Published in final edited form as:
Contraception. 2008 February ; 77(2): 84–90. doi:10.1016/j.contraception.2007.10.002.

Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093

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Abstract

Background—Concomitant use of antiretrovirals (ARV) and hormonal contraceptives may change the metabolism of each and the resulting safety profiles. We evaluated the safety and tolerability of depot medroxyprogesterone acetate (DMPA) among women on ARV.

Study Design—HIV-infected women on selected ARV regimens or no ARV were administered DMPA 150 mg intramuscularly and evaluated for 12 weeks for adverse events, changes in CD4+ count and HIV RNA levels, and ovulation.

Results—Seventy evaluable subjects were included, 16 on nucleoside only or no ARV, 21 on nelfinavir-containing regimens, 17 on efavirenz-containing regimens, and 16 on nevirapine-containing regimens. Nine grade 3 or 4 adverse events occurred in 7 subjects; none were judged related to DMPA. The most common findings possibly related to DMPA were abnormal vaginal bleeding (9, 12.7%), headache (3, 4.2%), abdominal pain, mood changes, insomnia, anorexia, and fatigue, each occurring in 2 (2.9%) subjects. No significant changes in CD4+ count or HIV RNA levels occurred with DMPA. No evidence of ovulation was detected, and no pregnancies occurred.

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Conflicts of interest Possible conflicts of interest (including financial and other relationships) for each author include the following: Juan J.L. Lertora, MD, PhD, was an investigator in protocols sponsored by Bristol Myers Squibb, Gilead, and Schering. Pamela A. Clax, DPM, is an employee of Pfizer, Inc. and owns stock in Pfizer. Alice Stek, MD, is on the Pfizer speakers' bureau. Susan E. Cohn, MD, MPH, had equity interest in Pfizer, Inc., Merck and Company, and Pharmacia before the start of this study. She currently has equity interest in Merck and Company, Inc.

Conclusions—The clinical profile associated with DMPA administration in HIV-infected women, most on ARV, appears similar to that seen in HIV-uninfected women. DMPA prevented ovulation and did not affect CD4+ counts or HIV RNA levels. In concert with previously published DMPA/ARV interaction data, these data suggest that DMPA can be used safely by HIV-infected women on the ARV studied.

Keywords

HIV; women; depotmedroxyprogesterone; antiretrovirals; contraception 1

1. Introduction

The proportion of AIDS cases among women continues to increase in the US, and worldwide, women account for nearly half of HIV-infected adults [1,2]. The majority of HIV-infected women are of reproductive age, and many choose to limit the chance of pregnancy. However, data are limited on the potential interactions of hormonal contraceptives and antiretroviral (ARV) medications, limiting the contraceptive options for HIV-infected women receiving ARVs.

Depot medroxyprogesterone acetate (DMPA) given as 150 mg intramuscular injection every three months, is a highly effective contraceptive agent, used by millions of women worldwide [3]. The most common side effects of its use in HIV-uninfected woman are menstrual irregularities or amenorrhea and weight gain, with headaches, abdominal discomfort, dizziness, and mood changes being less common [3]. Little data exist to assess the safety and tolerability of DMPA among HIV-infected women, especially those also receiving ARV l therapy. Side effects could be compounded by symptoms of HIV progression or toxicities of ARV agents such as dizziness occurring with efavirenz. The effects of initiation of DMPA on HIV RNA levels have not been evaluated, although one study demonstrated higher HIV RNA levels after initial infection among women who seroconverted to HIV-1 while on DMPA compared to those not on DMPA at seroconversion [4]. We evaluated the safety and tolerability of DMPA among HIV-infected women on a variety of ARV regimens by examining the frequency of symptoms potentially related to DMPA and assessing changes in HIV RNA levels and CD4+ cell counts.

2. Methods

AIDS Clinical Trials Group protocol 5093 (ACTG 5093) was a 12-week, open-label, non-randomized study of steady-state pharmacokinetic interactions between DMPA and selected ARV agents in women. More detailed methods and pharmacokinetic results have been reported previously [5] Women were eligible for enrollment if they were on stable ARV regimens for at least 30 days containing one of three targeted drugs (nelfinavir (Pfizer, New York, NY), efavirenz (Bristol-Myers Squibb, New York, NY), or nevirapine (Boehringer Ingelheim, Ridgefield, CT), on no ARV, or on a stable regimen of only nucleoside agents, and had no contraindications to receiving DMPA. Women on no ARV therapy were required to have a CD4+ cell count above 350 cells/uL consistent with current treatment guidelines, while those on antiretroviral regimens had to have a CD4+ cell count over 200 cells/uL to minimize the risk of concomitant illnesses. The protocol was approved by the Institutional Review Board at each participating site, and informed consent was obtained from each woman before participation. Baseline history, including recent menstrual history, and physical examination were performed. Women were classified as having abnormal menses if they reported cycles shorter than 25 days or longer than 35 days, or irregular cycles. Baseline laboratory data including complete blood count with differential, CD4+ cell counts, HIV RNA levels, liver transaminases, creatinine, amylase, bilirubin, international normalized ratio of the prothrombin

time, progesterone, and medroxyprogesterone levels were obtained. For women enrolled in the nelfinavir, efavirenz, and nevirapine arms, serial blood draws for ARVl levels were obtained over a 10-hour period at baseline before DMPA administration and again four weeks after DMPA administration. A negative pregnancy test was required within 24 h before DMPA administration, which occurred within seven days of onset of menses and more than 30 days after pregnancy. Because of the unproven efficacy of DMPA when used with ARV agents, women were required to use a second, non-hormonal method of contraception (barrier method, intrauterine device, or sterilization) during the study.

Subjects received a single 150-mg DMPA injection in the gluteal region (Pfizer, New York, NY), at study entry. Follow-up study visits occurred 2, 4, 6, 8, 10, and 12 weeks after DMPA administration. At each visit, an interval history was obtained, including questions regarding any new symptoms or change in baseline findings and use of prescription and non-prescription medications. A targeted physical examination was performed, and blood was drawn for progesterone and medroxyprogesterone levels. HIV RNA levels were repeated at weeks 2, 4, 8, and 12. CD4+ cell counts, complete blood counts, liver transaminases, and chemistries were repeated at weeks 4 and 12.

New symptoms, signs, or laboratory abnormalities were graded using the standardized Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences©, August, 1992 http://rcc.tech-res.com/tox_tables.htm. Signs and symptoms were graded as mild, moderate, severe, or life threatening, with mild symptoms usually requiring no therapy, moderate symptoms requiring no therapy or only outpatient treatment, and severe symptoms requiring medical intervention and possible treatment in the hospital. All signs and symptoms of any grade and laboratory abnormalities of grade 2 or higher were recorded on the case report forms. All adverse events reported were reviewed by the team on monthly calls and assigned causality as definitely, probably, possibly, unlikely or not treatment related to the primary study treatment which was DMPA.

HIV RNA assays were performed in laboratories certified by the DAIDS Virology Quality Assurance program using the Roche Ultra-sensitive or Roche RT-PCR (Amplicor, Pleasonton, CA) HIV-1 Monitor assays [6]. CD4+ cell counts were performed using standard flow cytometric methods in laboratories certified by the DAIDS Quality Assurance program [7]. Progesterone levels were measured at each visit using an enzyme-modified immunoassay . Progesterone concentrations above 5 ng/mL were considered as presumptive evidence of ovulation.

The sample size for the study was based on having 90% power to detect differences at the 0.05 significance level between the area under the concentration time curves for the selected ARV agents before and after DMPA administration and comparing DMPA metabolism between women on the selected ARV agents and those on no therapy or nucleoside therapy alone [5]. MPA levels were measured using high pressure liquid chromatography – mass spectroscopy with a lower limit of detection of 0.02 ng/mL. Levels were drawn pre-sode (week 0), and weeks, 2, 4, 6, 8, 10, and 12. The proportion of women with HIV RNA levels below 400 copies/mL was compared between the visit weeks within each arm using a chi-square test. A nonparametric Wilcoxon signed-rank test was used to compare differences between measurements from baseline to week 4 and week 12 in lymphocyte subsets.

Results

A total of 72 subjects (16 in the nucleoside reverse transcriptase inhibitors (NRTI) only or no ARV arm, 22 in the nelfinavir-based arm, 18 in the efavirenz-based arm, and 16 in the nevirapine-based arm) were enrolled. One subject from the nelfinavir arm and one from the

efavirenz arm were excluded because they were inadvertently enrolled to the wrong treatment arm, yielding 70 subjects included in this analysis. Characteristics of the 70 evaluable subjects are listed in Table 1. The median age was 35, and 81% were racial or ethnic minorities. Twenty-three percent reported injection drug use in the past but only one woman reported current injection drug use. Fifty-five (79%) of the women had HIV RNA levels below 400 copies/mL at enrollment, and the median CD4+ lymphocyte count was above 600 cells/uL in all groups. Most had been on their current ARV regimen for a year or more. None of the subjects had used hormonal contraception in the year before study entry. Menstrual cycle abnormalities were reported at baseline among 9 (13%) of the 68 women with gynecologic data collected.

Nine events judged as severe intensity occurred among seven subjects on study; none of these were judged to be related to study treatment. One subject had multiple events including neutropenia classified as grade 2 at baseline, grade 3 at week four, and grade 4 at week eight; she also had a grade 3 creatine kinase level at week four, increased from grade 1 at baseline. Other grade 3 toxicities occurring in one subject each included hip pain secondary to an abscess (not at the DMPA injection site), nausea and vomiting lasting two days 12 weeks after DMPA injection, self-limited diarrhea eight weeks after DMPA, neck pain, grade 3 neutropenia at baseline, and severe abdominal pain secondary to appendicitis.

Grade 2 toxicities judged to be possibly, probably, or definitely related to DMPA administration are listed in Table 2. The most common finding was abnormal vaginal bleeding, most often described as spotting, breakthrough bleeding, or prolonged menses but not categorized as heavy bleeding. Abnormal vaginal bleeding after DMPA was reported among two (22%) of nine women with baseline menstrual abnormalities and seven (12%) of 59 with normal cycles at baseline ($p= 0.34$). No cases of anemia occurred on study, suggesting no clinically important impact on hematocrit from the vaginal bleeding. Abnormal vaginal bleeding occurred in 1 (6.3%) of 16 women in the NRTI/control arm, 2 (9.5%) of 21 women in the nelfinavir arm, 3 (17.6%) of 17 women in the efavirenz arm, and 3 (18.8%) of 16 women in the nevirapine arm ($p=0.64$ comparing all arms, $p=0.67$ comparing control arm to all other arms). Three women reported the new onset of headaches after DMPA, and two women reported abdominal pain or cramping without specific cause. Two women reported mood changes. No women complained of weight gain as a side effect, but weight changes from baseline to the week 12 visit varied by study arm. The median (range) weight gain was 5.8 (−11.5, 11.5) pounds in the control/NRTI arm, 0.70 (−13.7, 17.0) pounds in the nelfinavir arm ($p= 0.06$ compared to the control arm), 1.0 (−26.8, 19.0) pounds in the efavirenz arm ($p= 0.07$ compared to control arm), and 3.5 (−11.6, 20.7) pounds in the nevirapine arm ($p= 0.54$ compared to the control arm). Sixteen women (22.5%) chose to receive a second DMPA injection after the 12-week study period, including 1 (11%) of 9 women with abnormal bleeding and 15 (24.2%) of 62 without abnormal bleeding ($p=0.67$), and 5 (27.8%) of 18 with any possibly drug-related toxicity and 13 (23.6%) of 55 without drug toxicity ($p=0.76$).

The proportion of subjects with HIV RNA levels below 400 copies/mL in each arm at baseline, and two, four, eight, and 12 weeks after DMPA injection are shown in Table 3. No significant increases were seen in HIV RNA levels after DMPA within each arm or within the group as a whole. Only one subject, in the nelfinavir arm, had a transient increase of over 0.5 logs at four weeks after DMPA but was below 400 copies/mL again at eight weeks. She denied missing any doses of ARV in the four days before her study visit. No significant changes in CD4+ lymphocyte counts were seen between baseline and four and 12 weeks after DMPA injection within each group (Table 3).

Progesterone levels were undetectable after DMPA administration in the majority of women throughout the study, and the maximum level detected was 1.6 ng/mL, below the threshold for evidence of ovulation. No pregnancies occurred among the women on the study. As previously

described, the pharmacokinetics of medroxyprogesterone were not altered by the ARV drugs, and therapeutic levels were maintained throughout the 12-week study period [5]. Similarly, as previously reported, there were no clinically significant changes in ARVal levels after administration of DMPA [5].

4. Discussion

In this small cohort of HIV-infected women, DMPA was well-tolerated, with no severe drug-related toxicity and minimal and expected side effects. The most commonly reported toxicity was abnormal bleeding, consistent with experience in HIV-uninfected women [8,9]. However, the rates of menstrual changes in the current study are actually lower than those reported in previous studies. In a cohort of 536 women in Houston receiving their first injection of DMPA, only 3% reported no change in bleeding pattern within three months of the first DMPA injection [8]. Forty-six percent reported spotting or irregular bleeding, 46% reported amenorrhea, 26% reported longer periods, and 4% reported shorter periods. After nine months of use, nearly 60% reported amenorrhea. Eight percent of women in the Houston cohort reported increased cramping, a higher rate than in the current study. Similarly, a World Health Organization study of over 500 women found that 91% of women had variations from their regular menstrual bleeding pattern in the first three months after initiation of DMPA, with irregular bleeding (46%) and prolonged bleeding (43%) being the most common changes [9]. Again, by one year of use, amenorrhea had increased and other bleeding changes had decreased in rate. The rate of bleeding abnormalities in our cohort may have been lower than that reported in the literature because we did not include specific questionnaires regarding bleeding patterns, whereas previous studies were designed specifically to assess bleeding changes. However, participants were asked about any new symptoms or changes at each visit, so that major changes should have been detected. In addition, the women in the current study had a median age of 35 and 13% of women reported abnormal menstrual cycles at baseline. The mean age in the Houston study was 24, typical of the population seen in family planning settings. Thus, the women in the current study may have had fewer changes from their already irregular bleeding patterns or may have been less likely to report them. However, even with these limitations, the rate of abnormal bleeding after DMPA does not appear to be increased among these HIV-infected women, most of whom were on ARV therapy.

Headaches were reported in 4.3% and dizziness in 1.4% of women in this study, well within the range of 3–19% reported for headache or dizziness in contraceptive trials [3]. In a WHO trial, the discontinuation rate for headache with any injectable contraceptives was 2/100 woman years of use, and with DMPA, discontinuation for dizziness occurred in 1.2/100 woman-years [10]. In a comparative trial of Norplant and intrauterine device users, the rate of headaches among IUD users was 7–10%, suggesting a high background rate of headaches unrelated to hormone use [3].

Mood changes or depressive symptoms such as anorexia and fatigue have been reported in 1–5% of DMPA users in large studies and in 8.9% of users in the first three months in the Houston cohort, consistent with the rate in the current study [8,11,12]. Most reports do not include the baseline rate of depressive symptoms, so many of these symptoms may antedate the use of DMPA. In one prospective study that assessed symptoms before and after administration of DMPA, depression scores actually improved after administration of DMPA, suggesting that DMPA does not increase the rate of depressive symptoms [13]. Mood changes were uncommon in the current study and reported to be of mild to moderate intensity.

Only 22.5% of the women in this study chose to receive a second DMPA injection, lower than the continuation rates reported in the general population, which vary from 57–70% at three months and from 23–51% at one year [8,14–17]. Change in bleeding pattern was the most

common reason for discontinuation in all studies, and continuation rates were improved with more intensive counseling at initiation regarding the potential changes in bleeding patterns and other side effects [14,15]. The low continuation rate in this study may in part be due to the requirement that participants use a second method of contraception in addition to the DMPA at study entry because of the uncertain efficacy of DMPA with concomitant use of ARVsls. Many women may have chosen to revert to their established method after trying DMPA for research purposes. In addition, while counseling regarding potential side effects was included at enrollment, the counseling may not have been as detailed regarding potential bleeding changes as that provided in family planning settings.

It is reassuring that no significant changes were observed in HIV RNA levels and CD4+ cell counts after administration of DMPA in this short-term study. One prospective study of women with known HIV seroconversion dates demonstrated the viral set point to be 0.29 log higher in women on DMPA at acquisition of HIV compared to those not on hormonal contraception, although the change in HIV RNA levels over time did not differ between women on DMPA or not on hormones [18]. No difference in HIV RNA levels was found between women on combined oral contraceptives or not on hormonal contraception at enrollment in that study. Of note, studies of the effects of pregnancy, associated with prolonged high levels of progesterone, on disease progression among HIV-infected women have not suggested a negative effect among women in industrialized settings, with access to ARV therapy [19,20]. Thus, although theoretically, DMPA could have an effect on viral set point if present at the time of infection because of effects on susceptibility of the genital tract to HIV yielding more infected cells or on early events in viral replication, DMPA does not appear to cause an increase in HIV RNA levels among women with established infection. Our data are consistent also with results from an analysis from the Women's Interagency HIV Study, finding no difference in HIV RNA levels among women on hormonal contraception and those not using hormones [21]. No clinically significant changes in metabolism of the ARV drugs studied were detected [5], although studies of the interaction of DMPA with newer protease inhibitors are still needed.

No evidence of ovulation was seen during the study, consistent with the previously reported finding that DMPA levels were not different between women taking or not taking ARV drugs [5]. These data are reassuring for the millions of HIV-infected women receiving ARVs and desiring effective contraception. The apparent lack of significant interaction between DMPA and efavirenz is especially important, providing an effective contraceptive option for women receiving a drug with potential teratogenic effects for whom additional effective contraception in combination with barrier methods is recommended [22].

Weight changes in the current study were quite variable, ranging from a nearly 27-pound loss to a 21-pound gain over the 12-week study. The reason for the variability between study arms is not clear. In a study of HIV-uninfected women, DMPA users were found to have a mean increase in weight of 6.1 kg (13.4 pounds) after 30 months of use, an increase in fat mass, and an increase in the ratio of central to peripheral fat mass [23]. Women studied over the same period not using hormonal contraception had no significant changes in weight, fat mass, or fat distribution. Thus, long-term use of DMPA is associated with increases in weight and fat redistribution, which may be exacerbated in HIV-infected women by use of ARVl agents.

One area not assessed in this study is other metabolic effects of DMPA, which may interact with or intensify the effects of ARV agents. Long-term use of DMPA has been associated with reversible decreased bone mineral density in HIV-uninfected populations [24]. Hip and spine bone mineral density decreased about 3% at 12 months of use and 5.7% at 24 months among women on DMPA compared to changes of under 0.9% among women not on DMPA [25]. Both decreased bone mineral density and fat redistribution have been reported with HIV

infection and ARV use [26,27], suggesting that effects on these parameters should be evaluated further in studies of HIV-infected women who choose to use DMPA for contraception.

These data suggest that DMPA is well-tolerated and effective for contraception in the short-term among HIV-infected women on selected ARV regimens. These data should be reassuring to women desiring effective contraception while on antiretroviral therapy. However, much work remains. More detailed studies of the effects of long term use of DMPA among HIV-infected women with specific attention to HIV RNA levels, clinical disease progression, and metabolic effects are warranted. In addition, this study evaluated a limited number of antiretroviral agents. More recently approved protease inhibitors are being used by the majority of women and need to be studied for their potential interactions with DMPA that may affect both antiretroviral and contraceptive efficacy.

Acknowledgements

This study was supported in part by the Adult AIDS Clinical Trials Group funded by the National Institute of Allergy and Infectious Diseases (grant AI68363), the Pediatric AIDS Clinical Trials Group of the National Institute for Allergy and Infectious Diseases, and the Pediatric/Perinatal HIV Clinical Trials Network of the National Institute for Child Health and Human Development (contract N01HD33345), (grants: UO1 AI27658 and 5M01 RR00044 to the University of Rochester Medical Center; AI38858 and U01 AI38855 to the Harvard School of Public Health; AI27664 to University of Washington School of Medicine; N01-HD-3-3345 to the University of Southern California School of Medicine; IU01AI3844 and M01 RR05096 to the Tulane University School of Medicine and the Tulane-LSU-Charity Hospital General Clinical Research Center). The following individuals and sites assisted in conducting A5093: Lorraine Sanchez-Keeland PA-C and Hannah Edmondson-Melancon, RN, MPH, University of Southern California (grant # AI27673), Kenneth Rich MD, Mark Vajaranant MD, Maureen Haak RN, Julia Camacho RN, University of Illinois, Chicago (contract NO1-HD33345), Richard Reichman, MD, Jane A. Reid, RNc, MS, University of Rochester (grant #s AI27658, M01 RR00044), Mobeen Rathore MD, Lucia Martinez MD, Ayesha Mirza MD, Ana Alvarez MD, University of Florida Health Science Center, Jacksonville (contract NO1-HD33345), William O'Brien MD,MS, Gerianne Casey RN, University of Texas Medical Branch, Galveston (grant # AI32782), Kenneth Fife MD, PhD, Janet Hernandez RN, Indiana University (grant #s AI25859 and M01RR000750), Donna Mildvan MD, Gwendolyn D. Costantini FNP, Beth Israel Medical Center (grant # AI46370), Mary Jo O'Sullivan MD, Gwendolyn Scott MD, University of Miami (grant # AI69451), N. Jeanne Conley RN, Jane Hitti MD, University of Washington (grant #s AI27644 and AI069434, contract HD33612), Cathi Basler MSN, Monica Carten MD, Colorado AIDS Clinical Trials Unit (grant #s U01-AI32783, CFAR P30-AI45008), Robert Gross MD, Kathryn Maffei RN, University of Pennsylvania (grant #s AI32783, P30-AI45008), Deb Goldman ARNP, Sharon Martens ARNP, Children's Hospital and Medical Center (grant # 27644 and contract N01-33345), Robert A. Salata MD, Jane Baum RSN, RN, Case Western Reserve University (grant # AI69501), Kristine Patterson MD, Susan Pedersen RN, University of North Carolina, Chapel Hill (grant #s RR00046, AI50410, AI69423), Chrisa Hunnewell ANP and Madeline Torres RN, BSN, Columbia Collaborative HIV/AIDS Clinical Trials Unit (grant # AI69470), Russell Van Dyke MD, Rebecca Clark MD, PhD, Tulane/LSU Pediatric AIDS Clinical Trials Unit (grant #s AI32913, M01-RR05096), Diane Allen RN, Tamika Watson RN, Children's Hospital of Michigan, Detroit (contract HD33612).

Support for analysis of MPA levels was provided through a grant from Pfizer, Inc. Additional research funding was provided by the following companies: Pfizer Inc., Bristol-Myers Squibb Company, Inc., Boehringer-Ingelheim Corporation, and Merck and Company, Inc.

References

1. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2004. 2005. p. 1-46.Also available at: http://www.cdc.gov/hiv/stats/hasrlink.htm
2. UNAIDS. AIDS epidemic update : December 2005. Available at http://www.who.int/hiv/epi-update2005_en.pdf
3. Lande, RE. New era for injectables; Population Rep. 1995. p. 1-32.Available at http://www.infoforhealth.org/pr/online.shtml
4. Lavreys L, Baeten JM, Kreiss JK, Richardson BA, Chohan BH, Hassan W, et al. Injectable contraceptive use and genital ulcer diseases during the early phase of HIV-1 infection increase plasma virus load in women. J Infect Dis 2004;189:303–311. [PubMed: 14722896]

5. Cohn SE, Park J-G, Watts DH, et al. Depot medroxyprogesterone in women on antiretroviral therapy : Effective contraception and lack of clinically significant interactions. Clin Pharmacol Ther 2007;81:222–227. [PubMed: 17192768]
6. Yen-Lieberman B, Brambilla D, Jackson B, et al. Evaluation of a quality assurance program for quantitation of human immunodeficiency virus type 1 RNA in plasma by the AIDS Clinical Trials Group virology laboratories. J Clin Microbiol 1996;34:2695–2701. [PubMed: 8897167]
7. Calvelli T, Denny TN, Paxton H, Gelman R, Kagan J. Guideline for flow cytometric immunophenotyping: a report from the National Institute of Allergy and Infectious Diseases, Division of AIDS. Cytometry 1993;14:702–715. [PubMed: 8243200]
8. Sangi-Haghpeykar H, Poindexter AN III, Bateman L, Ditmore JR. Experiences of injectable contraceptive users in an urban setting. Obstet Gynecol 1996;88:227–233. [PubMed: 8692507]
9. World Health Organization. Facts about once-a-month injectable contraceptives: Memorandum from a WHO meeting. Bull WHO 1993;71:677–689. [PubMed: 8313486]
10. World Health Organization. Multinational comparative clinical trial of long-acting injectable contraceptives: Norethisterone enanthate given in two dosage reimens and depot-medroxyprogesteron acetate: Final report. Contraception 1983;28:1–20. [PubMed: 6226488]
11. Schwallie P, Assenzo J. Contraceptive use efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. Fertil Steril 1973;24:331–339. [PubMed: 4698589]
12. Fraser I, Dennerstein G. Depo-Provera use in an Australian metropolitan practice. Med J Australia 1994;160:553–556. [PubMed: 8164553]
13. Westhoff C, Truman C, Kalmuss D, et al. Depressive symptoms and Depo-Provera. Contraception 1998;57:237–240. [PubMed: 9649914]
14. Canto De Cetina TE, Canto P, Luna MO. Effect of counseling to improve compliance in Mexican women receiving depot-medroxyprogesterone acetate. Contraception 2001;63:143–146. [PubMed: 11368986]
15. Hubacher D, Goco N, Gonzalez B, Taylor D. Factors affecting continuation rates of DMPA. Contraception 2000;60:345–351. [PubMed: 10715369]
16. Westfall JM, Main DS, Barnard L. Continuation rates among injectable contraceptive users. Fam Plan Perspect 1996;28:275–277.
17. Potter LS, Dalberth BT, Canamar R, Betz M. Depot medroxyprogesterone acetate pioneers: a retrospective study at a North Carolina health department. Contraception 1997;56:305–312. [PubMed: 9437559]
18. Lavreys L, Baeten JM, Martin HL Jr, et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. AIDS 2004;18:695–697. [PubMed: 15090778]
19. Saada M, Le Chenadec J, Berrebi A, et al. Pregnancy and progression to AIDS: results of the French prospective cohorts. AIDS 2000;14:2355–2360. [PubMed: 11089624]
20. Weisser M, Rudin C, Battegay M, Pfluger D, Kully C, Egger M. Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. J Acquir Immune Defic Syndr Hum Retrovirol 1998;15:404–410. [PubMed: 9562042]
21. Cejtin HE, Jacobson L, Springer G, et al. Effect of hormonal contraceptive use on plasma HIV-1 RNA levels among HIV-infected women. AIDS 2003;17:1702–1704. [PubMed: 12853757]
22. Efavirenz package insert. [Accessed on 1/17/2007]. available at http://www.bms.com/cgi-bin/anybin.pl?sql=select+PPI+from+TB_PRODUCT_PPI+where+PPI_SEQ=94&key=PPI
23. Clark MK, Dillon JS, Sowers M, Nichols S. Weight, fat mass, and central distribution of fat increase when women use depot-medroxyprogesterone acetate for contraception. Internat J Obesity 2005;29:1252–1258.
24. Scholes D, LaCroix AZ, Ichikawa LE, Barlow We, Ott SM. Injectable hormone contraception and bone density: results from a prospective study. Epidemiology 2002;13:581–587. [PubMed: 12192229]
25. Clark MK, Sowers MF, Nichols S, Levy B. Bone mineral density changes over two years in first-time users of depot medroxyprogesterone acetate. Fertil Steril 2004;82:1580–1586. [PubMed: 15589863]

26. Dolan SE, Huang JS, Killilea KM, Sullivan MP, Aliabadi N, Grinspoon S. Reduced bone density in HIV-infected women. AIDS 2004;18:475–483. [PubMed: 15090800]

27. Study of Fat Redistribution and metabolic changes in HIV infection (FRAM). Fat distribution in women with HIV infection. J Acquir Immune Defic Syndr 2006;42:562–571. [PubMed: 16837863]

Table 1

Characteristics of women at enrollment by antiretroviral treatment arm

	Control* n=16	Nelfinavir-based n= 21	Efavirenz-based n= 17	Nevirapine-based n= 16
Median age [range]	33 [22–46]	35[22–45]	37[23–41]	35[30–43]
Race/ethnicity				
Caucasian	1 (6%)	2 (10%)	6 (35%)	4 (25%)
African American	13 (81%)	11 (52%)	5 (29%)	9 (56%)
Hispanic	2 (13%)	6 (29%)	4 (24%)	3 (19%)
Native American	0	1 (5%)	2 (12%)	0
Asian	0	1 (5%)	0	0
Injection drug use				
Never	12 (75%)	16 (76%)	13(76%)	12 (75%)
Currently	1 (6%)	0	0	0
Previously	3 (19%)	5 (24%)	4 (24%)	4 (25%)
Median $\log_{10}$ HIV RNA level [range]	3.07 [BLD-4.12]	2.24 [BLD-4.01]	< 1.60 [BLD- 3.35]	2.30 [BLD-3.65]
Median CD4+ cell count [range] (cells/uL)	704 [328–1255]	718 [265–1141]	725 [367–1782]	620 [257–1085]
Median [range] duration of current ARV regimen, weeks		92 [4–422]	126 [16–244]	45 [4–293]
Abnormal menstrual cycles#	2/15	3/21	2/17	2/15

*Women in the control arm were on no ARV therapy or on ARTI r only. Women in all other arms were on two or more nucleoside agents along with the drug listed.

BLD= below limit of detection, which varied from 50 to 400 copies/mL.

#Cycle length < 25 days, > 35 days, or described as irregular.

Table 2

Toxicities evaluated to be possibly, probably, or definitely related to DMPA administration; all were graded as mild to moderate severity.

Toxicity	Number of women with event (%)
Abnormal bleeding	9 (12.9)
Headache	3 (4.3)
Abdominal pain	2 (2.9)
Anorexia	2 (2.9)
Fatigue	2 (2.9)
Insomnia	2 (2.9)
Mood changes	2 (2.9)
Body odor changes	1 (1.4)
Carpal tunnel syndrome	1 (1.4)
Dizziness	1 (1.4)
Excess salivation	1 (1.4)
Low platelet count (65,000/mm^3)	1 (1.4)
Malaise	1 (1.4)
Nausea	1 (1.4)
Vaginal dryness	1 (1.4)

Table 3

Proportion of subjects with HIV RNA levels <400 copies/mL and median CD4+ cell counts at each sampling

HIV RNA < 400 copies/mL	Control* n=16	Nelfinavir n= 21	Efavirenz n= 17	Nevirapine n= 16
Baseline	7/15 (47%)	19/21 (90%)	16/17 (94%)	13/16 (81%)
Week 2	5/14 (36%)	15/21 (71%)	16/17 (94%)	11/13 (85%)
Week 4	7/16 (44%)	12/19 (63%)	16/17 (94%)	14/16 (88%)
Week 8	6/13 (46%)	13/16 (81%)	15/16 (94%)	8/10 (80%)
Week 12	6/15 (40%)	15/17 (88%)	15/16 (94%)	12/12 (100%)
Median CD4+ cell count (cells/uL)				
Baseline	704	718	725	620
Week 4	692	620	650	671
Week 12	668	702	774	740

*Women in the control arm were on no ARVl therapy or on NRTI only. Women in all other arms were on two or more nucleoside agents along with the drug listed.

No significant differences were seen between visits within each arm or in the group overall.