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HIV shedding in the female genital tract of women on ART and progestin contraception: Extended follow-up results of a randomized clinical trial

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Abstract

Background: Progestin contraception has been linked to higher risk of female to male sexual HIV transmission.

Setting: A clinical trial among HIV-infected women in Lilongwe, Malawi, randomized to initiation of depomedroxyprogesterone acetate (DMPA) injectable or levonorgestrel (LNG) implant, and followed for up to 33 months, with the outcome of HIV shedding in the genital tract.

Methods: We compared the frequency and magnitude of HIV genital shedding before and after initiation of contraception and between study arms among women receiving antiretroviral therapy (ART). Genital HIV RNA was measured in TearFlo Strips using the Abbott RealTime HIV-1 assay.

Results: Among 68 HIV-infected Malawian women on ART, randomization to DMPA compared with the LNG implant was not associated with genital shedding, and neither progestin contraceptive was associated with increased HIV genital shedding, for up to 33 months after contraceptive initiation. Having detectable plasma HIV (adjusted RR 10.5; 95% CI 3.18–34.7) and detectable genital shedding prior to contraceptive initiation (adjusted RR 3.53; 95% CI 1.31–9.47) were associated with a higher risk of detectable genital shedding after contraceptive initiation. Higher plasma efavirenz concentrations were associated with a lower risk of detectable genital shedding (adjusted RR 0.85; 95% CI 0.73–0.99, per increase of 1,000 ng/ml).

Conclusion: Among HIV-infected women receiving ART, our results provide evidence that progestin contraception does not impact women's risk of transmission of HIV to partners. Our finding that detectable genital shedding prior to contraceptive initiation independently predicts

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shedding suggests that there may be other individual level biological or behavioral factors that increase the risk for shedding.

Summary: Among 68 HIV-infected Malawian women on ART, randomization to DMPA compared with the LNG implant was not associated with genital shedding, and neither progestin contraceptive was associated with increased HIV genital shedding, for up to 33 months after, compared to before,contraceptive initiation. Having detectable plasma HIV (adjusted RR 10.5; 95% CI 3.18–34.7) and detectable genital shedding prior to contraceptive initiation (adjusted RR 3.53; 95% CI 1.31–9.47) were associated with a higher risk of detectable genital shedding after contraceptive initiation, and higher plasma efavirenz concentrations were associated with a lower risk of detectable genital shedding (adjusted RR 0.85; 95% CI 0.73–0.99, per increase of 1,000 ng/ml).

Keywords

genital shedding; HIV; women; ART; Depo-medroxyprogesterone acetate; Levonorgestrel implant

Shedding of Human Immunodeficiency Virus type-1 (HIV) in the genital tract can lead to sexual transmission of HIV to partners; studies have confirmed an association of plasma and genital tract HIV load with risk of transmission[1,2]. Factors that increase genital HIV shedding, such as other concurrent genital infections, have been associated with increased risk of transmission in several studies[3, 4]. Suppression of viral replication with effective antiretroviral therapy (ART) decreases systemic HIV load, as well as genital tract HIV shedding[5]. It has also been found that, among women with undetectable plasma HIV, efavirenz-based ART regimens were associated with lower odds of genital HIV shedding compared to PI-based or other regimens[5]. Effective penetration of ART into the genital tract may counteract other factors associated with increased genital HIV shedding, but it also may be affected by factors such as the composition of the genital microbiome, menstrual phase, or hormonal contraception. Hormonal contraceptives, particularly depot medroxyprogesterone acetate (DMPA), have been linked with increased risk of HIV acquisition in uninfected women or transmission to sexual partners[6]. We recently performed a randomized clinical trial among 68 HIV-infected Malawian women on ART initiating hormonal contraception, to assess its effects on HIV shedding in the genital tract[7]; women were randomly assigned to either DMPA (N=33) or the levonorgestrel (LNG) implant (N=35) between May 2014-April 2015. We compared the frequency and magnitude of HIV genital shedding before and for 6 months following initiation of contraception and between study arms among women receiving ART. Our results showed that neither DMPA nor the LNG implant was associated with increased genital HIV shedding in HIV-infected women receiving ART[8]. Overall, there was little HIV detected in genital secretions when the plasma viral load (VL) was undetectable (<4% of such visits), regardless of contraceptive use[8].

Here we report results of extended follow-up of these women for up to 33 months after initiation of contraception. A study extension was added in October 2015 after most participants had completed their 6-month follow-up and exited the initial phase of the study. Fifty-nine of the 68 women were consented to enroll in the study extension and completed additional follow-up visits every 3 months until April 2017. Women contributed to the follow-up visits according to the time that had elapsed since their initiation of their

contraceptive method. However, there were no differences in baseline characteristics by participation in the study extension or by number of months participating in the study. After the initial 6 months of follow-up, women had genital HIV RNA testing performed at months 12, 18, 24, 27, 30, and 33 after contraceptive initiation, although not all women were able to complete all study visits within the study time period. Genital HIV RNA was measured in TearFlo Strips (TFS) via methods previously described[8]. Briefly, TFS were collected from each woman by using a ring forceps to hold two strips in the cervical os for approximately 1 minute and then transferring them to a cryovial for frozen storage. Collection was rescheduled if the woman had any vaginal bleeding at the time of the study visit. HIV-1 RNA levels were measured in TFS eluates using the Abbott RealTime HIV-1 assay (Abbott Laboratories, Abbott Park, IL, USA): TFS samples were eluted in 0.9 ml Abbott DBS Elution Buffer prior to the assay; the limit of quantitation was 40 copies/ml without dilution. HIV RNA viral loads were not adjusted for elution volume and so were considered copies/ml of eluates, as previously described[8].

Efavirenz was quantified in plasma and Weck-Cel sponges using validated HPLC-MS/MS methods. Cervicovaginal fluid (CVF) was eluted from 2 sponges using 1ml of 70:30 methanol:water. Following protein precipitation efavirenz was extracted from plasma and eluted in CVF with internal standard, efavirenz-d5, using reverse-phase chromatography on a Waters Atlantis T3 (50 × 2.1mm, 3μm) column. Standards and quality controls were prepared in blank human plasma (50–20,000ng/ml) or 70:30 methanol:water (0.2–500ng/ml) for plasma and eluted CVF, respectively with ±15% (20% at the lower limit of quantification) acceptance criteria.

Percent detectable (≥200 copies/ml) genital HIV RNA was compared between study arms at each study visit. We also compared efavirenz concentrations in the plasma and Weck-Cel between women with detectable vs undetectable genital HIV RNA using the Wilcoxon rank-sum test. Associations of detectable genital tract HIV RNA with initiation of contraception and with possible risk factors were evaluated using a multivariable log-binomial model with repeated measurements fit with generalized estimating equations. The study was approved by the University of North Carolina Institutional Review Board (IRB), the Malawi National Health Sciences Research Committee, the Malawi Pharmacy Medicines and Poisons Board and an IRB of the U.S. Centers for Disease Control and Prevention.

Baseline study characteristics of the women who participated in the study extension are given in Table 1. Consistent with our earlier results, extended follow-up of the women up until 33 months after contraceptive initiation demonstrated infrequent detection of HIV RNA in the TFS cervical specimens in both study arms (<15% detectable shedding found at all study visits, Table 2). The median genital HIV RNA for follow-up visits with detectable genital HIV RNA was 2,441 copies/ml (range = 276 – 13,317 copies/ml). Detection of genital HIV RNA was even less frequent when restricted to study visits with undetectable plasma HIV RNA (<4% at all study visits). The median efavirenz concentration for all study visits was 2,925 ng/ml in the plasma and 79 ng/ml in the Weck-Cel for women with detectable genital HIV RNA, compared with 3,150 ng/ml in the plasma and 105 ng/ml in the Weck-Cel for women with undetectable genital HIV RNA (p=0.03 in the plasma; p=0.08 in the Weck-Cel). When adjusted for multiple confounders including study arm, weeks post-

initiation of the contraceptive method, baseline genital HIV RNA, CD4 count, plasma HIV RNA, and plasma efavirenz concentration, detectable plasma HIV RNA at the time of the study visit (adjusted Risk Ratio, aRR, 10.5, 95% CI, 3.18–34.7), and detectable genital HIV RNA at baseline (aRR, 3.53, 95% CI, 1.31–9.47), were the only factors predictive of detection of genital HIV RNA. Conversely, higher plasma efavirenz concentration was associated with lower risk of detection of genital HIV RNA (aRR, 0.85, 95% CI, 0.73–0.99, per increase of 1,000 ng/ml). A significant association with genital HIV RNA was not observed for Weck-Cel efavirenz concentrations. Risk of detectable genital HIV RNA did not change over time after initiation of hormonal contraception (aRR, 0.97, 95% CI, 0.84–1.13, per increase of 6 months of follow-up), and was not significantly different in the DMPA study arm compared to the LNG implant study arm (aRR, 1.92, 95% CI, 0.97–3.79). Detectable genital HIV RNA was not significantly different prior to initiation of hormonal contraception compared with follow-up visits (p=0.47).

The results of our study are limited by a small sample size, particularly for the more extended follow-up visits, given the timeframe of the study. Whereas the small size may limit the generalizability of our results, they are consistent with emerging evidence reported previously by us and others[4,5,8,9] that indicates that genital HIV shedding is infrequent and of low magnitude in women who are on effective ART, regardless of the type of progestin contraception. Our results extend our previous findings and provide evidence that progestin contraception does not meaningfully impact women's risk of transmission of HIV to partners provided they are on effective ART. They stress the importance of ART adherence for optimal protection, as detectable HIV in the plasma was the strongest predictive factor of HIV shedding in the female genital tract, and higher plasma efavirenz concentrations were protective against shedding. Our finding that detectable genital shedding prior to contraceptive initiation independently predicts shedding (even after adjusting for plasma viral load and ART concentrations) suggests that there may be other individual-level biological or behavioral factors that increase the risk for shedding and need to be further explored.

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Table 1

Baseline characteristics for 59 HIV-infected women on antiretroviral therapy enrolled and randomized in the extension phase of the study, Lilongwe, Malawi

	Study Arm	
	DMPA (n=28)	**LNG-Implant (n=31)**
Characteristics at Baseline		
	N (%)	**N (%)**
Detectable genital HIV RNA viral load (≥ 200 copies)	3 (10.7)	5 (16.1)
Detectable plasma HIV RNA viral load (≥ 40 copies)	4 (14.3)	8 (25.8)
Started on antiretroviral therapy > 1 year ago	24 (85.7)	25 (80.7)
Currently taking efavirenz	24 (85.7)	26 (83.9)
	Median (IQR)	**Median (IQR)**
Age (years)	36 (30–39)	34 (29–39)
CD4+ T cell count (cells/μL)	416 (259–499)	308 (207–446)
Plasma EFV concentration (ng/ml)	5050 (2550–10200)	3120 (2280–5190)
Weck-Cel EFV concentration (ng/ml)	159.9 (71.2–288.0)	92.7 (59.2–157.3)

Table 2:

Detectable genital HIV RNA viral load after initiation of progestin contraception by study visit and study arm among 68 women on antiretroviral therapy in Lilongwe, Malawi.

	Study Arm	
	DMPA (n=33)	**LNG-Implant (n=35)**
Study Visit	**# ≥ 200 copies/N (%)**	**# ≥ 200 copies/N (%)**
3 days post initiation of contraceptive method	3/32 (9.4%)	4/33 (12.1%)
1 month post initiation	4/28 (14.3%)	3/34 (8.8%)
3 months post initiation	2/27 (7.4%)	1/32 (3.1%)
6 months post initiation	3/29 (10.3%)	2/33 (6.1%)
12 months post initiation	1/18 (5.6%)	1/14 (7.1%)
18 months post initiation	0/27 (0.0%)	1/28 (3.6%)
24 months post initiation	1/25 (4.0%)	1/28 (3.6%)
27 months post initiation	1/18 (5.6%)	2/20 (10.0%)
30 months post initiation	0/6 (0.0%)	1/12 (8.3%)
33 months post initiation	0/1 (0.0%)	0/3 (0.0%)

DMPA: Depot-medroxyprogesterone acetate; LNG: Levonorgestrel.