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Medroxyprogesterone acetate concentrations among HIV-infected depot-medroxyprogesterone acetate users receiving antiretroviral therapy in Lilongwe, Malawi☆,☆☆

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Abstract

Objective: To compare medroxyprogesterone acetate (MPA) concentrations between HIV-positive women on antiretroviral therapy (ART) and HIV-negative women initiating depot medroxyprogesterone (DMPA) injectable.

Study design: Secondary analysis of 28 HIV-positive women on non-nucleoside reverse transcriptase inhibitor-containing ART regimens and 10 HIV-negative women randomized to initiate DMPA in a clinical trial of progestin contraception in Malawi.

Results: MPA concentrations were significantly lower among HIV-positive women on ART, compared with HIV-negative women, at week 4 and week 13 (p=.03 for both), but not at day 3 or week 26 post-DMPA initiation.

Conclusions: Antiretroviral medications may affect MPA metabolism in HIV-positive African women.

Keywords

HIV; Depot medroxyprogesterone acetate; Africa; Antiretroviral therapy

☆**Disclosure:** The findings and conclusions presented in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention nor the Association of Schools and Programs of Public Health. Yasaman Zia and Shivika Trivedi are no longer CDC affiliates.

☆☆This study was registered with Clinicaltrials.gov (NCT02103660).

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.07.144.

1. Introduction

Depot medroxyprogesterone (DMPA) use has risen globally [1], including among HIV-positive women in Africa. The World Health Organization (WHO) does not limit use of DMPA among women on antiretroviral therapy (ART), as most available evidence does not indicate clinically significant pharmacokinetic interactions [2]. Only one study, which evaluated medroxyprogesterone acetate (MPA) concentrations in HIV-negative Kenyan women taking tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) combination pre-exposure prophylaxis (PrEP), has suggested that ART may interact with DMPA [3]. However, the pharmacological mechanisms for an ART interaction with MPA are unclear, as neither TDF nor FTC are known liver enzyme inducers. In contrast, the non-nucleotide reverse transcriptase inhibitor (NNRTIs) efavirenz (EFV) and nevirapine (NVP) are known to induce the CYP3A4 enzymes that metabolize MPA [4]. We compared MPA concentrations between DMPA-using HIV-positive women on ART containing TDF, lamivudine (3TC), and either EFV or NVP, with DMPA-using HIV-negative women in Malawi.

2. Materials and methods

This is a secondary analysis of a randomized clinical trial assessing the effects of progestin contraception in the genital tract of HIV-positive and negative women. The study methods have been previously described, and the eligibility criteria are included in Supplement [5]. Women aged 18 to 45 years were enrolled at Bwaila Hospital in Lilongwe, Malawi from April 2014 to May 2015. Visits 1 and 2 were completed during the follicular and luteal phases, respectively, prior to contraceptive initiation. Women were then randomized to receive either DMPA or the 5-year levonorgestrel implant at Visit 3. Women returned on Day 3 (Visit 4), and Weeks 4 (Visit 5), 13 (Visit 6) and 26 (Visit 7) after randomization, and those randomized to DMPA received repeat injections at Weeks 13 and 26. All women received their DMPA injection within two weeks of their scheduled dose, which were scheduled at 13-week intervals.

This sub-analysis focused on women randomized to DMPA and was restricted to HIV-negative women and HIV-positive women on either EFV- or NVP-based ART (both in combination with TDF and 3TC), which were the two most-commonly prescribed ART regimens during this study per Malawi guidelines [6]. Women who had MPA detected at Visit 1 were excluded from analysis. ART regimen used was confirmed by medical record review; urine pregnancy testing was performed at each visit.

MPA concentrations were assessed at Visits 1 and 4–7. Serum was stored at −80 °C until shipped for analysis in the Reproductive Endocrinology Laboratory at the University of Southern California. MPA concentrations were measured using radioimmunoassay (RIA) (Coat-A-Count, Siemens Healthcare Diagnostics Inc., Deer-field, IL). The level of quantification was 70 pg/mL, with an interassay coefficient of variation of 13.0%.

Comparisons of participant characteristics were made between HIV-positive and negative women using chi-squared and Wilcoxon signed-rank tests for categorical and continuous

variables, respectively. Wilcoxon exact tests assessed for differences in distributions of MPA concentrations between HIV-positive women and negative women over time. Wilcoxon ranked sum tests assessed the difference in median MPA trough concentrations between Week 13 and 26 in the same woman (paired analysis). SAS version 9.4 was used for all analyses, and p-values <.05 were considered significant.

This study was approved by institutional review boards at the University of North Carolina, Malawi National Health Sciences Research Committee, Malawi Pharmacy Medicines and Poisons Board, and the U.S. Centers for Disease Control and Prevention.

3. Results

This analysis included 28 HIV-positive women on ART and 10 HIV-negative women. All ART users received TDF and lamivudine; 27 women also received efavirenz while one woman received nevirapine. Most women (93%) were using ART for over 1 year. HIV-positive women were older than negative women (median age, 36 vs 26 years, p=.002) but similar in weight and other characteristics (Appendix A). Individual MPA levels over time are displayed in Fig. 1 for HIV-positive and HIV-negative women, and Fig. 2 for women with MPA less than 200 pg/mL at any time point.

MPA concentrations were significantly higher in HIV-negative women than in HIV-positive women at Weeks 4 and 13 after DMPA initiation, but not at Day 3 or Week 26 (Table 1). MPA concentrations were below 200 pg/mL in two women at Week 13 and in one woman at Week 26; all 3 were HIV-positive (Fig. 2). Two of these women had MPA concentrations below the presumed contraceptive threshold of 100 pg/mL, one at Week 13 (below level of quantification of 70 pg/mL) and the other at Week 26 (78.8 pg/mL) [7,8]. No pregnancies occurred over 26 weeks of follow-up.

When comparing trough MPA concentrations in the same woman, trough concentrations were higher at Week 26 compared with Week 13 (p=.001, Table 2). However, for only HIV-positive women, these differences reached statistical significance between week 13 and 26 (p=.001). One participant with a missing MPA result at Week 13 was not included in this sub-analysis. When stratified by weight (above or below median) among HIV-positive women, we found that weight did not mediate this increase between week 13 and 26.

4. Discussion

MPA concentrations were significantly lower among HIV-positive women on NNRTI-based ART compared to HIV-negative women at Week 4 and 13 post DMPA initiation, though not at Day 3 or Week 26. Two HIV-positive women (7%) had MPA concentrations below 100 pg/mL, the minimum value needed to prevent ovulation [7,8]. Even though no pregnancies were observed over 26 weeks, our findings raise concern regarding potential interactions between DMPA and EFV-based ART.

Evidence is relatively limited for drug–drug interactions with concomitant use of DMPA and ART [4]. Even though the World Health Organization does not restrict DMPA use with any ART [2], some studies suggest that DMPA efficacy may vary with ART use [3,4]. For

example, a study by Patel et al. in Kenya observed slightly elevated (but not statistically significantly different) pregnancy rates in women on DMPA and EFV, when compared to DMPA users on other ART [9]. In addition, genetic variants in African populations are hypothesized to influence pharmacokinetics because of their diverse genetic heterogeneity and variation of alleles associated with drug metabolism [10,11]. In Kenya, 61 HIV-negative women randomized to TDF/FTC PrEP versus placebo had lower than expected MPA concentrations at Week 12 after DMPA initiation, with 20.0% of placebo users and 34.6% of TDF/FTC users having MPA concentrations <100 pg/mL [3]. Our study used RIA to analyze MPA concentrations, whereas the Nanda et al. 2016 study used mass spectrometry, which could account for some of the differences. Studies that established 100 pg/mL as the MPA concentration when ovulation resumes used RIA [7,8].

Limitations of our study include the small sample size and the inability to assess individual ART drug effects on DMPA, since all HIV-positive women were on both TDF and 3TC and most were on EFV. In addition, variations in MPA concentrations occur between individuals and within an individual throughout the day [7], but our samples could only capture a single time point, so they may not necessarily be predictive of contraceptive efficacy. Larger studies with clinical endpoints (such as pregnancy) may further inform the assessment of interactions between DMPA and ART, particularly among African women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A

Appendix Table 1 Baseline characteristics of participants by HIV status

Characteristic	HIV − (N=10) N (%)	HIV + on ART (N=28) N (%)	P-Value
Marital status			0.39
Married	9 (90%)	17 (60.7%)	
Single/Separated/ Divorced	1 (10%)	11 (39.3%)	
Completed at least primary education	8 (80%)	14 (50%)	0.10
Plasma HIV viral load >40 copies/ml *	N/A	2 (7.4%)	--
Years since HIV diagnosis			--
≤1 year	N/A	2 (7.1%)	
1–5 years	N/A	18 (64.3%)	

Characteristic	HIV − (N=10)	HIV + on ART (N=28)	P-Value
	N (%)	N (%)	
≥5 years	N/A	8 (28.8%)	
Years since ART initiated			--
≤1 year	N/A	5 (7.4%)	
>1 year	N/A	23 (92.6%)	
	Mean (S. D.)	**Mean (S.D.)**	
Age (years)	26.0 (5.72)	36.0 (5.73)	**0.0017**
Weight (kg)	54.0 (6.5)	53.3 (8.58)	0.78
Parity	2.0 (1.4)	3.0 (1.6)	0.78
CD4 count *	N/A	490.0 (135.03)	--

* Measured at visit 1 (pre-randomization, follicular phase).

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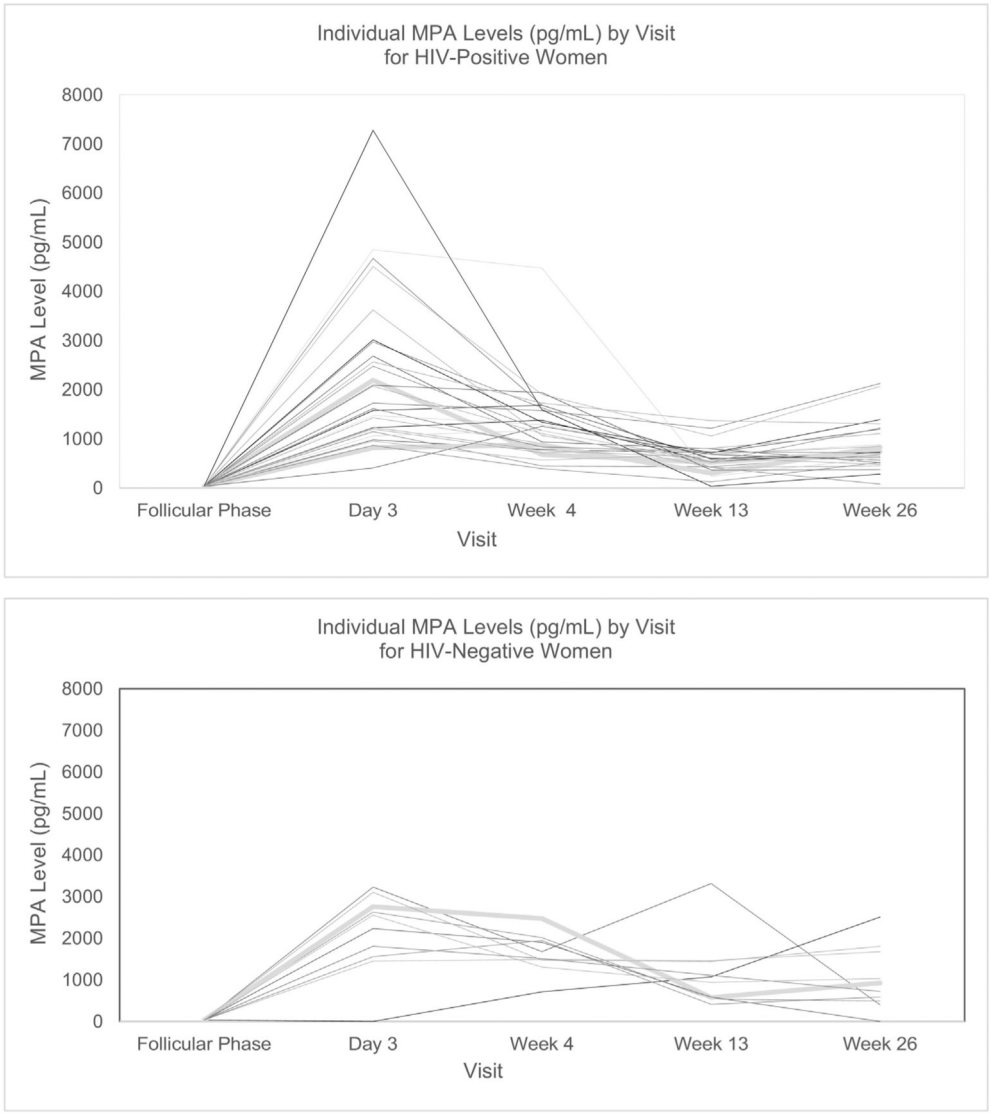

Fig. 1.

Individual MPA Levels (pg/mL) by Visit for HIV-positive Women (n=28) and HIV-negative Women (n=10). *MPA, medroxyprogesterone acetate.

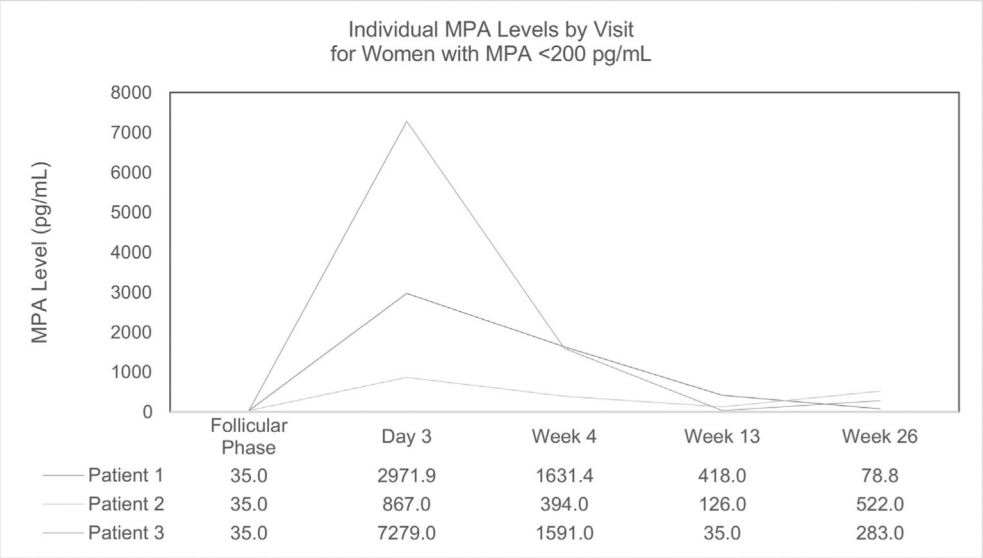

Fig. 2.

MPA Levels (pg/mL) by Visit for Women with MPA<200 At Any Time*MPA, Medroxyprogesterone acetate. **Note: The level of quantification for MPA was 70 pg/mL, and all MPA results below the level of quantification were converted to 35 pg/mL.

Table 1

MPA concentrations at each time point post-DMPA initiation, by HIV status, the Progestin Study, Lilongwe, Malawi

Time point after DMPA initiation	N	Mean (S.D.) (pg/ml)	Wilcoxon Exact Test	n (%) <200 pg/mL	n (%) <100 pg/mL
Day 3					
HIV+	28	2240.4 (1554.4)	0.21		
HIV−	9	2371.1 (649.3)			
Week4					
HIV+	28	1282.1 (763.9)	**0.03**		
HIV−	10	1651.5 (475.6)			
Week 13					
HIV+	27	603.2 (295.5)	**0.03**	2 (7.4%)	1 (3.7%)
HIV−	10	1145.8 (849.7)			
Week 26					
HIV+	28	836.1 (469.8)	0.41		1 (3.6%)
HIV−	9	1129.3 (716.5)			

Abbreviations: MPA, medroxyprogesterone acetate.

Table 2

Differences in MPA trough concentrations between first and second DMPA Injection (Week 13 and Week 26), overall and by HIV status and baseline weight Note: Participants with a missing MPA value at Week 13 were not included in this analysis.

	N	Median difference (pg/ml)	Signed rank test
All	**36**	195.77	**0.001**
H1V+	**27**	197.54	**0.001**
HIV−	**9**	177.25	0.57
HIV+, by weight			
Weight >Median	**13**	85.70	0.95
Weight ≤Median	**14**	−16.4	1.00