Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy

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Objective: To evaluate the effect of an antiretroviral (ARV) therapy regimen containing zidovudine (AZT), lamivudine (3TC), and efavirenz (EFV) on the pharmacokinetics of depot medroxyprogesterone acetate (DMPA).
Design: Open-label, nonrandomized, clinical trial.
Setting: University hospital clinic.
Patient(s): Thirty HIV-infected women; 15 using ARV therapy (AZT, 3TC, and EFV) and 15 non-users of ARV therapy, followed biweekly for 12 weeks.
Intervention(s): Single injection of DMPA (150 mg IM) for both groups.
Main Outcome Measure(s): Pharmacokinetic parameters of DMPA by liquid chromatography with mass spectrometry, and ovulation by serum P.
Result(s): Maximum serum concentrations of DMPA were reached at 14 days after injection. The area under the curve was similar in both groups, as were the minimum concentration, half-life, and clearance. Only 1 woman, not using ARV therapy, ovulated at 11 weeks after DMPA.
Conclusion(s): Pharmacokinetics of DMPA were similar in HIV-infected women, regardless of ARV therapy use, suggesting that triple therapy with AZT, 3TC, and EFV is not likely to interfere with the contraceptive effectiveness of DMPA. (Fertil Steril® 2008;90:965–71. ©2008 by American Society for Reproductive Medicine.)

Key Words: Depot medroxyprogesterone acetate, contraception, HIV, antiretroviral therapy, pharmacokinetics

Hormonal contraceptive methods are among the most effective and widely used options to prevent pregnancy, but data about their use by HIV-infected women are scarce. Concerns remain about hormonal contraceptive use among HIV-infected women who use antiretroviral (ARV) therapies because of potential pharmacokinetic drug interactions, especially with regard to liver metabolism. The liver's cytochrome P-450 (CYP) enzymes, especially CYP 3A4, are involved in the metabolism of many drugs, including both contraceptive steroids and ARV drugs (1).

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Human immunodeficiency virus–infected women requiring treatment generally use combination ARV therapy. Initial therapy includes three drugs: two nucleoside analogue reverse transcriptase inhibitors and one nonnucleoside analogue reverse transcriptase inhibitor or protease inhibitor (2, 3). One recommended starting regimen that is used widely worldwide includes zidovudine (AZT), lamivudine (3TC), and efavirenz (EFV) (3). Individual ARV drugs act differently in terms of liver metabolism. Nucleoside analogue reverse transcriptase inhibitors and nucleotide analogue reverse transcriptase inhibitors generally do not affect hepatic enzyme activity and have limited drug interactions (4, 5). In contrast, protease inhibitors and nonnucleoside analogue reverse transcriptase inhibitors are metabolized by CYP3A4 and can also inhibit or induce this enzyme, resulting in increases or decreases in the concentration of concomitantly administered drugs (4).

Drug interactions between ARV drugs and hormonal contraceptive methods could lead to a reduction of contraceptive or ARV efficacy or an increase in adverse events. Two published studies have included data on the effect of ARV drugs on combined oral contraceptive pharmacokinetics. Both

studies were small, nonrandomized, open label, and evaluated only a single dose of a combined oral contraceptive. In one study (6), oral ritonavir resulted in statistically significant decreases in ethinyl E_2 levels from a single dose of a contraceptive pill. In another study (7), oral nevirapine significantly reduced both ethinyl E_2 and norethindrone levels. No studies have evaluated clinical outcomes such as pregnancy, though one study did not find evidence that use of hormonal contraceptives strongly affected responses to ARV therapy (8).

Because of concerns regarding the effectiveness of combined oral contraceptives in HIV-infected women using ARV drugs, many such women are counseled to use alternate methods of contraception, including injectable contraceptive methods (4). In a recent report from West Africa, progestin injectables were the contraceptive method used by 65% of 740 HIV-infected women using AZT–3TC–EFV therapy (9). Studies have shown effects on the pharmacokinetic of oral but not IV MPA with aminoglutethimide and other drugs that affect hepatic enzyme activity (10, 11), and in clinical practice depot medroxyprogesterone acetate (DMPA) is often given every 10 weeks to women using liver enzyme inducers (12, 13).

The primary objective of this study was to evaluate the effect of a common ARV regimen (AZT plus 3TC, with EFV) on the pharmacokinetics of DMPA. Secondary objectives were to evaluate the effects of ARV drugs on bleeding patterns in users of DMPA and to determine whether potential pharmacokinetics interactions between selected ARV drugs and DMPA affected the suppression of ovulation.

MATERIALS AND METHODS

This was an open-label, nonrandomized, pharmacokinetic study of two groups of HIV-infected reproductive-age women (users of an ARV regimen containing AZT, 3TC, and EFV, and non-users of ARV therapy), followed biweekly for 12 weeks. We conducted this study at the Department of Obstetrics and Gynecology, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil. The institutional review boards at UNICAMP and Family Health International approved the protocol before implementation. All women provided written, informed consent before entering the study.

Eligible women were aged 19–40 years, HIV infected, with regular menstrual cycles, with uterus and at least one ovary intact, with a body mass index of 18–30 kg/m^2, and not recently pregnant or breast-feeding. They had to agree to use DMPA for contraception for the duration of the study and no other hormonal methods. In addition, women in the ARV group were required to have been using ARV therapy (AZT and 3TC plus EFV) for a minimum of 30 days, to be expecting to continue using this treatment for the duration of their study participation, and to be abstinent or using a barrier method of contraception during the study. We excluded women with medical contraindications to DMPA, other known hematologic, hepatic, lipid, or carbohydrate abnormalities, other hormonal therapies within 30 days of study entry, acute infection or other opportunistic diseases requiring therapy within 14 days before study entry, active drug or alcohol use, methadone maintenance treatment that started less than 60 days before study entry, or any use of liver enzyme inducers. Furthermore, women in the ARV group could not have chronic diarrhea, malabsorption or inability to maintain an adequate oral intake, or be nonadherent to ARV therapy. Women who were currently using DMPA for contraception were eligible if they were between 12 and 14 weeks of their last injection.

We administered 150 mg of DMPA (150 mg/mL IM Depo-Provera; Pfizer, São Paulo, Brazil) to each eligible and enrolled participant. We observed participants at 2-week intervals ($\pm$3 days) through 12 weeks. At each visit we asked participants about adverse events, bleeding patterns, ARV adherence (if appropriate), and concomitant medications. We obtained blood samples for determination of plasma DMPA concentration before administration of the DMPA (admission) along with serum P levels at each subsequent visit. We also obtained baseline viral load and CD4 counts.

Laboratory Assays

Laboratory specimens were batched and assayed at the end of the study. Specimens for MPA analysis were initially frozen at $-20^{\circ}C$ after collection, transported to the reference laboratory (Serviço de Farmacocinética, Departamento de Patologia e Farmacocinética, Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil), and then frozen at $-70^{\circ}C$ until analysis.

The laboratory analyzed MPA plasma concentrations using a validated method of high-performance liquid chromatography in conjunction with tandem mass spectrometry. Laboratory procedures followed the Good Practices in Bioavailability/Bioequivalence of Medicines approved by the Brazilian National Authority on Sanitary Surveillance. The standards of MPA used were U.S. Pharmacopeia (Rockville, MD) and MPA-D3 from the National Institute for Public Health and Environment (Bilthoven, the Netherlands). Biological specificity of the method was assessed by processing independent plasma samples and blank samples obtained from men (to avoid previous use of DMPA). The lower limit of detection was 0.05 ng/mL. Sample concentrations were automatically calculated by the instrument software through calibration curves built according to extracted plasma samples at different levels of concentration. Calibration curves were accepted if the mean values of all three quality control pools were within acceptance limits ($\pm$15% of the target value), four of six (67%) quality control results met these criteria, and the correlation coefficient was $\geq$0.98. The observed coefficient of variation was $<$5%.

We measured serum P in duplicate by using commercial kits of a microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL) with a measurement range of 0.2–35.17 ng/mL and within- and between-run coefficients of variation of 9.5% and 2.85%, respectively.