A Semimechanistic Pharmacokinetic Model for Depot Medroxyprogesterone Acetate and Drug–Drug Interactions With Antiretroviral and Antituberculosis Treatment

Jose Francis[1], Rosie Mngqibisa[2], Helen McIlleron[1], Michelle A Kendall[3], Xingye Wu[3], Kelly E. Dooley[4], Cynthia Firnhaber[5], Catherine Godfrey[6], Susan E. Cohn[7,†], and Paolo Denti[1,*,†] the A5093, A5283, A5338 study teams

Depot medroxyprogesterone acetate is an injectable hormonal contraceptive, widely used by women of childbearing potential living with HIV and/or tuberculosis. As medroxyprogesterone acetate is a cytochrome P450 (CYP3A4) substrate, drug–drug interactions (DDIs) with antiretroviral or antituberculosis treatment may lead to subtherapeutic medroxyprogesterone acetate concentrations (< 0.1 ng/mL), resulting in contraception failure, when depot medroxyprogesterone is dosed at 12-week intervals. A pooled population pharmacokinetic analysis with 744 plasma medroxyprogesterone acetate concentrations from 138 women treated with depot medroxyprogesterone and antiretroviral/antituberculosis treatment across three clinical trials was performed. Monte Carlo simulations were performed to predict the percentage of participants with subtherapeutic medroxyprogesterone acetate concentrations and to derive alternative dosing strategies. Medroxyprogesterone acetate clearance increased by 24.7% with efavirenz coadministration. Efavirenz plus antituberculosis treatment (rifampicin + isoniazid) increased clearance by 52.4%. Conversely, lopinavir/ritonavir and nelfinavir decreased clearance (28.7% and 15.8%, respectively), but lopinavir/ritonavir also accelerated medroxyprogesterone acetate's appearance into the systemic circulation, thus shortening the terminal half-life. A higher risk of subtherapeutic medroxyprogesterone acetate concentrations at Week 12 was predicted on a typical 60-kg woman on efavirenz (4.99%) and efavirenz with antituberculosis treatment (6.08%) when compared with medroxyprogesterone acetate alone (2.91%). This risk increased in women with higher body weight. Simulations show that re-dosing every 8 to 10 weeks circumvents the risk of subtherapeutic medroxyprogesterone acetate exposure associated with these DDIs. Dosing depot medroxyprogesterone every 8 to 10 weeks should eliminate the risk of subtherapeutic medroxyprogesterone acetate exposure caused by coadministered efavirenz and/or antituberculosis treatment, thus reducing the risk of contraceptive failure.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The pharmacokinetics (PK) of depot medroxyprogesterone has not been well characterized, and there is limited evidence regarding the impact of various drug–drug interactions affecting medroxyprogesterone acetate exposure.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study provides a mechanistic model characterizing the PK of depot medroxyprogesterone and the effect of drug–drug interactions and body weight. It was used to identify patients at risk of low concentrations and suggest dosing adjustments.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Medroxyprogesterone acetate clearance was increased by 24.7% and 52.4% with efavirenz and efavirenz plus antituberculosis treatment (rifampicin + isoniazid), respectively. An increased risk of subtherapeutic medroxyprogesterone acetate concentrations at Week 12 was predicted for a typical 60-kg woman on efavirenz (4.99%) and efavirenz with antituberculosis treatment (6.08%) when compared with medroxyprogesterone acetate alone (2.91%). This risk appears worse in women with higher body weight. Simulations show that re-dosing every 8 to 10 weeks would help to overcome these risks.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The study identified the factors that can lead to treatment failure after depot medroxyprogesterone administration in women. The simulations demonstrated that dosing depot medroxyprogesterone every 8 to 10 weeks will help to overcome the subtherapeutic exposure associated with drug–drug interactions and body weight. These findings will guide to minimize the contraception failure associated with subtherapeutic medroxyprogesterone acetate exposure in real-world settings.

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[1]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; [2]Enhancing Care Foundation, Durban International CRS, Wentworth Hospital, Durban, South Africa; [3]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [4]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [5]Division of Infectious Diseases, Department of Medicine, Anschutz Medical Center, University of Colorado, Aurora, Colorado, USA; [6]Division of AIDS, National Institutes of Allergy and Infectious Diseases, Bethesda, Maryland, USA; [7]Division of Infectious Diseases, Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, USA.
*Correspondence: Paolo Denti (paolo.denti@uct.ac.za)
†Both authors contributed equally

Effective contraception is an important concern for millions of women of reproductive age living with HIV worldwide, and it decreases the risk of perinatal HIV transmission and maternal mortality.[1] In sub-Saharan Africa, adolescent girls and young women accounted for 26% of new HIV infections among adults.[2] People living with HIV are 19 times more likely to develop active tuberculosis than the general population,[3] and tuberculosis is the leading cause of death among people living with HIV. Therefore, in establishing effective contraceptive options for women living with HIV, consideration should be given to tuberculosis coinfection.

Depot medroxyprogesterone acetate is a progesterone-based contraceptive injection used globally.[4] Depot medroxyprogesterone, a microcrystalline suspension given as a 150-mg intramuscular dose, produces medroxyprogesterone acetate concentrations that remain above the therapeutic target (> 0.1 ng/mL) needed to inhibit ovulation for up to 12 weeks.[5] Medroxyprogesterone acetate is primarily metabolized by cytochrome P450 (CYP) 3A4 isoenzyme.[6] Many antiretroviral and antituberculosis drugs inhibit or induce CYP3A4, thus potentially affecting systemic medroxyprogesterone acetate concentrations.[7,8] Rifampicin, the mainstay for the treatment of tuberculosis, is a potent inducer of CYP3A4.[9] Efavirenz induces CYP3A4; whereas ritonavir, nelfinavir, and isoniazid (coadministered with rifampicin) are net inhibitors.[10] These drug–drug interactions (DDIs) may lead to suboptimal medroxyprogesterone acetate concentrations, thereby potentially failing to suppress ovulation and prevent pregnancy. Lopinavir is a mild inhibitor of CYP3A4 compared with ritonavir, but it is routinely boosted with ritonavir.[11] The effect of lopinavir/ritonavir on P-glycoprotein is time dependent, with inhibition occurring with acute exposure, but extended exposure results in induction.[12] Studies have reported that medroxyprogesterone acetate exposures are increased when coadministered with lopinavir/ritonavir–based antiretroviral therapy (ART) and reduced when coadministered with efavirenz, and to an even larger extent when efavirenz is administered along with rifampicin-based tuberculosis treatment.[13–16] Antiretrovirals like nevirapine and nelfinavir were reported to have minimal impact on medroxyprogesterone acetate exposure.[14]

The purpose of this analysis was to use a model-based approach, pooling available pharmacokinetic data from women given depot medroxyprogesterone, to characterize the medroxyprogesterone acetate pharmacokinetics and to quantify the effects of various DDIs after adjusting for possible confounders. By pooling individual participant data (IPD) from different studies, we leveraged the increased sample size and more diverse study population to quantify the extent of drug–drug interactions and other covariates more robustly than in the individual primary studies. The model created allowed the use of simulations to identify women at risk of subtherapeutic medroxyprogesterone acetate and to derive alternative dosing recommendations to overcome the subtherapeutic medroxyprogesterone acetate exposure to prevent treatment failure.

METHODS

Study design

The clinical data from three clinical studies investigating the pharmacokinetics of depot medroxyprogesterone conducted by the AIDS Clinical Trial Group (ACTG) were pooled for this analysis; namely, A5093, A5283, and A5338.[13–15] All study participants were women of childbearing potential living with HIV. A 150-mg intramuscular injection of depot medroxyprogesterone (Depo-Provera, Pfizer) was administered at study entry after a negative pregnancy test. Pharmacokinetic assessment involved plasma drug concentration sampling at pre-dose, 2, 4, 6, 8, 10, and 12 weeks after dose administration in all three studies. Information about study participant enrollment, study procedures, ethical considerations, and medroxyprogesterone acetate concentration estimation are given in detail in the respective study publications.[13–15]

Population pharmacokinetic modeling

Pharmacokinetic data of medroxyprogesterone acetate was analyzed using nonlinear mixed-effects modeling with NONMEM software (version 7.4.3, Ellicott City, MD, USA) using the algorithm first-order conditional estimation with eta-epsilon interaction (FOCE-INTER).[17] Various tools such as Perl speaks NONMEM, Pirana, Xpose, and R software were used to support model development and generate diagnostics.[18,19] Pharmacokinetic profiles were reconstructed across various DDI scenarios and body weight using the ordinary differential equation solver with the Berkeley Madonna software (version 9.2.1, Berkeley, CA, USA).[20]

Several structural models were tested, from one-compartment to two-compartment disposition, with first-order elimination to describe the pharmacokinetics of medroxyprogesterone acetate. Monophasic/biphasic absorption pathways were tested to characterize the release of medroxyprogesterone acetate from the site of injection into the systemic circulation. Semimechanistic approaches for drug absorption such as transit compartment absorption and deconvolution method using the sum of inverse Gaussian functions were then tested.[21–23]

Allometric scaling was used to adjust for the effect of body weight on disposition parameters with allometric exponents fixed to 0.75 for clearance (CL) parameters and 1 for volumes of distribution.[24] Besides total body weight, fat-free mass and normal fat mass were tested as alternative descriptors to characterize the size of drug-clearing organs and blood flows through them and to explore the possibility that medroxyprogesterone acetate may distribute differentially between muscle or fat.[25] Between-subject variability and between-occasion variability were assumed to be log-normally distributed, except for the random effects characterizing the fraction of the drug absorbed, for which a logit transformation was used.[26] A combined additive and proportional error model was used to describe residual unexplained variability. All samples with concentrations below the limit of quantification (BLQ) were handled with the M6 method

as described by Beal,[27] i.e., BLQ samples were replaced with half of the lower limit of quantification (LLOQ) value, except for consecutive values in a series, where the trailing BLQ values were omitted from the model fit but were included in simulation-based diagnostic plots, such as visual predictive checks (VPCS). Additionally, the additive error for these imputed values was inflated by half of the imputed value (i.e., by LLOQ/2) to allow for extra uncertainty due to the imputation (and proportionally to the size of the LLOQ for that specific assay). Finally, the additive error for all samples obtained from a specific assay was bound to be at least 20% of the LLOQ of that assay.

Implausible concentrations (single samples within a profile) were initially identified based on graphical exploration of the data and temporarily excluded from model development. To then confirm their exclusion from the final model, we used a criterion based on the absolute value of conditional weighted residual (CWRES) being larger than 3. CWRES follow a normal distribution with mean 0 and variance 1; hence, for a model that fits adequately, less than 0.3% of data is expected to have $|CWRES| > 3$.[28]

Model development and inclusion of parameter-covariate relationships were guided by drops in the NONMEM objective function value, (OFV, assumed to be χ^2-distributed and thus using a 3.84-point drop as significant at $P < 0.05$ for the inclusion of a single parameter in a nested model), an inspection of diagnostic plots including VPC, and considering at each step the physiological and scientific plausibility of proposed modification.[29,30] Robustness of the final pharmacokinetic model estimates was evaluated using the sampling importance resampling method.[31] Monte Carlo simulations (n = 10,000) based on the final model were used to calculate the percentage of participants falling below the therapeutic target of 0.1 ng/mL after either a single or five 12-weekly depot medroxyprogesterone injections across various DDI scenarios and body weights. Subsequently, alternative dosing schedules were simulated to overcome the risk of subtherapeutic medroxyprogesterone acetate exposure across different body weights and concomitant medications.

RESULTS

Study population

The IPD population pharmacokinetic analysis included 138 patients and 744 drug concentration observations pooled from three clinical studies of depot medroxyprogesterone. Of these, concentrations in 4 (< 1%) samples were BLQ. All preinjection samples (n = 121) and outlying observations deemed implausible (as detailed in methods) or samples with missing dosing/sampling times (n = 52) were excluded from the analysis. Median body weight and age were 62.5 kg (range: 41.0–125.0) and 34 years (range: 15–47), respectively. More details on the participants and their demographic characteristics are presented in **Table 1**.

Population pharmacokinetics of medroxyprogesterone acetate

A one-compartment model with first-order elimination well characterized the disposition of medroxyprogesterone acetate. In a typical patient weighing 62.5 kg, mean value of apparent clearance was 47.2 L/h (95% confidence interval: 43.1; 51.5). Allometric scaling using total body weight was included in the model for all disposition parameters to adjust for differences in body weight (objective function value reduction (ΔOFV) of 17 and 13 points, $P < 0.001$ for CL and volume of distribution, respectively). Fat-free mass or normal fat mass were tested as alternative body size descriptors instead of total body weight, and a trend toward CL being better scaled with fat-free mass was detected in the model (ΔOFV = 5.6 and reduction in between-subject variability of clearance from 24.1% to 23.3%), but as the magnitude of the effect did not meet our criteria for clinical relevance, total body weight was used for simplicity. Release of medroxyprogesterone acetate from the microcrystalline suspension after the intramuscular injection was described with a biphasic absorption pathway with fast (F_{fast}, fraction available for immediate absorption) and slow (F_{slow}, fraction available for delayed absorption) release components, accounting for early release and prolonged release into the systemic circulation. A schematic illustration of the pharmacokinetic model is given in **Figure 1**. F_{fast} fraction is readily available in the absorption compartment, and it appears in the bloodstream with a first-order process with a half-life of 1.19 hours. The remaining F_{slow} fraction appears in the same absorption compartment more gradually, modeled with a series of transit compartments, which is then absorbed into the bloodstream. The F_{fast} and F_{slow} fractions were estimated to be 24% and 76%, respectively. Inclusion of the

Table 1 Distribution of patients and their characteristics across the studies

Study Name (reference) (country)	Participants (samples)	Weight (kg)	Fat-free mass (kg)	Age (years)	LLOQ (ng/mL)
A5093 (14) (United States)					
DMPA alone	16 (74)	64.5 (51.8–107.5)	40.7 (34.4–54.3)	33.0 (22.0–46.0)	0.02 ng/mL
DMPA & NFV	21 (104)	74.3 (45.3–122.9)	43.1 (31.5–55.6)	36.0 (22.0–45.0)	
DMPA & EFV	17 (95)	70.5 (41.0–116.9)	43.9 (29.3–59.9)	37.0 (27.0–41.0)	
DMPA & NVP	15 (76)	74.2 (53.1–125.0)	44.3 (33.9–56.3)	34.0 (30.0–43.0)	
A5283 (13) (United States)					
DMPA & LPV/r	25 (144)	65.3 (43.5–110.0)	41.9 (30.3–57.5)	31.0 (15.0–47.0)	0.02 ng/mL
A5338 (15) (Sub-Saharan Africa[a])					
DMPA & anti-TB treatment + EFV	44 (251)	53.7 (41.0–96.0)	36.1 (29.5–50.6)	31.5 (22.0–45.0)	0.078 ng/mL
Overall	138 (744)	62.5 (41.0–125.0)	40.7 (29.3–59.9)	34.0 (15.0–47.0)	

Weight, fat-free mass, and age are reported as median (range).
Anti-TB, antituberculosis; DMPA, depot medroxyprogesterone; EFV, efavirenz; LLOQ, lower limit of quantification; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine.
[a]Participants were recruited from South Africa, Zimbabwe, Botswana, and Kenya.

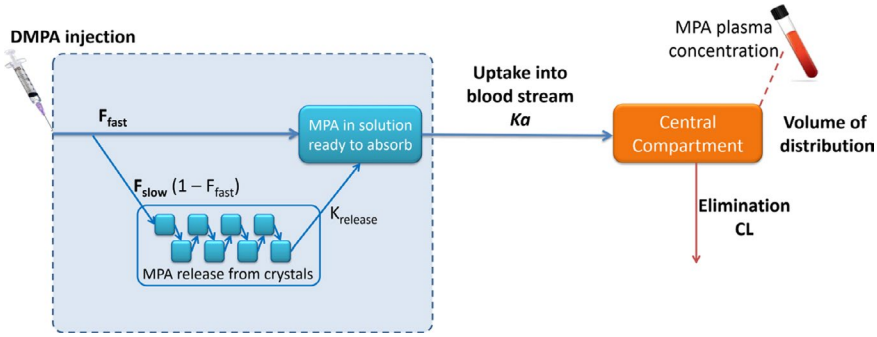

Figure 1 Schematic illustration of the final model. Semimechanistic PK model: After the injection of DMPA, the appearance of MPA in the bloodstream follows a biphasic pattern. A fraction F_{fast} is immediately available for uptake into the bloodstream, while the remaining F_{slow} slowly releases from crystals. CL, clearance; DMPA, depot medroxyprogesterone; F_{fast}, fraction available for immediate absorption; F_{slow}, fraction available for delayed absorption; *Ka*, first-order absorption rate constant; $K_{release}$, final release rate constant; MPA, medroxyprogesterone acetate; PK, pharmacokinetics.

Table 2 Final medroxyprogesterone acetate population pharmacokinetic parameter estimates

Parameter	Typical Value	95% CI	BSV[+]/BOV[++]	95% CI
Clearance (CL) (L/hour)[a]	47.2	43.1; 51.5	24.2%[+]	21.5; 27.7
Volume of distribution (L)[a]	8910	7240; 10500	—	
Fraction of medroxyprogesterone acetate available for immediate absorption (F_{fast}) (%)	24	20.5; 26.9	0.203[b++]	0.11; 0.321
Fraction of medroxyprogesterone acetate in delayed-release crystals (F_{slow}) (%) (1-F_{fast})	76			
First-order absorption rate constant (Ka) (1/day)	0.578	0.358; 0.871	—	—
Half-life (days)[c]	1.19 days			
Mean transit time for release from crystals (days)	11.6	10.3; 13.1	45.5%[++]	35.1; 58.6
Number of transit compartments for release from crystals	0.954	0.503; 1.45	—	—
Final release rate constant - $K_{release}$ (1/day)	0.0193	0.0168; 0.0223	76.9%[++]	69.3; 86.6
Half-life (days)[c]	36 days			
Nelfinavir on CL (%)	−15.8	−5.16; −24.9	—	—
Efavirenz on CL (%)	+24.7	9.78; 43.2	—	—
Lopinavir/r on CL (%)	−28.7	−36.8; −69.5	—	—
Anti-TB treatment + Efavirenz on CL (%)	+52.4	−19.9; −36.3	—	—
Lopinavir/r on $K_{release}$ (%)	+107	54.5; 184.2	—	—
Additive error (ng/mL)[d]	0.0147	0.00409; 0.0284	—	—
Proportional Error (%)	17.7	16.5; 18.9	—	—

BSV & BOV are expressed as an approximate coefficient of variation (% CV).
95% CI of parameter estimates computed with sampling importance resampling (SIR) on the final model.
BOV, between-occasion variability; BSV, between-subject variability; CI, confidence interval; —, not applicable; +, BSV; ++, BOV.
[a]The typical values of clearance and volume of distribution were allometrically scaled with body weight, and the typical values reported are for a study participant with a body weight of 62.5 kg. [b]The standard deviation reported in logit space. [c]The half-life is derived from the value of the rate constant and calculated using the formula, half-life = logn(2)/(rate constant). [d]The value of the additive component of the error was obtained as 20% of the lower limit of quantification (LLOQ), plus a value estimated in the model, which is reported in the table. Given the values of LLOQ for the different assays, the resulting additive errors were 0.0187 (0.0081–0.0324) ng/mL for Study A5093 and A5283, and 0.0303 (0.0197–0.044) ng/mL for Study A5338.

F_{fast} fraction significantly improved the model fit (ΔOFV = 136, $P < 0.001$).

Final pharmacokinetic parameter estimates are presented in **Table 2**, and a VPC stratified by study/treatment arm is provided in **Figure 2**, showing an adequate model fit to the pharmacokinetic data.

Drug–drug interactions

Coadministration of continuation-phase antituberculosis treatment (rifampicin plus isoniazid) and efavirenz-based ART in women living with HIV and tuberculosis significantly increased the clearance of medroxyprogesterone acetate by 52.4%, thereby reducing exposure (ΔOFV = 3 points, $P < 0.001$). Without

antituberculosis treatment, efavirenz-based ART increased the clearance of medroxyprogesterone acetate by 24.7% (ΔOFV = 6.4, $P < 0.01$). Nevirapine-based ART did not alter medroxyprogesterone acetate exposure. Coadministration of lopinavir/ritonavir-based and nelfinavir-based ART decreased medroxyprogesterone acetate clearance by 28.7% (ΔOFV = 18, $P < 0.001$) and 15.7% (ΔOFV = 4.2, $P < 0.05$), respectively. The participants on lopinavir/ritonavir cotreatment were also found to have a two-fold faster rate of release of medroxyprogesterone acetate from the slow-release component (final release rate constant) into the systemic circulation (ΔOFV = 10.4, $P < 0.01$). Since release from the slow-release component is the rate-limiting process in the pharmacokinetics of depot medroxyprogesterone (flip-flop kinetics), this shortened the terminal half-life of medroxyprogesterone acetate in plasma. **Figure 3** shows simulated pharmacokinetic profiles for the various DDIs and bodyweights. After adjusting for body weight and DDIs, no between-study differences were observed in the final model.

Monte-Carlo simulations of the final model

Monte Carlo simulations were performed using the final model to calculate the percentage of study participants who fell below the purported therapeutic threshold of 0.1 ng/mL of medroxyprogesterone acetate at 12 and 60 weeks of 12-weekly depot medroxyprogesterone injections (to evaluate the exposure after single or repeated dosing) (**Table 3**).

The model predicted that a typical 60-kg participant (62.5 kg is the median body weight in the study) administered depot medroxyprogesterone alone has a 2.91% chance of falling below 0.1 ng/mL at 12 weeks, and this risk is predicted to increase to 4.72% for a 120-kg person. Simulations proved that the risk of falling below the therapeutic threshold after five repeated doses remained similar to that of the first dose.

Coadministration of nelfinavir slightly lowers the chances of falling below the therapeutic threshold. On the contrary, a typical 60-kg woman cotreated with lopinavir/ritonavir had a 7.61% probability of falling below the therapeutic threshold. Cotreatment with efavirenz or efavirenz with rifampicin/isoniazid–based antituberculosis treatment presents a risk of 4.99% and 6.08%, respectively. These risks are exacerbated with higher body weight: For a 120-kg participant, the probability increased to 8.03% or 12.02% for cotreatment with efavirenz or antituberculosis treatment plus efavirenz, respectively. The effects of drug–drug interactions and body weight are depicted in Supplementary **Figure 1** (**S1**).

Though the probability of falling below the purported therapeutic threshold was not alarming, we performed simulations to design alternative dosing regimens to reduce the risk of falling below the therapeutic threshold. The model predicts that the probability of falling below the therapeutic threshold is <1% if the participants are re-dosed either at 8-week or 10-week intervals when participants are cotreated with efavirenz or efavirenz with antituberculosis drugs, demonstrated in Supplementary **Figure 2** (**S2**).

DISCUSSION

In this IPD-pooled population pharmacokinetic analysis of depot medroxyprogesterone, we characterized the pharmacokinetics of medroxyprogesterone acetate and quantified the effect of commonly prescribed antiretrovirals and first-line antituberculosis treatment on medroxyprogesterone acetate exposure. To the best of our knowledge, this is the first population pharmacokinetic

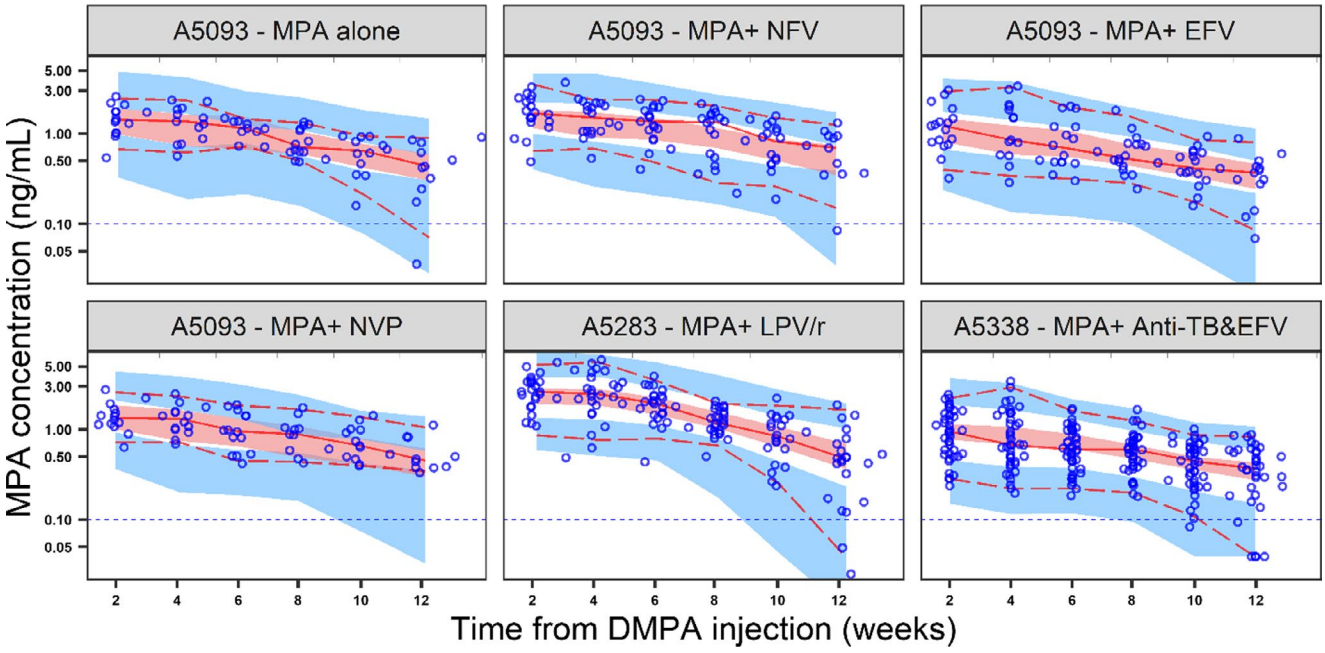

Figure 2 Visual predictive check of MPA (medroxyprogesterone acetate) concentrations (log scale) vs. time, stratified by study, and treatment arm. The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the 90% confidence intervals for the same percentiles, as predicted by the model. The blue horizontal dashed line denotes the therapeutic threshold (0.1 ng/mL). DMPA, depot medroxyprogesterone; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine; TB, tuberculosis.

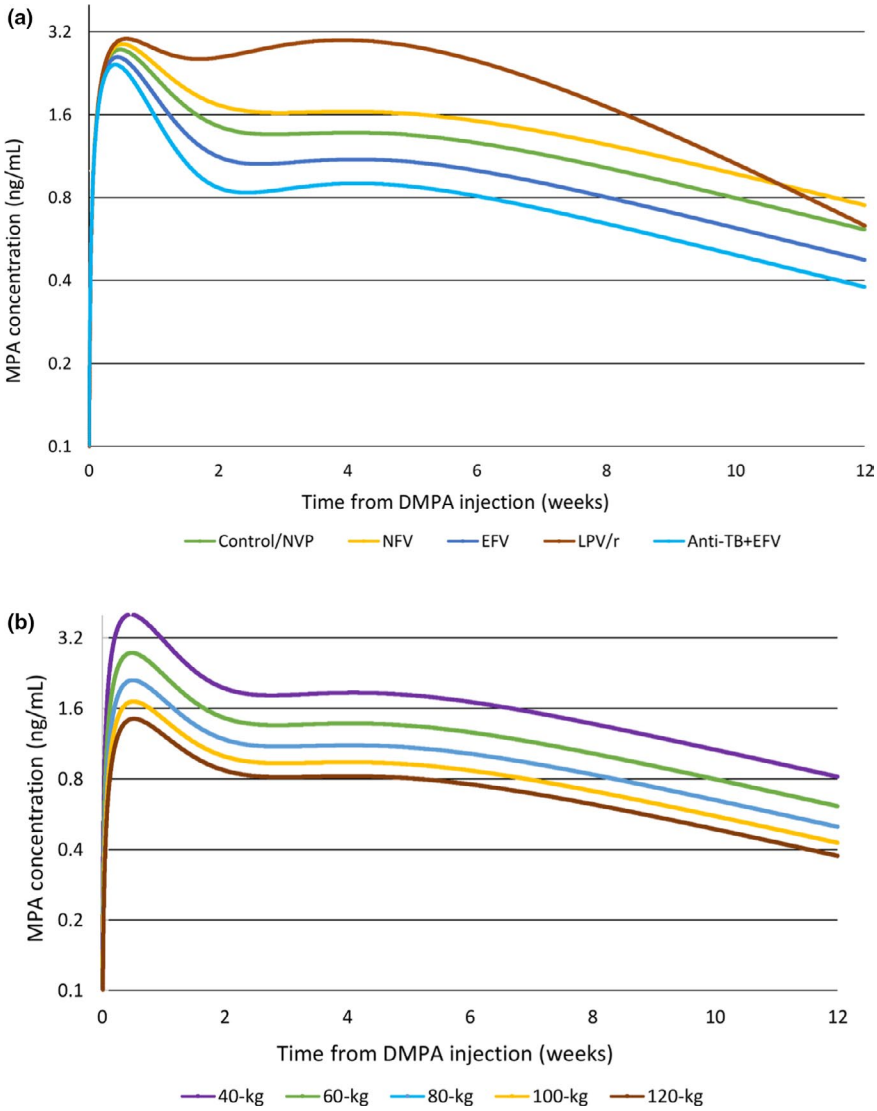

Figure 3 The pharmacokinetic profile reconstructed using the parameter estimates from the model. (**a**) Typical profile for a 60-kg participant with the effect of various drug–drug interactions. (**b**) Typical profile with the effect of body weight on MPA exposure in the control arm (DMPA alone). DMPA, depot medroxyprogesterone; EFV, efavirenz; LPV/r, lopinavir/ritonavir; MPA medroxyprogesterone acetate; NFV, nelfinavir; NVP, nevirapine; TB, tuberculosis.

model of depot medroxyprogesterone and the largest analysis focusing on DDIs of medroxyprogesterone acetate with antiretrovirals and rifampicin to date, combining 744 concentrations from 138 adult women from three clinical trials across North America (68%) and sub-Saharan Africa (32%). The pooling of individual participant data allowed us to re-evaluate and characterize the time course of medroxyprogesterone acetate in the body and to quantify the various DDIs more robustly and reliably than in the single contributory studies.

The primary aim of this pooled analysis was to characterize the effect of nelfinavir-based, efavirenz-based, nevirapine-based, and lopinavir/ritonavir–based antiretroviral treatment and antituberculosis treatment containing rifampicin/isoniazid on medroxyprogesterone acetate exposure. Medroxyprogesterone acetate exposure is a key determinant of the depot medroxyprogesterone contraceptive effect, as it is reported that ovulation resumes when medroxyprogesterone acetate blood concentrations fall below < 0.1 ng/mL.[5] Therefore, a decrease in concentration may increase the risk of unplanned pregnancies.

Efavirenz with antituberculosis cotreatment and efavirenz alone were found to increase the clearance of medroxyprogesterone acetate by 52.4% and 24.7%, respectively, thus reducing exposure, attributed to the induction of CYP3A4 by rifampicin and efavirenz. As the alternatives for long-acting contraceptive choices are limited in sub-Saharan Africa, drugs that adversely impact depot medroxyprogesterone's efficacy, including most prominently those drugs used to treat HIV or tuberculosis, can pose serious challenges to women in the region. Previous noncompartmental analyses reported by Nanda *et al.* and Cohn *et al.* (data included in this pooled analysis) reported no significant difference in medroxyprogesterone acetate exposures when given with efavirenz.[14,16] This IPD meta-analysis characterized semimechanistically the absorption

Table 3 Percentage of participants with MPA concentration < 0.1 ng/mL at 12 and 60 weeks

	The typical participant with body weight									
	40-kg women		60-kg women		80-kg women		100-kg women		120-kg women	
Treatment arm	Week 12	Week 60	Week 12	Week 60	Week 12	Week 60	Week 12	Week 60	Week 12	Week 60
DMPA alone	2.31	2.30	2.91	2.89	3.94	3.88	4.23	4.08	4.72	4.48
DMPA & nelfinavir	1.63	1.63	1.69	1.68	2.50	2.46	2.38	2.33	2.67	2.56
DMPA & efavirenz	3.69	3.64	4.99	4.89	5.85	5.58	6.94	6.52	8.03	7.35
DMPA & nevirapine	2.25	2.24	3.01	2.98	3.57	3.52	4.39	4.29	4.71	4.46
DMPA & lopinavir/ritonavir	6.10	6.09	7.61	7.59	7.05	7.05	7.72	7.70	8.8	8.76
DMPA & anti-TB treatment + efavirenz	4.87	4.80	6.08	5.83	8.04	7.49	10.58	9.46	12.02	10.30

Values are reported as the percentage of simulated participants who fall below 0.1 ng/mL at 12 and 60 weeks of 12-weekly DMPA injections (n = 10,000 per group).
DMPA, depot medroxyprogesterone.

and elimination processes and further accounted for the effect of body weight on pharmacokinetics, thus providing a stronger platform to evaluate the effect of concomitant medications on medroxyprogesterone acetate exposure, as opposed to individual previous studies.

Previous reports showed that efavirenz reduces exposures of levonorgestrel and etonogestrel in drug-releasing implants.[32,33] Rifampicin is a more potent inducer of CYP3A4 than efavirenz,[34] but the additional risk of incurring subtherapeutic medroxyprogesterone acetate exposures when rifampicin is added to efavirenz had not been quantified prior to this pooled analysis.[15] Our study findings corroborate previous research demonstrating efavirenz's effects on medroxyprogesterone acetate pharmacokinetics and extend our collective knowledge in showing that rifampicin/isoniazid–based antituberculosis treatment and efavirenz coadministration can put individuals at a higher risk of unwanted pregnancies. With the current data, the induction effect of rifampicin *per se* could not be disentangled from that of efavirenz, as there were no participants receiving rifampicin alone in this analysis. Additionally, isoniazid, a CYP3A4 inhibitor given along with rifampicin as part of the antituberculosis treatment, might have mitigated the induction effect of rifampicin, and this three-way drug interaction could not be characterized here. Considering previous reports showing that rifampicin is a stronger CYP3A4 inducer than efavirenz, it could be speculated that the effect of tuberculosis treatment containing rifampicin on medroxyprogesterone acetate exposure is probably just as strong as that of efavirenz alone, if not stronger, but additional studies are warranted to investigate this further.

Nelfinavir-based and lopinavir/ritonavir–based ART were found to decrease the medroxyprogesterone acetate clearance due to their inhibition of CYP3A4. The extent of inhibition by nelfinavir was smaller compared with lopinavir/ritonavir, consistent with nelfinavir's lower CYP3A4 inhibition potential compared with lopinavir/ritonavir.[35] Lopinavir/ritonavir cotreatment was also found to accelerate the rate of release of medroxyprogesterone acetate from the crystals (final release rate constant), and thus its appearance into the systemic circulation; this ultimately resulted in a shorter terminal half-life. So, even though concentrations of medroxyprogesterone acetate in the initial period after dosing were higher in the lopinavir/ritonavir arm, the increased rate of appearance of medroxyprogesterone acetate in the bloodstream eventually resulted in decreased medroxyprogesterone acetate exposure at Week 12. The reasons for this phenomenon are unclear, but it might be related to the dual inducer/inhibitor effect of lopinavir/ritonavir on P-glycoprotein and other transporters affecting the distribution of the medroxyprogesterone acetate at the site of injection.[36] Given that all lopinavir/ritonavir data in this analysis were collected in a single study, A5283, we considered the possibility that this effect was due to a different study procedure, such as the depot medroxyprogesterone injection or formulation. However, all studies used the same protocol in terms of depot medroxyprogesterone injection, the drug formulation was the same, and A5283 was conducted at 11 different sites, thus making the possibility of a study-specific effect unlikely.

Nevirapine, a drug reported to have both inducing and inhibitory effects on CYP3A4, had no significant interaction with medroxyprogesterone acetate in our analysis. Our findings are in line with those of a study by Mouly *et al*. that also showed no induction of nevirapine on CYP3A4 enzymes.[37]

Moreover, thanks to the use of population pharmacokinetic modeling, we were able to describe the release of depot medroxyprogesterone from the formulation at the site of injection semimechanistically. Using a biphasic absorption model, we characterized release of medroxyprogesterone acetate from the microcrystalline suspension after intramuscular injection: A first-order absorption described the fast release, whereas we applied a series of transit compartments representing the slow release of the medroxyprogesterone acetate into the absorption compartment. Our model estimated that about 1/4 of the medroxyprogesterone acetate dose is available for rapid absorption into the systemic circulation, whereas the remaining 3/4 is slowly released over a few weeks, then absorbed. This produces a double-peak pharmacokinetic profile, as shown in **Figure 3**. These results are consistent with an early study on depot medroxyprogesterone by

Ortiz *et al*., where three patients were very intensively sampled after depot medroxyprogesterone administration.[38] Results from Ortiz *et al*. show a double-peak pharmacokinetic profile with rapid increase in medroxyprogesterone acetate concentration within 1–3 days after the injection and then forming a protracted peak occurring between 3 and 6 weeks, with marked variability between the three volunteers and a gradual elimination thereafter. Although in our pharmacokinetic sampling schedule, no samples were taken during the initial phase (i.e., 0–24 h after the intramuscular injection); few samples were obtained after the dose administration at 12 weeks (n = 8), when the participants were scheduled to receive the second dose according to the study protocol, and those samples were consistent with the early appearance of medroxyprogesterone acetate in the blood a few hours from the injection.

Monte Carlo simulations from the model helped us identify participants who were at risk of not attaining the therapeutic threshold of 0.1 ng/mL 12 weeks after the 1st or the 5th 12-weekly injection of depot medroxyprogesterone. Most participants treated with medroxyprogesterone acetate alone or in combination with nevirapine and nelfinavir were predicted to achieve satisfactory concentrations above the therapeutic target. However, higher-weight individuals were at a relatively higher risk of falling below the desired therapeutic concentrations. Finding that medroxyprogesterone acetate exposure is lowered in overweight and obese women is well known and described in the depot medroxyprogesterone product summary by the manufacturer.[39] The risk of falling below the Week 12 concentration of 0.1 ng/mL was higher in participants cotreated with efavirenz alone and even higher when efavirenz was given together with rifampicin-based antituberculosis drugs. Because of adverse outcomes with unintended pregnancies, alternative dosing regimens are needed to overcome this subtherapeutic exposure resulting from the DDIs. Since depot medroxyprogesterone is typically available in prefilled syringes with 150-mg/mL dosages, it appears from our simulation models that dosing depot medroxyprogesterone in women taking depot medroxyprogesterone in the setting of efavirenz and rifampicin every 8 or 10 weeks would likely overcome the risk of falling below the therapeutic limit, thereby preventing the risk of unwanted pregnancies. The 8-weekly dosing is ideal based on collection timelines for antiretroviral and antituberculosis regimens for ease of administration. This is a welcome finding, as it means that women with HIV or tuberculosis who require these medications for treatment can still receive depot medroxyprogesterone, a nearly universally available contraceptive that is easy to administer and favored by many women seeking contraception.

Limitations

Our pooled analysis has some limitations. There were only a few drug concentration observations available to characterize the early-phase absorption of medroxyprogesterone acetate into the systemic circulation. While the biphasic absorption was included considering the physiological explanation, the consistency with literature, and its statistical relevance (improvement in model fit), our data did not allow for accurately characterizing the early phase in all participants, and our findings should be confirmed in pharmacokinetic studies with intensive sampling during the initial phase of medroxyprogesterone acetate absorption (0–24 hours). Additionally, we could find no clear mechanistic explanation for the somewhat puzzling effect of lopinavir/ritonavir on medroxyprogesterone acetate exposure, and further confirmatory studies would be beneficial. Finally, based solely on the data included in this analysis, we could not reliably predict the effect of antituberculosis treatment alone (i.e., without efavirenz) on medroxyprogesterone acetate exposure. While there are good reasons to believe that women receiving depot medroxyprogesterone and antituberculosis treatment alone might also benefit from a dose adjustment in depot medroxyprogesterone, this would need to be confirmed with additional studies.

CONCLUSION

We used results from three clinical trials to develop a semimechanistic population pharmacokinetic model to describe medroxyprogesterone acetate pharmacokinetics. Coadministration of efavirenz decreases medroxyprogesterone acetate exposure, an effect enhanced by antituberculosis cotreatment containing rifampicin/isoniazid. This increases the risk of not attaining the desired therapeutic concentration at 12 weeks, particularly in patients with higher body weight. Dosing depot medroxyprogesterone every 8 to 10 weeks appears to mitigate this risk and would allow use of this popular contraceptive among women with HIV and/or tuberculosis.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTERESTS

C.G. wrote this in her capacity as a US Government employee; the views expressed should not be construed to represent those of the NIH or the Department of State. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.F., P.D., S.E.C., and R.M. wrote the manuscript. S.E.C., H.M., P.D., and R.M. designed the research. J.F. and P.D. performed the research. J.F., P.D., S.E.C., R.M., M.A.K., X.W., K.E.D., C.G., and C.F. analyzed the data.

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