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Hormonal contraceptive use and risk of HIV-1 disease progression

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Abstract

Background—For HIV-1 infected women, hormonal contraception prevents unintended pregnancy, excess maternal morbidity, and vertical HIV-1 transmission. Hormonal contraceptives are widely used but their effects on HIV-1 disease progression are unclear.

Methods—In a prospective study among 2269 chronically HIV-1 infected women from 7 countries in East and southern Africa and with enrollment CD4 counts ≥250 cells/mm^3, we compared rates of HIV-1 disease progression among those using and not using hormonal contraception (i.e. oral or injectable methods). The primary outcome was a composite endpoint of CD4 decline to <200 cells/mm^3, initiation of antiretroviral therapy, or death.

Results—372 women experienced HIV-1 disease progression during 3242 years of follow up (incidence rate=11.5 events per 100 person-years). Rates of HIV-1 disease progression among women who were currently using and not using hormonal contraception were 8.54 and 12.31 per 100 person-years, respectively (adjusted hazard ratio [HR] 0.74, 95% CI 0.56–0.98, p=0.04). Rates were 8.58 and 8.39 per 100 person-years for the subsets using injectable and oral contraception (adjusted HR=0.72, p=0.04 for injectable users and adjusted HR=0.83, p=0.5 for oral users compared to women not using hormonal contraception). Sensitivity analyses assessing

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Conflicts of interest:
None.

enrollment or cumulative contraceptive use during the study demonstrated risk estimates closer to 1.0 with no evidence for accelerated disease progression.

Conclusions—Among African women with chronic HIV-1 infection, use of hormonal contraception was not associated with deleterious consequences for HIV-1 disease progression.

Keywords

HIV-1; women; hormonal contraception; death; CD4 count; antiretroviral therapy

Introduction

For HIV-1 infected women, effective and safe contraception is important to reduce unintended pregnancy and thus avoid excess maternal morbidity and risk of vertical HIV-1 transmission. It has been hypothesized that hormonal contraceptives could accelerate HIV-1 disease progression by increasing viral diversity, viral replication, or the set point viral load.[1–3] In secondary data analysis of a clinical trial evaluating the safety of different contraceptive methods among HIV-1 infected Zambian women, women using hormonal methods (either injectable depot medroxyprogesterone acetate [DMPA] or oral contraceptive pills [OCP]) had accelerated HIV-1 disease progression relative to women using an intrauterine device (IUD).[4] However, several observational studies have not consistently demonstrated increased risk for faster HIV-1 disease progression with hormonal methods.[3, 5–8]

Understanding the scope of risks and benefits associated with different contraceptive methods is critical to counseling messages for women with HIV-1 and for development of public health policies. At a recent WHO technical consultation on hormonal contraceptives and HIV-1 risk, experts recommended that no restrictions be placed on the use of hormonal contraceptives by HIV-1 infected women. However, the body of evidence for hormonal contraceptives and HIV-1 disease progression was determined to have data limitations and further research was recommended.[9] We assessed the relationship between hormonal contraceptive use and HIV-1 disease progression in a large and geographically diverse cohort of chronically HIV-1 infected African women prior to their initiation of antiretroviral therapy (ART).

Methods

Population and procedures

From 2004–2008, we conducted the Partners in Prevention HSV/HIV Transmission Study, a randomized, placebo-controlled, clinical trial of daily acyclovir herpes simplex virus type 2 (HSV-2) suppressive therapy among 3408 HIV-1/HSV-2 dually-infected persons (2317 women, 1091 men) from seven countries in East and southern Africa as an intervention to reduce HIV-1 transmission to their heterosexual HIV-1 uninfected partners (Clinicaltrials.gov number NCT00194519). Acyclovir did not significantly reduce HIV-1 transmission in the study but it did reduce plasma HIV-1 concentrations (by 0.25 $\log_{10}$ copies/mL on average) and modestly slowed HIV-1 disease progression (adjusted hazard ratio [HR] 0.84, p=0.03 for a composite endpoint of death, ART initiation, or CD4 decline to <200 cells/mm^3).[10, 11] The present study is a secondary analysis of the clinical trial dataset, limited to female partners who were HIV-1 infected at enrollment.

Participants were ≥18 years of age and sexually active. At the time of study enrollment, HIV-1 infected participants had no history of AIDS-defining conditions, were not using ART, and had a CD4 count ≥250 cells/mm^3 (i.e., all were ineligible for ART under the

national guidelines in place at the time of the study). Follow-up in the study was for up to 24 months and HIV-1 infected participants were seen monthly. CD4 counts were measured every six months. Participants who became eligible for ART initiation based on national ART guidelines as a result of CD4 decline or clinical symptoms were referred to local HIV-1 care clinics.

All participants received comprehensive HIV-1 prevention services, including individual and couples risk reduction counseling, free condoms, and treatment of sexually transmitted infections (STIs). The study protocol was approved by institutional review boards at the University of Washington and collaborating institutions at each study site. Participants provided written informed consent.

Laboratory testing

Rapid HIV-1 antibody tests were used for HIV-1 serologic testing and positive results were confirmed by HIV-1 ELISA and Western blot.[10] Nucleic acid amplification testing for bacterial STIs and serologic testing for HSV-2 using HSV-specific Western blot was performed on samples collected at study enrollment.[12, 13] Plasma HIV-1 RNA levels were quantified from samples collected at study enrollment using the COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN) with 240 copies/mL being the lower limit of quantification.

Measurement of hormonal contraceptive exposure

At all monthly visits, women were asked about their current contraceptive method using a standardized questionnaire. Hormonal contraceptive use was defined as use of an oral or injectable method. Contraceptive use was by self-report and other analyses from this study have demonstrated that self-reported use of oral and injectable contraceptive methods was associated with statistically significant reductions in pregnancy incidence.[14] Hormonal contraceptive use was analyzed as a time-dependent exposure and we assumed that women used the same method for the entire month that elapsed between study visits. Analyses were conducted for exposure to any hormonal contraception and then separately for injectable and oral methods. The comparison group was women not using hormonal contraception, which included women who had undergone a hysterectomy or tubal ligation, women who reported only using condoms for birth control, and women not using any contraceptive method. Due to small numbers, follow-up time when women reported use of implantable methods or an IUD was excluded (<2% of study visits). Data on condom use for HIV/STI prevention were captured separately and used in our assessment of potential confounders.

Outcome

The primary study outcome was a composite measure of HIV-1 disease progression, defined as the first occurrence of 1) initiation of a combination ART regimen (i.e., excluding single- or dual-antiretroviral use for prevention of mother-to-child transmission of HIV-1), 2) CD4 count decline to <200 cells/mm^3, or 3) death not due to trauma. Follow-up time was censored after the first occurrence of any event that was part of the composite measure. In secondary analyses, we examined each component of the primary outcome separately and censored women's observations after the first occurrence of each component. In an additional secondary analysis, we examined time to CD4 count decline to <350 cells/mm^3 (the current WHO guideline for ART initiation) among women whose enrollment CD4 level was at least 350 cells/mm^3.

Statistical analysis

We used time-dependent Cox proportional hazards regression with robust standard errors and the Efron method for handling ties to determine the effect of contraceptive method on HIV-1 disease progression among women with chronic HIV-1 infection.[15] Models were stratified by study site to account for national differences in ART initiation guidelines and included treatment arm (acyclovir versus placebo) – because acyclovir reduced the risk of HIV-1 disease progression in the study population.[11] Acyclovir may alternatively modify the effect of hormonal contraception on HIV-1 disease progression and we tested for this possibility by including an interaction term between hormonal contraception and treatment arm in our adjusted primary model. In the relationship between hormonal contraception and HIV-1 disease progression, pregnancy could act potentially as a confounder or as a mediating factor (e.g. following cessation/non-use of hormonal contraception and responsible for CD4 count decline due to hemodilution).[16] We maintained pregnancy in our multivariate models because we wanted to determine the effect of hormonal contraceptive use on HIV-1 disease progression above and beyond the role of pregnancy and reduce the possibility of bias. In addition, we assessed confounding by variables known to be associated with HIV-1 disease progression and/or hormonal contraception as well as demographic characteristics: enrollment CD4 count, enrollment HIV-1 plasma viral load, enrollment WHO stage, condom use, sex with partners other than the study partner, age, education level, having an income and marital status. Of these potential confounders, age and enrollment CD4 count changed the risk estimate for the association between contraception and HIV-1 disease progression by ≥10% and thus these covariates were also included in the final multivariate model, along with study site, treatment arm, and pregnancy.

To explore the possibility that HIV-1 disease progression affects contraceptive use (a case of reverse causality), we conducted a number of sensitivity analyses using different definitions of hormonal contraceptive use exposure. First, we considered a woman's contraceptive use during her visit six months prior to the current visit as the exposure to account for the potentially persistent effect of hormonal contraceptives.[17–19] Then we considered a woman's contraceptive use at enrollment as her exposure status for her entire study follow-up to account for her potential exposure prior to study enrollment. In a third sensitivity analysis, we defined contraceptive use for each observation based on whether the woman had never used, sometimes used or always used any hormonal contraception up until that visit. All analyses were conducted using SAS 9.2 (Cary, NC).

Results

Population

Data from 2269 chronically HIV-1 infected women who contributed 3242 person-years of follow up were included in the primary analysis. The median follow up time was 1.7 (interquartile range [IQR] 1.3–2.0) years per woman. On average, women were 30 years old with 8 years of education and 2 children (Table 1). At enrollment, the median CD4 count was 483 (IQR 355–663) cells/mm^3 and HIV-1 RNA was 3.9 (IQR 3.2–4.5) $\log_{10}$ copies/mL. Most women (80.1%) were not using hormonal contraception at the time of study entry; 4.2% were using oral contraception and 14.5% were using injectable contraception. Women were exposed to injectable and oral contraceptive use during 33.7% and 10.8% of follow up periods, respectively. During one or more follow-up visits, 31.7% of women reported using injectable contraceptives, 12.1% of women reported using oral contraceptives. 810 (35.7%) women changed their contraceptive method at least once during the study and 478 (21.2%) women experienced a pregnancy.

Occurrence of disease progression events

During follow-up, 372 women experienced an HIV-1 disease progression event (initiation of ART, a CD4 count decline to <200 cells/mm^3, or non-trauma death). There were 500 total events experienced: 35 women experienced death as their only event, 73 women initiated ART as their only event, 139 women experienced a CD4 count <200 cells/mm^3 as their sole event, 2 women initiated ART and died, 4 women experienced a CD4 count <200 cells/mm^3 and died, 116 women experienced a CD4 count <200 cells/mm^3 and initiated ART, and 3 women experienced all three indicators.

Hormonal contraceptive use and HIV-1 disease progression

Rates of disease progression were lower among women using hormonal contraception than women not using hormonal contraception (Table 2, 8.54 vs. 12.31 per 100 person-years, adjusted HR 0.74, 95% CI 0.56–0.98, p=0.04). Among injectable contraceptive users, the rate was 8.58 per 100 person-years and significantly lower than non-contracepting women (p=0.04). Among oral contraceptive users, the rate was 8.39 per 100 person-years but few women used this method and the difference was not statistically different than the rate among women not using hormonal contraception (p=0.5). The hazard ratio was similar among women who were randomized to the acyclovir and placebo groups (interaction p-value=0.61; adjusted HR for any hormonal contraception and disease progression in the acyclovir arm = 0.79, 95% CI 0.52–1.21; in the placebo arm = 0.72, 95% CI 0.49–1.06). The hazard ratio was also similar in a model that excluded pregnancy (adjusted HR = 0.72, 95% CI 0.54–0.96).

When we looked at each indicator of disease progression separately, hormonal contraception was not significantly associated with any single event (adjusted HR for progression to CD4 count <200 cells/mm^3=0.87, p=0.4; adjusted HR for ART initiation=1.03, p=0.9; and adjusted HR for death=0.45, p=0.1). Among women whose CD4 count was ≥350 cells/mm^3 at enrollment, hormonal contraceptive users were less likely to have their CD4 count decline to <350 cells/mm^3 during follow up (adjusted HR 0.78, p=0.03).

When we defined the exposure based on hormonal contraceptive use 6 months prior to each visit (as opposed to current use, as in the primary analysis), and hormonal contraceptive use at enrollment, there was no evidence of a harmful effect of hormonal contraception of HIV-1 disease progression (Table 2). Women who sometimes or always used hormonal contraception experienced similar rates of HIV-1 disease progression to women who never used hormonal contraception during the study.

Discussion

In a large prospective study of over 2200 women with chronic HIV-1 infection from diverse African settings, we found that hormonal contraceptive use does not accelerate disease progression and may be associated with slower progression. When we looked at each component of our composite disease progression measure separately and in sensitivity analyses, the moderately protective effect of hormonal contraception was attenuated yet none of these analyses suggested any acceleration in HIV-1 disease progression rates among hormonal contraceptive users.

Our finding of no increased risk for HIV-1 disease progression is consistent with recent observational analyses among HIV-1 infected women.[5–8] Only one study, a randomized trial of hormonal contraceptives versus IUDs among chronically HIV-1 infected postpartum Zambian women, demonstrated increased risk of progression to AIDS, ART initiation or death among women using oral or injectable contraceptives. While randomized trials are less likely to suffer from selection bias and confounding that can affect the results from

observational data, this particular trial suffered from a high prevalence of contraceptive switching and loss to follow-up, which may have biased the results. Previous studies have suggested that injectable contraception increases set point viral load,[20] but our results suggest these changes do not appear to translate into long-term effects on measures of clinical HIV-1 disease. Hormonal contraception effectively prevents pregnancy; pregnancy and postpartum periods are often periods of CD4 count decline among HIV-1 infected women.[21, 22] Thus, by preventing pregnancy, hormonal contraceptives may act to reduce HIV-1 disease progression. The moderate risk reduction that we observed in our primary analysis, however, was not robust in sensitivity analyses and may be due confounding by clinical or behavioral characteristics that were not fully accounted for by statistical adjustment.

We recently reported in another analysis from this cohort that injectable contraceptives may be an independent risk factor for HIV-1 transmission from HIV-1 infected women to their male partners.[23] In that report, injectable contraceptive users had increased genital HIV-1 RNA levels but not plasma HIV-1 RNA levels, suggesting that injectable contraceptives may act to increase HIV-1 infectiousness through direct effects on genital mucosal HIV-1 replication. Importantly, the present results suggest that HIV-1 infected women can use hormonal contraception without concern for advancing their own HIV-1 disease. Women should be counseled about the importance of combining hormonal contraception with effective HIV-1 prevention interventions, such as condom use, initiating ART [24], and pre-exposure prophylaxis use by their partners.[25, 26]

The main limitation of our study is that we used data from HIV-1 chronically infected women and are not able to quantify the amount of time since their HIV-1 infection or their contraceptive use between the time of their HIV-1 infection and enrollment into our study. Our study is also limited by its observational nature and self-reported data on contraceptive method. Women who choose to use hormonal contraception may have different lifestyles from women who do not and these differences could effect HIV-1 disease progression. We did not collect longitudinal data on alcohol use or other lifestyle factors that could mask an effect of hormonal contraception on HIV-1 disease progression. In addition, we did not collect data on contraceptive adherence nor the specific brand of hormonal contraception used. However, low-dose combination oral contraceptives and long-acting injectable depot medroxyprogesterone acetate were the most commonly used methods in the national family planning programs where the study was conducted. We chose a composite measure of HIV-1 disease progression that incorporates ART initiation, a CD4 count <200 cells/mm^3 and death from causes other than trauma as our main outcome measure. These factors, however, may not always reflect HIV-1 disease progression – for example, we did not assess whether deaths were due to HIV-1-related causes.

Our objective for conducting this study was to determine whether or not hormonal contraception might have deleterious health consequences for HIV-1 infected women; we conclude that there is no detrimental effect on HIV-1 disease progression. Multiple studies have now concluded that hormonal contraceptive use is not associated with accelerated HIV-1 disease progression. Access to effective contraception is an imperative for HIV-1 infected women who do not immediately desire children. HIV-1 infected women should be reassured that using hormonal contraception does not have consequences for their HIV-1 disease progression. More emphasis is needed on the integration of HIV-1 care and family planning programs to improve safe and effective contraceptive uptake and its sustained use among HIV-1 infected women.

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Table 1

Characteristics of HIV-1 infected women by enrollment contraceptive use*

	Injectable contraceptive users Median (IQR) or N (%)	Oral contraceptive users Median (IQR) or N (%)	Non hormonal contraceptive users Median (IQR) or N (%)
Number of women	324	95	1817
Age, years	29.6 (25.0 – 33.3)	29.0 (25.3 – 32.6)	30.0 (25.3 – 35.5)
Education, years	8.0 (7.0 – 11.0)	8.0 (6.0 – 10.0)	8.0 (6.0 – 10.0)
Married to study partner	205 (63.3)	74 (77.9)	1350 (74.3)
Partnership duration, years	4.8 (2.3 – 8.5)	5.0 (2.2 – 8.2)	4.8 (2.0 – 9.4)
Number of children	2.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)
Number of children with study partner	1.0 (0.0 – 2.0)	1.0 (1.0 – 2.0)	1.0 (0.0 – 2.0)
Any unprotected sex with study partner, last month	108 (33.3)	43 (45.3)	487 (26.8)
Ever pregnant during follow up	47 (14.5)	24 (25.3)	407 (22.4)
Bacterial STI at enrollment	63 (21.1)	20 (23.5)	328 (19.6)
CD4 count at enrollment (cells/mm^3)	492 (348 – 644)	478 (351 – 610)	479 (356 – 668)
HIV-1 RNA at enrollment (log_{10} copies/μL)	4.0 (3.2 – 4.5)	3.9 (3.4 – 4.6)	4.0 (3.2 – 4.5)

* Data from 14 IUD users and 19 implant users are not shown.

Table 2

Association of hormonal contraception and HIV-1 disease progression among chronically HIV-1 infected women

			Univariate		Multivariate**	
	# events / person-years	Incidence rate*	HR (95% CI)	p-value	HR (95% CI)	p-value
Current contraception (primary analysis)						
All women	372/3242	11.48				
No hormonal contraception	311/2527	12.31	REFERENCE		REFERENCE	
Any hormonal contraception ***	61/715	8.54	0.67 (0.51 – 0.88)	0.004	0.74 (0.56 – 0.98)	0.04
Injectable contraception	48/560	8.58	0.67 (0.50 – 0.90)	0.009	0.72 (0.53 – 0.98)	0.04
Oral contraception	13/155	8.39	0.66 (0.38 – 1.14)	0.140	0.83 (0.48 – 1.44)	0.5
Contraception 6 months ago						
All women	346/2268	15.26				
No hormonal contraception	282/1795	15.71	REFERENCE		REFERENCE	
Any hormonal contraception	64/473	13.54	0.88 (0.67 – 1.16)	0.4	0.92 (0.69 – 1.22)	0.6
Injectable contraception	46/368	12.51	0.81 (0.59 – 1.11)	0.2	0.81 (0.58 – 1.14)	0.2
Oral contraception	18/105	17.13	1.15 (0.71 – 1.86)	0.6	1.33 (0.82 – 2.14)	0.2
Contraception at enrollment						
All women	372/3258	11.42				
No hormonal contraception	302/2667	11.32	REFERENCE		REFERENCE	
Any hormonal contraception	70/592	11.83	1.04 (0.80 – 1.36)	0.7	0.97 (0.74 – 1.27)	0.8
Injectable contraception	51/464	11.00	0.96 (0.71 – 1.29)	0.8	0.85 (0.62 – 1.16)	0.3
Oral contraception	19/128	14.84	1.38 (0.85 – 2.24)	0.2	1.56 (0.98 – 2.50)	0.06
Cumulative contraception exposure since enrollment						
All women	342/3298	10.37				
Never on	231/2152	10.73	REFERENCE		REFERENCE	
Sometimes on	91/833	10.93	0.90 (0.70 – 1.15)	0.4	0.95 (0.74 – 1.22)	0.7

			Univariate		Multivariate**	
	# events / person-years	Incidence rate*	HR (95% CI)	p-value	HR (95% CI)	p-value
Always on	20/313	6.38	0.68 (0.43 – 1.07)	0.1	0.62 (0.38 – 1.02)	0.06

*per 100 person-years of the first occurrence of CD4 count decline to <200 cells/mm^3, ART initiation or non-trauma death

**Adjusted for study site, trial arm, age, enrollment CD4 count, and pregnancy.

***In the primary multivariate model for use of any hormonal contraceptive method and HIV-1 disease progression, women with an enrollment CD4 count <500 cells/mm^3 were more likely to experience disease progression (adjusted HR 11.38, 95% CI 8.07–16.03 for CD4 count 200–349 and 3.32, 95% CI 2.31–4.79 for CD4 count 350–499) compared with those with an enrollment CD4 count ≥500 cells/mm^3. Disease progression risk was also increased for women with an enrollment HIV-1 plasma viral load >50,000 copies/mL compared with those with lower viral loads (adjusted HR 2.22, 95% CI 1.49–3.30) and women with a WHO stage of 3 or 4 (compared with 1 or 2) during follow-up (adjusted HR 1.80, 95% CI 1.21–2.69). Disease progression was moderately accelerated during pregnant periods (adjusted HR 1.45, 95% CI 1.03–2.04). Treatment arm and age were not independently associated with disease progression (HR 0.89, p=0.29 for receiving acyclovir, HR 1.11, p=0.51 for women ages 25–34 and HR 1.05, p=0.77 for women ages ≥35).