted mean changes in CD4 cell count when comparing COCs (p=.7) or DMPA (p=.3) with nonhormonal methods.

Among participants choosing COCs at enrollment, 23 were virally suppressed at enrollment of whom 20 (87%) remained suppressed during follow-up. Among participants choosing DMPA at enrollment, 12 were virally suppressed at enrollment of whom 10 (83%) remained suppressed. Among participants choosing a nonhormonal method at enrollment, 29 were virally suppressed at enrollment of whom 24 (83%) remained suppressed.

4. Discussion

In our study of women with prevalent HIV infection in St. Petersburg, Russia, we did not find a statistically significant association between hormonal contraceptive use and measures of HIV disease progression among women not taking ART. Our results are consistent with previous cohort studies examining both incident [12–15] and prevalent [4,15–20] HIV cases, none of which reported an association between hormonal contraceptive use and accelerated HIV disease progression, as measured by CD4 <200 or 250 cells/mm^3, ART initiation, clinical AIDS, death or change in CD4 count or viral load. Only one study has reported an association between hormonal contraception and HIV disease progression. A randomized controlled trial among postpartum HIV-infected women in Zambia reported an association between hormonal contraceptive use (OCs and DMPA) and accelerated HIV disease progression (CD4 decline to <200 cells/mm^3, ART initiation or death) compared with copper IUD use [2]. However, interpretation of these findings is complicated by the potential biases introduced by high rates of method switching and high and differential rates of loss to follow-up by method assignment. Our study differs from previous investigations in the setting and outcomes studied. Whereas other studies were conducted in settings where ART was unavailable or only recommended for those with advanced disease, in our study population, ART was available and was initiated using broader criteria. Because of this, we included CD4 count decline to <350 cells/mm^3 as an outcome, rather than progression to clinical AIDS. As a result, our findings may be more applicable to settings with expanded access to ART, which will become more common given recent recommendations [5].

While we were limited by the small number of women using ART at enrollment in our study, we did not find evidence to indicate that hormonal contraceptive use had a detrimental effect on ART effectiveness. The interpretation of our findings may be complicated by variation in ART regimens and duration of use. Nonetheless, our findings are consistent with the limited body of evidence examining the association between hormonal contraception and ART effectiveness. A prospective cohort study of women on established ART found no difference in the estimated trend in CD4 cell count over time between implant users and nonhormonal users [6]. Two additional studies examined the use of hormonal contraception among women initiating ART. One found no association between DMPA and ART failure (detectable viral load, regimen change or death) [7], while the other one found no differences between hormonal contraceptive users (OCs, injectable contraceptive or implants) and nonusers on CD4 count or viral load response [8]. Current WHO guidance states that, in general, women taking ART are eligible to use all hormonal contraceptive methods, but special consideration may be necessary with certain ART regimens (particularly some NNRTIs and ritonavir-boosted PIs), as pharmacokinetic data suggest a potential reduction in the effectiveness of some hormonal contraceptives when taken with these regimens [21]. As more women with HIV will have access to ART, it will be important to clarify these issues.

The strengths of our study include use of time-varying contraceptive measures and the ability to verify self-reported contraceptive use with dispensing logs. Also, the start of study follow-up coincided with contraceptive method initiation, minimizing the influence of recent hormonal contraceptive use. Additionally, our sample included women seeking HIV

services who wished to use contraception, which may better reflect real-world scenarios than studies including women choosing to not use contraception. Finally, our findings were robust when we examined multiple definitions of exposure and outcome.

Our study has several limitations. Participants had prevalent HIV infection, and while we adjusted for enrollment CD4 cell count, we cannot rule out residual confounding related to disease stage or duration. Contraceptive methods were self-selected, and while we attempted to control for participant characteristics related to method choice [9] or other differences between method groups at enrollment, residual confounding may remain. There may be misclassification in some outcomes we examined, as an event may have occurred based on a single follow-up CD4 measurement. As CD4 counts can be variable [22], some events may represent clinically inconsequential fluctuations. Additionally, ART was not provided as part of the study; thus, we cannot be sure that standard criteria were used to initiate ART. Finally, as our sample was a convenience sample of women seeking HIV clinical services in one city, the generalizability of our findings to other populations may be limited.

Safe, effective options to prevent unintended pregnancy are a necessity for women with HIV. Our results are consistent with findings of most previous studies that hormonal contraceptive use is not associated with accelerated disease progression among women with HIV not using ART. In addition, our results and those of previous studies suggest that the use of hormonal contraception by women with HIV concurrently using ART is not associated with changes in ART effectiveness; however, the evidence addressing this question is quite limited. As eligibility and access to ART are expanded, more women of reproductive age will be using ART, making it increasingly important to understand the effects of simultaneous use of hormonal contraception and ART on the effectiveness of both drugs.

Acknowledgements

This research was supported by the United States Agency for International Development, Russia, through an Interagency Agreement with the Centers for Disease Control and Prevention. The authors wish to thank the study participants as well as past and present members of the study team for their important contributions to this study.

References

[1]. Stringer E, Antonsen E. Hormonal contraception and HIV disease progression. Clin Infect Dis. 2008; 47(7):945–51. [PubMed: 18715161]

[2]. Stringer EM, Levy J, Sinkala M, Chi BH, Matongo I, Chintu N, et al. HIV disease progression by hormonal contraceptive method: secondary analysis of a randomized trial. AIDS. 2009; 23(11): 1377–82. [PubMed: 19448528]

[3]. Phillips SJ, Curtis KM, Polis CB. Effect of hormonal contraceptive methods on HIV disease progression: a systematic review. AIDS. 2013; 27(5):787–94. [PubMed: 23135169]

[4]. Heffron R, Mugo N, Ngure K, Celum C, Donnell D, Were E, et al. Hormonal contraceptive use and risk of HIV-1 disease progression. AIDS. 2013; 27(2):261–7. [PubMed: 23079806]

[5]. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach, June 2013. World Health Organization; Geneva: 2013.

[6]. Hubacher D, Liku J, Kiarie J, Rakwar J, Muiruri P, Omwenga J, et al. Effect of concurrent use of anti-retroviral therapy and levonorgestrel sub-dermal implant for contraception on CD4 counts: a prospective cohort study in Kenya. J Int AIDS Soc. 2013; 16:18448. [PubMed: 23458102]

[7]. Polis CB, Nakigozi G, Ssempijja V, Makumbi FE, Boaz I, Reynolds SJ, et al. Effect of injectable contraceptive use on response to antiretroviral therapy among women in Rakai, Uganda. Contraception. 2012; 86(6):725–30. [PubMed: 22717186]

[8]. Chu JH, Gange SJ, Anastos K, Minkoff H, Cejtin H, Bacon M, et al. Hormonal contraceptive use and the effectiveness of highly active antiretroviral therapy. Am J Epidemiol. 2005; 161(9):881–90. [PubMed: 15840621]

[9]. Whiteman MK, Kissin DM, Samarina A, Curtis KM, Akatova N, Marchbanks PA, et al. Determinants of contraceptive choice among women with HIV. AIDS. 2009; 23(Suppl 1):S47–54. [PubMed: 20081388]

[10]. World Health Organization. Medical Eligibility for Contraceptive Use. Fourth. World Health Organization; Geneva: 2009. 2010.

[11]. Cohen MH, French AL, Benning L, Kovacs A, Anastos K, Young M, et al. Causes of death among women with human immunodeficiency virus infection in the era of combination antiretroviral therapy. Am J Med. 2002; 113(2):91–8. [PubMed: 12133746]

[12]. Polis CB, Wawer MJ, Kiwanuka N, Laeyendecker O, Kagaayi J, Lutalo T, et al. Effect of hormonal contraceptive use on HIV progression in female HIV seroconverters in Rakai, Uganda. AIDS. 2010; 24(12):1937–44. [PubMed: 20502314]

[13]. Morrison CS, Chen PL, Nankya I, Rinaldi A, Van Der Pol B, Ma YR, et al. Hormonal contraceptive use and HIV disease progression among women in Uganda and Zimbabwe. J Acquir Immune Defic Syndr. 2011; 57(2):157–64. [PubMed: 21358412]

[14]. Lavreys L, Baeten JM, Kreiss JK, Richardson BA, Chohan BH, Hassan W, et al. Injectable contraceptive use and genital ulcer disease during the early phase of HIV-1 infection increase plasma virus load in women. J Infect Dis. 2004; 189(2):303–11. [PubMed: 14722896]

[15]. Kilmarx PH, Limpakarnjanarat K, Kaewkungwal J, Srismith R, Saisorn S, Uthaivoravit W, et al. Disease progression and survival with human immunodeficiency virus type 1 subtype E infection among female sex workers in Thailand. J Infect Dis. 2000; 181(5):1598–606. [PubMed: 10823759]

[16]. Stringer EM, Giganti M, Carter RJ, El-Sadr W, Abrams EJ, Stringer JS. Hormonal contraception and HIV disease progression: a multicountry cohort analysis of the MTCT-Plus Initiative. AIDS. 2009; 23(Suppl 1):S69–77. [PubMed: 20081390]

[17]. Cejtin HE, Jacobson L, Springer G, Watts DH, Levine A, Greenblatt R, et al. Effect of hormonal contraceptive use on plasma HIV-1-RNA levels among HIV-infected women. AIDS. 2003; 17(11):1702–4. [PubMed: 12853757]

[18]. Richardson BA, Otieno PA, Mbori-Ngacha D, Overbaugh J, Farquhar C, John-Stewart GC. Hormonal contraception and HIV-1 disease progression among postpartum Kenyan women. AIDS. 2007; 21(6):749–53. [PubMed: 17413696]

[19]. Allen S, Stephenson R, Weiss H, Karita E, Priddy F, Fuller L, et al. Pregnancy, hormonal contraceptive use, and HIV-related death in Rwanda. J Womens Health (Larchmt). 2007; 16(7): 1017–27. [PubMed: 17903079]

[20]. Study Group for the MRC Collaborative Study. Survival and progression of HIV disease in women attending GUM/HIV clinics in Britain and Ireland. Sex Transm Infect. 1999; 75:247–52. [PubMed: 10615311]

[21]. World Health Organization. Hormonal Contraceptive Methods for Women at High Risk for HIV and Living with HIV 2014 Guidance Statement. World Health Organization; Geneva: 2014.

[22]. Hughes MD, Stein DS, Gundacker HM, Valentine FT, Phair JP, Volberding PA. Within-subject variation in CD4 lymphocyte count in asymptomatic human immunodeficiency virus infection: implications for patient monitoring. J Infect Dis. 1994; 169(1):28–36. [PubMed: 7903975]

Table 1

Characteristics of women with prevalent HIV infection not using ART at enrollment, by contraceptive method selected.

	COCs (*N*=183)	DMPA (*N*=87)	Nonhormonal[a] (*N*=156)
Enrollment CD4 count (cells/mm^3): median, IQR[b]	545, 342–753	606, 379–807	456, 319–599
Enrollment $\log_{10}$ HIV RNA: median, IQR[b]	3, 2–4	3, −1 −3	4, 3–4
Previously used ART[c]	76 (41.5)	58 (66.7)	41 (26.3)
Use of ART within the past month[c,d]	51 (27.9)	43 (49.4)	11 (7.0)
Time since HIV diagnosis[c]			
<1 year	74 (40.4)	33 (37.9)	40 (25.6)
1–2 years	28 (15.3)	16 (18.4)	28 (18.0)
>2 years	81 (44.3)	38 (43.7)	88 (56.4)
Age (years)			
16–24	67 (36.6)	33 (37.9)	50 (32.1)
25–29	84 (45.9)	30 (34.5)	68 (43.6)
30–45	32 (17.5)	24 (27.6)	38 (24.4)
Married or nonmarital union	149 (81.4)	71 (81.6)	131 (84.0)
Previous abortion[c]			
Yes	105 (57.4)	55 (63.2)	98 (62.8)
No	51 (27.9)	31 (35.6)	45 (28.9)
Never pregnant	27 (14.8)	1 (1.2)	13 (8.3)
Previous live births [c]			
0	53 (29.0)	4 (4.6)	40 (25.6)
1	102 (55.7)	50 (57.5)	91 (58.3)
≥2	28 (15.3)	33 (37.9)	25 (16.0)
Postpartum (≤6 weeks)[c]	85 (46.5)	54 (62.1)	36 (23.1)
Prior hormonal contraception use[c]	73 (39.9)	33 (37.9)	32 (20.5)
Frequency of condom use[c]			
Always	61 (33.3)	15 (17.2)	81 (51.9)
Rarely/sometimes/almost always	99 (54.1)	57 (65.5)	70 (44.9)
Never	23 (12.6)	15 (17.2)	5 (3.2)
Multiple partners in previous year	18 (9.8)	9 (10.3)	16 (10.3)
Positive STD test at enrollment[c,e]	12 (6.6)	11 (12.6)	5 (3.2)
Use of intravenous drugs in the past 3 months[c]	6 (3.3)	15 (17.2)	5 (4.1)

Data are shown as number (percentage) unless otherwise indicated.

ART, antiretroviral therapy; IQR, interquartile range.

[a] Includes participants choosing the copper IUD (*n*=33) and condoms (*n*=123).

[b] p<.05, Wilcoxon rank sum test.

[c] p<.05, chi-squared test.

[d] Data on timing of ART use missing for *n*=17 (COC), *n*=12 (DMPA) and *n*=17 (nonhormonal).

[e] Chlamydia or gonorrhea.

Table 2

Association between contraceptive method use and measures of HIV disease progression among women with prevalent HIV infection not using ART at enrollment.

	Time to CD4 count decline to <350 cells/mm^3, ART initiation or death[a]				Time to CD4 count decline ≥20% or death[b]			
	Events	Person-months at risk	HR[c]	95% CI	Events	Person-months at risk	HR[c]	95% CI
Current contraceptive method (time-varying)[d]								
COCs	31	2194	0.91	0.56–1.48	85	2219	0.85	0.61–1.18
DMPA	17	882	1.28	0.71–2.31	45	782	1.14	0.77–1.71
Nonhormonal	49	2247	1.00	Ref	73	2131	1.00	Ref
Contraceptive method at enrollment								
COCs	32	2246	0.91	0.56–1.47	79	2265	0.82	0.58–1.16
DMPA	20	1106	1.27	0.71–2.26	53	881	1.23	0.82–1.85
Nonhormonal	45	1996	1.00	Ref	64	2032	1.00	Ref

ART, antiretroviral therapy; HR, hazard ratio.

[a] Time to first occurrence of CD4 count decline to <350 cells/mm^3, ART initiation or death among participants with enrollment CD4 counts ≥350 cells/ mm^3 and ≥1 follow-up CD4 measurement (n=315).

[b] Time to first occurrence of CD4 count decline to ≥20% of enrollment CD4 count or death among all participants with ≥1 follow-up CD4 measurement (n=426).

[c] Adjusted for CD4 count at enrollment, postpartum status, prior hormonal contraceptive use and age.

[d] If a method switch occurred between two CD4 measurements, the previous method was censored at the date of the last CD4 measurement before the switch.

Table 3

Characteristics of women with prevalent HIV infection using ART at enrollment, by contraceptive method selected.

	COCs (*N*=24)	DMPA (*N*=17)	Nonhormonal[a] (*N*=36)
Enrollment CD4 count (cells/mm^3): median, IQR	305, 213–420	430, 319–493	351, 252–449
Viral suppression at enrollment (HIV RNA ≤150 copies per milliliter)	23 (95.8)	12 (70.6)	29 (80.6)
HAART regimen	22 (91.7)	15 (88.2)	32 (88.9)
Months on ART[b]			
3–6 months	8 (33.3)	11 (64.7)	7 (19.4)
7–12 months	6 (25.0)	3 (17.7)	10 (27.8)
>12 months	10 (41.7)	3 (17.7)	19 (52.8)
Time since HIV diagnosis			
<1 year	3 (12.5)	1 (5.9)	2 (5.6)
1–2 years	4 (16.7)	1 (5.9)	7 (19.4)
>2 years	17 (70.8)	15 (88.2)	27 (75.0)
Age (years)			
16–24	9 (37.5)	5 (29.4)	3 (8.3)
25–29	9 (37.5)	7 (41.2)	18 (50.0)
30–45	6 (25.0)	5 (29.4)	15 (41.7)
Married or nonmarital union	20 (83.3)	14 (82.4)	30 (83.3)
Previous abortion			
Yes	13 (54.2)	12 (70.6)	27 (75.0)
No	7 (29.2)	5 (29.4)	6 (16.7)
Never pregnant	4 (16.7)	0 (0.0)	3 (8.3)
Previous live births			
0	10 (41.7)	1 (5.9)	9 (25.0)
1	12 (50.0)	11 (64.7)	21 (58.3)
>2	2 (8.3)	5 (29.4)	6 (16.7)
Postpartum (≤6 weeks)	5 (20.8)	8 (47.1)	8 (22.2)
Prior hormonal contraception use	11 (45.8)	3 (17.7)	8 (22.2)
Frequency of condom use[c]			
Always	6 (25.0)	6 (35.3)	22 (61.1)
Rarely/sometimes/almost always	16 (66.7)	7 (41.2)	14 (38.9)
Never	2 (8.3)	4 (23.5)	0 (0.0)
Multiple partners in previous year	3 (12.5)	0 (0.0)	3 (8.3)
Positive STD test at enrollment[d]	2 (8.3)	1 (5.9)	0 (0.0)
Use of intravenous drugs in the past 3 months[c]	1 (4.2)	2 (11.8)	0 (0.0)

Data are shown as number (percentage) unless otherwise indicated.

Statistical tests of significant differences were based on Kruskal–Wallis test, chi-squared test or Fisher's Exact Test, as appropriate. ART, antiretroviral therapy; IQR, interquartile range.

[a] Includes participants choosing the copper IUD (*n*=9) and condoms (*n*=27).

[b] p<.05, chi-squared test.

[c] p<.05, Fisher's Exact Test.

[d] Chlamydia or gonorrhea.

Table 4

Predicted mean change in CD4 cell count at 6, 12 and 18 months among women with prevalent HIV infection using ART at enrollment, by contraceptive method.

	Predicted mean change in CD4 cell count, cells/mm^3 (95% CI)[a]			p Value (vs. nonhormonal)
	6 months	12 months	18 months	
Current contraceptive method (time-varying)				
COCs	83.2 (23.0–143.4)	106.0 (47.8–164.2)	128.8 (68.9–188.7)	0.1
DMPA	83.8 (8.5–159.2)	106.6 (33.5–179.8)	129.4 (55.7–203.2)	0.3
Nonhormonal	45.9 (−10.3 to 102.0)	68.7 (14.0–123.3)	91.4 (34.5–148.4)	
Contraceptive method at enrollment				
COCs	52.7 (−12.2 to 117.6)	85.4 (24.2–146.7)	118.2 (56.9–179.6)	0.7
DMPA	80.3 (4.7–155.9)	113.1 (41.5–184.7)	145.8 (75.0–216.6)	0.3
Nonhormonal	39.9 (−15.8 to 95.7)	72.7 (20.1–125.4)	105.5 (51.6–159.3)	

ART, antiretroviral therapy.

[a] Adjusted for CD4 cell count at enrollment, duration of ART use at enrollment (months), HAART regimen (yes/no) and time under observation in the study.