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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

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Abstract

Depot medroxyprogesterone acetate (DMPA) use among HIV-1 infected women may increase transmission by increasing plasma and genital HIV-1 RNA shedding. We investigated associations between DMPA use and HIV-1 RNA in plasma and cervical secretions. 102 women initiated ART, contributing 925 follow-up visits over a median of 34 months. Compared to visits with no hormonal contraception exposure, DMPA exposure did not increase detection of plasma (adjusted odds ratio (AOR) 0.81, 95% CI 0.47–1.39) or cervical HIV-1 RNA (AOR 1.41, 95% CI 0.54–3.67). Our results suggest that DMPA is unlikely to increase infectivity in HIV-positive women who are adherent to effective ART.

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SD, RSM, SMG, BAR, WJ, JNK, and KM were involved in the study conception and design. BAR and SD performed the statistical analysis. VC performed and JO oversaw and provided equipment for the laboratory experiments. WJ, JNK, KSM and LNM oversaw the collection of clinical and laboratory data. All authors revised the manuscript and approved the final draft.

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Keywords

hormonal contraception; HIV-1; antiretroviral therapy; DMPA

INTRODUCTION

Ninety percent of the 13 million HIV-1-infected women in sub-Saharan Africa are between 15 and 49 years old.[1] For these women, safe and effective contraception is important for prevention of unintended pregnancy and maternal-to-child HIV-1 transmission.[2] Use of the injectable contraceptive depot medroxyprogesterone acetate (DMPA) is common among women in sub-Saharan Africa, where HIV prevalence is also high.[1,3]

A recent study has suggested that use of injectable contraception by HIV-1-seropositive women may increase their risk for sexual transmission of the virus.[4] Among 2476 HIV-1 serodiscordant couples, use of injectable contraceptives including DMPA was associated with a two-fold increase in the risk of HIV-1 transmission to male partners. Use of injectables was also associated with increased detection of endocervical HIV-1 RNA, an important predictor of transmission risk.[5] All but one study of DMPA as a risk factor for genital HIV shedding have demonstrated significant associations.[6–9] In contrast, most studies do not find a significant association between DMPA use and plasma viral load.[10]

One study demonstrating an association between DMPA and genital HIV-1 shedding has been conducted in women receiving ART.[8] This study found that DMPA use was associated with a slower decline in cervical HIV at month three, but this difference was no longer significant at month six. Other studies finding an association between injectable contraception and HIV-1 shedding have been conducted in ART-naïve populations.[4,6,7] Antiretroviral therapy rapidly reduces plasma and genital HIV-1 levels,[11] lowering the risk of transmission by about 95%.[12] A small proportion of women have persistent genital HIV-1 shedding despite effective ART, which may represent ongoing transmission risk.[11,13–15] We conducted a prospective cohort study designed to test the hypothesis that DMPA would be associated with increased detection of genital HIV-1 RNA in women initiating and continuing ART.

METHODS

HIV-1-seropositive, non-pregnant women in Mombasa, Kenya were invited to participate if they were eligible for ART according to Kenyan National Guidelines at the time of this study (CD4 cell count ≤200 cells/mL or AIDS-defining illness). The standard ART regimen was zidovudine or stavudine, lamivudine, and nevirapine.[16] The first 102 women who initiated ART were included. All participants gave written informed consent. Ethical review committees of the Kenya Medical Research Institute and University of Washington approved the study.

At treatment initiation and monthly thereafter, participants were interviewed using standardized questionnaires including sexual behavior and contraceptive practices. Adherence to ART was monitored by monthly pill count, having participants estimate ART

use with a validated visual analog scale (VAS),[17] and determining late refills (overdue by ≥2 days). At ART initiation and every three months thereafter, women had pelvic examinations for diagnosis of sexually transmitted infections (STIs) and collection of genital specimens.[18] Cervical specimens were collected by inserting a Dacron swab gently into the cervical os and rotating two full turns. If women were menstruating, the examination was rescheduled. At the same visits, blood was collected for CD4 count and HIV-1 quantitation.

Laboratory testing for HIV-1 serostatus, CD4 cell count, and STIs were performed as previously described.[18] Plasma and genital specimens were frozen at −70°C until shipment to Seattle on dry ice for HIV-1 RNA quantitation using the Gen-Probe HIV-1 viral load assay. Detection was defined as ≥400 copies per milliliter in plasma and ≥400 copies per swab in cervical secretions.

Exposure to hormonal contraception was defined as reported use within the past 70 days.[19–21] Hormonal contraception included DMPA, Norplant, and oral contraceptive pills (OCPs). The comparison group was women not using hormonal contraception, which included no contraception, condoms only, hysterectomy or tubal ligation. No women reported use of spermicides, diaphragms, or IUDs during the study. Generalized estimating equation models with a binary link and exchangeable correlation structure were used to compare DMPA with no hormonal contraception and determine the associations between DMPA and detection of cervical and plasma HIV-1 RNA during follow-up visits (excluding baseline visits). Few women reported use of Norplant and OCPs, so analyses of these methods are not presented.

Multivariate models adjusted *a priori* for adherence to ART.[8] Adherence by pill count and VAS estimates was dichotomized at ≥95% versus <95% based on the distribution of data. The adherence measure most associated with detection of HIV-1 RNA was included in the models. Baseline plasma viral load, CD4 cell count, and presence of STIs were included if they changed the relationship between DMPA and detection of HIV-1 RNA by ≥10%.

RESULTS

Between February 2005 and January 2008, 102 non-pregnant HIV-1-seropositive women initiated ART. Their median age was 36 (IQR 32–40) years. At ART initiation, the median CD4 cell count was 122 (IQR 78–164) cells/ml, and the median plasma HIV-1 RNA was 5.54 (IQR 5.17–5.97) $\log_{10}$ copies/ml. At baseline, 32 (31.4%) women reported being sexually active in the past week. Sixty-four (62.7%) women reported no current contraception, 18 (17.6%) reported DMPA, 5 (4.9%) reported Norplant and 5(4.9%) reported OCPs.

Participants contributed a median of 11 (IQR 7–11) quarterly follow-up visits over 34 (IQR 31–35) months. The median interval between visits was 90 (IQR 85–96) days. Ninety (88.2%) women contributed follow-up to 12 months, 78 (76.4%) to 24 months, and 72 (70.6%) to ≥ 33 months (Figure 1). Two (2%) women died, 12 (11.8%) transferred care or withdrew, and 16 (15.7%) were lost-to- follow-up. Fourteen (13.7%) women changed ART regimen due to interactions with tuberculosis medications, drug toxicity, or treatment

failure. Thirty-four (33.3%) women contributed follow-up time on DMPA for a median duration of 12 (IQR 6–22) months.

Ninety-nine women completed 925 follow-up visits. Their HIV-1 RNA was undetectable in plasma at 787 (85%) visits and in cervical secretions at 865 (94%) visits. Following initiation of ART, 55 (55.6%) women had at least one visit with detectable plasma HIV-1 RNA, and 30 (30.3%) women had at least one visit with detectable cervical HIV-1 RNA. Among these women, the median number of visits with detectable HIV-1 RNA was 2 (IQR 1–3) for plasma and 1 (IQR 1–2) for cervical samples. At visits where viral loads were detectable, the median plasma viral load was 3.56 (3.07–4.46) $\log_{10}$ copies/ml and the median cervical viral load was 3.45 (IQR 2.88–4.20) $\log_{10}$ copies/swab.

The median VAS adherence across all study visits was 100% (IQR 100–100%). Only forty (4.3%) of the 925 follow-up visits had VAS adherence ≤ 95% adherence. Compared to the other measures, VAS adherence ≤ 95% was most strongly associated with detection of plasma HIV-1 RNA (OR 2.84, 95% CI 1.59, 5.08) and was included in the multivariate models.

Plasma HIV-1 RNA was detectable at 113/671 (16.8%) visits without hormonal contraceptive exposure compared to 20/174 (11.5%) visits exposed to DMPA (Table 1). There was no association between DMPA exposure and detection of plasma HIV-1 RNA in either univariate (OR 0.64, 95% CI 0.39–1.03) or multivariate analysis adjusted for baseline plasma viral load, concurrent CD4 count, and VAS adherence (AOR 0.81, 95% CI 0.47–1.39). Cervical HIV-1 RNA was detectable at 40/664 (6%) visits without hormonal contraceptive exposure compared to 8/174 (4.6%) visits exposed to DMPA (OR 0.96, 95% CI 0.44–2.13, Table 1). The relationship between DMPA and detection of cervical HIV-1 RNA was similar after controlling for potential confounding factors (AOR 1.41, 95% CI 0.54–3.67). An additional model adjusting for detection of plasma HIV-1 RNA at time of cervical sampling did not change this relationship (AOR 1.41, 95% CI 0.43–4.64).

In light of the lack of an association between DMPA use and genital HIV-1 shedding, a post-hoc power calculation was performed to clarify the magnitude of differences in cervical HIV-1 shedding that could have been detected. This study had 80% power to detect a 1.6-fold or greater increase in the likelihood of detection of cervical HIV-1 RNA in DMPA users compared to women using no hormonal contraception.

Since HIV detected in genital samples could represent virus from a male partner, we conducted a sensitivity analysis excluding visits with sperm observed in genital secretions (52/925 [5.6%] visits). This analysis did not substantially alter the findings (data not shown).

DISCUSSION

In this prospective cohort study, there was no association between use of DMPA and increased detection of either plasma or cervical HIV-1 RNA. This finding is reassuring, given the extensive use of DMPA in areas of high HIV-1 seroprevalence.

In this same cohort, we have previously observed an association between DMPA and cervical HIV-1 RNA shedding at month three but not month six following ART initiation.[8] This increase in shedding suggested a potential effect of DMPA on infectivity. However, the prior study had little statistical power to address the question of DMPA as a risk factor for HIV-1 shedding and was not designed to assess the effect of contraception beyond six months of treatment. The data presented here clarify that DMPA is not associated with increased genital HIV-1 RNA shedding in women on long-term antiretroviral therapy.

This study had several strengths. Women were followed for a median of nearly three years, with repeated measures for each participant. This allowed us to examine the effect of DMPA on plasma and genital HIV-1 RNA shedding in women on long-term ART, reflecting the reality of treatment over many years of a woman's reproductive life course. In addition, ART adherence and other potential confounding factors were measured frequently, facilitating careful statistical adjustment. Finally, DMPA use was common in this cohort, allowing us to conduct an analysis with substantial power to detect even relatively small differences in the prevalence of genital HIV-1 RNA shedding with DMPA compared to no contraception.

This study also had a number of limitations. First, these data do not directly measure HIV-1 transmission to sex partners. While there is evidence that genital viral load is a good marker of infectivity,[5] the absolute concentration of genital HIV-1 required for transmission is unknown.[10] A second potential limitation is that we only measured endocervical HIV-1 RNA. There are several ways to measure genital HIV shedding, and limited consensus about the best approach.[10] However, studies measuring multiple compartments have only found an association between DMPA and genital HIV-1 shedding in the cervical compartment.[7,8] Additionally, we have previously shown that HIV-1 genotypic drug resistance is associated with genital shedding.[8] We did not evaluate resistance in the present study, and some episodes of HIV shedding in this study could be related to development of resistance. We also did not collect data on blood contamination of swabs, so could not adjust for this. However, we systematically avoided collecting specimens during menses. Finally, use of hormonal contraception in our cohort was by self-selection rather than random allocation. To address this issue, we adjusted for known and suspected confounding factors. Nonetheless, we cannot rule out effects due to differences between women who choose DMPA versus women who choose not to use hormonal contraception.

The high prevalence of DMPA use in this research cohort parallels data from the Kenya Demographic and Health Survey, in which 75% of women using hormonal contraception reported using DMPA.[3] DMPA is used extensively throughout Africa due to its ease of administration and suitability for discrete use.[22] It is considered to be a fairly effective form of hormonal contraception, following only WHO first-tier methods including sterilization, implants, and intrauterine devices.[23] DMPA is a safe form of hormonal contraception for HIV-positive women, as nearly all studies have found no association between DMPA use and progression of HIV-1 infection.[24,25] Furthermore, although there have been concerns regarding drug interactions between most hormonal contraceptives and ART, no interactions have been identified between DMPA and antiretroviral medications.[26]

In regions with both high HIV seroprevalence and frequent use of injectable hormonal contraception, limiting the availability of this method due to concerns about HIV infectiousness and susceptibility would be expected to lead to an increase in unplanned pregnancies, mother-to-child transmission, and maternal and infant mortality.[1,25,27–29] Our results suggest that DMPA is unlikely to increase infectivity in HIV-positive women who are adherent to effective ART. In light of these findings, early ART initiation could be considered in the context of "treatment as prevention" for HIV-positive women who desire injectable hormonal contraception. Moreover, these data highlight the importance of retaining DMPA as a safe and effective contraceptive option for HIV-positive women on ART.

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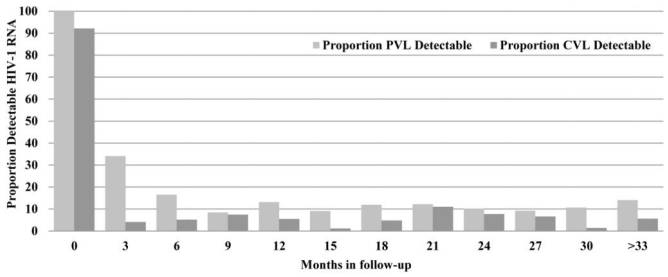

Months in follow-up	0	3	6	9	12	15	18	21	24	27	30	>33
Number of women	102	99	97	94	90	88	84	82	78	76	75	72
Proportion with detectable PVL (%)	100	34	16	8	13	9	12	12	10	9	11	14
*Median PVL (log_{10} copies/mL)	5.54	3.09	3.41	4.26	3.42	4.23	3.60	3.67	4.49	4.17	3.59	3.80
Proportion with detectable CVL (%)	92	4	5	7	5	1	5	11	8	7	1	6
*Median CVL (log_{10} copies/swab)	4.04	4.54	4.07	3.67	3.35	4.77	2.80	3.13	3.10	3.71	3.46	3.62

*Among women with detectable HIV-1 RNA

Figure 1.

Plasma HIV-1 RNA (PVL) and cervical HIV-1 RNA (CVL) in 102 women throughout 36 months of follow-up on ART in Mombasa, Kenya.

*Among women with detectable HIV-1 RNA

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Table 1

DMPA use and detection of plasma and cervical HIV-1 RNA in HIV-1 infected women on ART in Mombasa, Kenya

Contraceptive Method	n(%) visits with detected virus	Univariate OR (95% CI)	p-value	AOR* (95% CI)	p-value	AOR† (95% CI)	p-value
Plasma HIV-1 RNA							
No hormonal contraception	113/671 (16.8%)	1.0		1.0		NA	NA
DMPA	20/174 (11.5%)	0.64 (0.39, 1.04)	0.07	0.81 (0.47, 1.39)	0.4	NA	NA
Cervical HIV-1 RNA††							
No hormonal contraception	40/664 (6%)	1.0		1.0		1.0	
DMPA	8/174 (4.6%)	0.96 (0.44, 2.11)	0.9	1.41 (0.54, 3.67)	0.5	1.41 (0.43, 4.64)	0.6

DMPA, depot medroxyprogesterone acetate; ART, antiretroviral therapy; AOR, adjusted odds ratio

*Multivariate generalized estimating equation models adjusted for ART adherence *a priori* (VAS adherence ≤95%). Baseline plasma viral load and time-varying CD4 cell count changed the relationship between DMPA and detection of HIV-1 RNA by ≥10%, so were included in final model. Adjustment for presence of STIs (time-varying) did not change the findings.

†Additional adjustment was made for plasma HIV-1 RNA at time of cervical viral load sampling to evaluate the possible contribution of DMPA to HIV-1 RNA shedding, independent of any DMPA effect on plasma viral load.

††One woman had a hysterectomy and was excluded from analysis of cervical samples