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Physiologically based pharmacokinetic modelling prediction of the effects of dose adjustment in drug–drug interactions between levonorgestrel contraceptive implants and efavirenz-based ART

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Background: HIV-positive women receiving efavirenz-based ART and levonorgestrel contraceptive implants are at risk of low levonorgestrel exposure and unintended pregnancy.

Objectives: To investigate clinically applicable dose-adjustment strategies to overcome the known drug–drug interaction (DDI) between levonorgestrel and efavirenz, using a physiologically based pharmacokinetic (PBPK) modelling-based approach.

Methods: A PBPK model was qualified against clinical data to predict levonorgestrel plasma concentrations when standard-dose (150 mg) levonorgestrel implants were administered alone (control group), as well as when standard-dose or increased-dose (300 mg) levonorgestrel implants were coadministered with either 600 or 400 mg of efavirenz.

Results: No difference was seen between *in vivo* clinical and PBPK-model-simulated levonorgestrel plasma concentrations ($P > 0.05$). Simulated levonorgestrel plasma concentrations were ∼50% lower at 48 weeks post-implant-placement in virtual individuals receiving standard-dose levonorgestrel with either 600 or 400 mg of efavirenz compared with the control group (efavirenz:control geometric mean ratio = 0.42 and 0.49, respectively). Conversely, increased-dose levonorgestrel in combination with either 600 or 400 mg of efavirenz was sufficient to restore levonorgestrel concentrations to levels similar to those observed in the 150 mg levonorgestrel control group 48 weeks post-implant-placement (efavirenz:control geometric mean ratio = 0.86 and 1.03, respectively).

Conclusions: These results suggest that the clinically significant DDI between efavirenz and levonorgestrel is likely to persist despite efavirenz dose reduction, whereas dose escalation of implantable levonorgestrel may represent a successful clinical strategy to circumvent efavirenz–levonorgestrel DDIs and will be of use to inform clinical trial design to assess coadministration of efavirenz and levonorgestrel implants.

Introduction

Long-acting reversible contraception (LARC) methods such as subdermal hormonal implants offer a reversible, yet highly effective, means of long-term pregnancy prevention,[1] which can decrease mother and child morbidity and mortality,[2] especially in low- and middle-income countries (LMICs), where 99% of maternal mortality occurs.[3] The importance of family planning and access to LARC is especially vital for women living in countries where the burden of HIV is high. Worldwide, an estimated 17.8 million women aged 15 years or above were living with HIV in 2015,[4] of which ∼95% resided in LMICs.[4] In women living with HIV, effective contraception can decrease mother-to-child HIV transmission,[5] as well as pregnancy-related complications;[6] however, countries with the highest prevalence of HIV worldwide also exhibit the lowest use of contraception.[7] The WHO recommends progestin-containing implants, such as the levonorgestrel implant system (Jadelle®), as a preferred method of LARC for HIV-positive women.[8–10]

The levonorgestrel implant system consists of two sealed silastic tubes, each containing 75 mg of levonorgestrel.[11]

Drug–drug interactions (DDIs) between antiretroviral (ARV) drugs and hormonal contraceptives, including implants, have been reported.[12–17] Importantly, although efavirenz-based ART remains the preferred first-line regimen for treatment-naive patients in LMICs,[9] it has recently been concluded that efavirenz-based ART gives rise to the most clinically significant DDIs between ARVs and hormone-based contraceptives.[15] Indeed, Carten *et al.*[18] reported that coadministering efavirenz decreased the exposure of orally administered levonorgestrel emergency contraception by 56%. Furthermore, Scarsi *et al.*[13] showed that administering efavirenz-based ART in women whom were also using levonorgestrel-releasing implants caused a 47% reduction in levonorgestrel plasma concentrations, resulting in unintended pregnancies in 3 of 20 participants. These pharmacokinetic data also support retrospective clinical evaluations that demonstrated higher rates of contraceptive failure in women using progestin-releasing implants with efavirenz compared with HIV-positive women receiving other or no ARVs.[19,20] The most recent WHO guidelines for HIV treatment include an option to use a reduced dose of efavirenz (400 mg) as an alternative regimen to the standard dose of efavirenz (600 mg), once daily,[9] based upon non-inferior virological outcomes and fewer adverse events with reduced-dose efavirenz.[9,21] Nevertheless, the effect of reduced-dose efavirenz on the magnitude of change in efavirenz-related DDIs, including the interaction with levonorgestrel, has not been elucidated.

Despite the clinical importance of understanding potential ARV–LARC DDIs, information regarding such interactions is relatively sparse.[12] Over recent years, physiologically based pharmacokinetic (PBPK) modelling has been increasingly used to simulate and predict drug pharmacokinetics through the comprehensive integration of experimental data into a mathematical description of the processes regulating drug distribution.[22,23] This computational approach can simulate variability in drug exposure, facilitating prospective evaluation of DDIs and prediction of likely clinical outcomes.[24,25] Conducting prospective PBPK model-based investigations into the likely outcome of coadministering various drugs can aid clinical trial design, allowing better-informed choices when identifying the trials that are most likely to yield clinically beneficial outcomes, as well as potentially reducing the number of patients to be included in future studies.[26] Furthermore, PBPK modelling is now recognized by regulatory agencies as a method to predict DDIs and optimize dose selection during clinical investigations.[23,24]

The aim of this study was to investigate clinically applicable strategies to overcome the known DDI between levonorgestrel implants and efavirenz-based ART using a PBPK modelling-based approach. To this end, the following objectives were set. First, to use existing *in vitro* and clinical data to inform a PBPK model designed to predict DDIs between levonorgestrel and efavirenz, and to qualify this model by comparing the results generated with existing clinical data evaluating efavirenz–levonorgestrel DDIs in HIV-infected women over 48 weeks. Second, to utilize a qualified PBPK model to predict the effects of decreasing the dose of efavirenz from 600 to 400 mg once daily on levonorgestrel plasma concentrations when coadministered with standard-dose levonorgestrel implants (150 mg; 2×75 mg rods). Third, to use a qualified efavirenz–levonorgestrel PBPK model to evaluate whether increasing the levonorgestrel implant dose from 150 to 300 mg (4×75 mg rods) may overcome the efavirenz–levonorgestrel DDI.

Table 1. Physicochemical and metabolic characteristics of efavirenz and levonorgestrel used in the PBPK model

Parameter	Efavirenz	Levonorgestrel	Reference
Molecular mass (g/mol)	315.68	312.45	—
log$P_{o:w}$	4.6	NA	27
pK_a	10.2	NA	27
f_u	0.015	NA	27
B/P	0.74	NA	27
P_{app} (cm/s)	2.5×10^{-6}	NA	30
Release rate (μg/day)	NA	100 (month 1), 40 (months 2–12)	11
Volume of distribution (L/kg)	NA	1.8±0.8	52
Clearance (L/h)	NA	7.06±2.69	53
CYP1A2 CL_{int} (μL/min/pmol)	0.07	NA	36
CYP2A6 CL_{int} (μL/min/pmol)	0.08	NA	36
CYP3A4 CL_{int} (μL/min/pmol)	0.007	NA	36
CYP2B6 CL_{int} (μL/min/pmol)	0.55	NA	36
CYP3A4 Ind_{max} (fold)	6.3	NA	30
CYP3A4 $IndC_{50}$ (μM)	3.9	NA	30

log$P_{o:w}$, logarithm of the octanol–water partition coefficient; pK_a, acid dissociation constant; f_u, fraction of unbound drug in plasma; B/P, blood to plasma ratio; P_{app}, apparent permeability; CYP, cytochrome P450; CL_{int}, intrinsic clearance; Ind_{max}, maximal induction; $IndC_{50}$, inducer concentration that supports half-maximal induction; NA, parameter not applicable to the development of the current model.

Methods

Design of a PBPK model to predict efavirenz and levonorgestrel interactions

The PBPK model used in this study was designed using Simbiology® version 4.3.1, a product of MATLAB® version 8.2 (MathWorks, Natick, MA, USA), and was based on a previously described qualified model, which had been used to describe virtual DDIs between efavirenz and other drugs.[27] The physicochemical and metabolic characteristics of simulated drugs used in this PBPK model are provided in Table 1.

Virtual individuals used in PBPK simulations

Virtual individuals were created using the population physiology model *physB*,[28] for use in efavirenz–levonorgestrel PBPK simulations. The *physB* model provided a statistical description of physiological parameters representative of interindividual variability observed within the general female adult population (age range 18–60 years, mean age 36.5±13 years).[28] The parameters of age, height, weight, BMI and body surface area were used to allometrically scale organ weights and tissue weights. Blood circulatory values accounted for variations in cardiac output and differential blood flow to the organs, as previously described.[28]

Oral absorption of efavirenz

The oral absorption of efavirenz was simulated using a compartmental absorption and transit model, with transit times of 30 min and 3.3 h in the

stomach and small intestine, respectively, as reported previously.[29] The effective permeability (P_{eff}) of efavirenz in Caco-2 cells[30] was used to derive the absorption rate constant (k_a) of efavirenz, as described previously.[31]

Subcutaneous release rate of levonorgestrel

In the PBPK model, the subcutaneous release rate of levonorgestrel from 150 mg levonorgestrel implants (2×75 mg rods), was set at 100 μg/day for the first month and 40 μg/day from the second month through month 12 to reflect the reported release rate of levonorgestrel from standard-dose levonorgestrel implants in humans *in vivo* (Table 1).[11]

Hepatic metabolism of efavirenz and levonorgestrel

The contribution of individual hepatic cytochrome P450 (CYP) enzymes to the total intrinsic clearance ($TotCL_{int}$) of efavirenz was calculated by considering the *in vitro* intrinsic clearance (CL_{int}) of efavirenz, the abundance of each CYP enzyme in 1 mg of microsomal protein per g of liver and the liver weight, as described previously.[32] The systemic clearance of levonorgestrel was derived from a previously published value[53] (see Table 1), with the metabolism of levonorgestrel assumed to be mediated by CYP3A4.[11]

Integration of efavirenz-mediated induction [Equation (1)] and inhibition [Equation (2)] of hepatic metabolic enzyme activity in the calculation of $TotCL_{int}$ was achieved as follows:

$$\text{Induction} = 1 + [(E_{max} \times I_h)/(EC_{50} + I_h)] \quad (1)$$

$$\text{Inhibition} = 1 + (I_h/K_i) \quad (2)$$

where: E_{max} = maximum induction of metabolic enzyme activity (net maximum fold-increase); EC_{50} = concentration of inducer producing 50% of E_{max}; K_i = concentration of inhibitor producing 50% of maximum inhibition of metabolic enzyme activity; and I_h = concentration of inducer/inhibitor within liver tissue.

Thereafter, the total liver CL_{int} (CL_{liver}) was calculated as the sum total of $TotCL_{int}$ of each hepatic CYP contributing to the clearance of efavirenz, as previously described.[31]

Finally, the systemic clearance of efavirenz was determined by taking into account the blood flow into the liver (Q_h) as shown in Equation (3):

$$\text{Systemic clearance} = (Q_h \times f_u \times CL_{liver})/(Q_h + f_u \times CL_{liver}) \quad (3)$$

where f_u is the fraction of unbound drug in blood.

The amount of efavirenz escaping hepatic metabolism (F_h) to reach the systemic circulation was calculated using Equation (4):

$$F_h = (Q_h)/(Q_h + f_u \times CL_{liver}) \quad (4)$$

Volume of distribution of efavirenz and levonorgestrel

The volume of distribution of efavirenz was simulated by calculating the tissue-to-plasma partition coefficient for each organ and using previously published equations[33,34] for organ volumes, which were derived from the *physB* model.[28] The volume of distribution of levonorgestrel was derived from a previously reported value[52] (see Table 1).

Design of parameters for efavirenz and levonorgestrel metabolism

Efavirenz induces the activity of CYP3A4 in a dose-dependent manner,[35] whilst levonorgestrel is reported to undergo metabolism mainly by CYP3A4.[11] The PBPK model used herein was developed using *in vitro* values obtained from published literature (Table 1).[11] Efavirenz-mediated induction of CYP3A4 activity was qualified by measuring the simulated effects of coadministering efavirenz on the CYP3A4 substrate maraviroc, as described previously.[27] Efavirenz is primarily metabolized by CYP2B6;[36] however, polymorphisms in the *CYP2B6* gene, including *CYP2B6* c0.516G>T, are known to result in differential metabolism of efavirenz.[37,38] Given that this polymorphism affects efavirenz disposition and has been shown to impact levonorgestrel metabolism,[39] the PBPK model was designed to reflect the genotypic frequency of *CYP2B6* genotypes 516GG, 516GT and 516TT as 0.45, 0.43 and 0.12, respectively, typical of the genotypic frequency observed in an African population.[40]

Design of virtual DDI studies

PBPK model simulations of efavirenz–levonorgestrel coadministration were performed in 100 virtual individuals receiving either 400 or 600 mg of efavirenz once daily in combination with either 150 mg of implantable levonorgestrel (2×75 mg rods) or 300 mg of implantable levonorgestrel (4×75 mg rods) for the duration of the study. The simulated steady-state plasma concentration (C_{ss}) of levonorgestrel and efavirenz was measured at 1, 4, 12, 24, 36 and 48 weeks after virtual placement of the levonorgestrel implant system(s) for each dosing strategy, to facilitate comparison with a recent clinical study.[13] In addition, the effect of increased-dose implantable levonorgestrel (300 mg) on the efavirenz–levonorgestrel DDI was simulated in multiple groups of 25 patients to evaluate the potential effects of smaller sample sizes, akin to the numbers of individuals observed in previous[13] and current (NCT02722421)[41] clinical trials on pharmacokinetic variability in this specific context.

Qualification of the efavirenz–levonorgestrel PBPK model and comparison of simulated pharmacokinetics with clinical data

In order to qualify the efavirenz–levonorgestrel PBPK model, efavirenz and levonorgestrel concentrations observed in a clinical study reported by Scarsi *et al.*[13] were compared with PBPK model-simulated pharmacokinetics of both efavirenz and levonorgestrel to evaluate potential differences between PBPK-computed predictive values and observed clinical data. The geometric mean and 90% CI for log_{10}-transformed plasma concentrations of levonorgestrel and efavirenz at weeks 12 and 24 (representative of steady-state conditions) in 100 virtual individuals were calculated and evaluated against data obtained *in vivo*[13] by a parametric *t*-test. To evaluate potential discrepancies between the simulated and observed DDI, the relationship between log_{10} levonorgestrel and efavirenz exposure was investigated using linear regression analysis (significance threshold $P < 0.2$, $\alpha = 0.05$). To compare the effects of 600 and 400 mg of efavirenz on levonorgestrel exposure, the geometric mean ratio (GMR) and 90% CI between each efavirenz group and the control group [standard-dose (150 mg) levonorgestrel implants without efavirenz] was calculated. A GMR between 0.8 and 1.25 represented bioequivalent pharmacokinetic exposure.[42,43]

Statistical analysis

Statistical analyses were carried out using IBM® SPSS® Statistics (version 22; IBM Corporation, Armonk, NY, USA). Graphs were drawn using GraphPad Prism software (version 5; GraphPad Software, Inc., La Jolla, CA, USA). Geometric means were compared using an independent samples non-parametric *t*-test, in which *P* values ≤0.05 were considered statistically significant.

Results

Qualification of the efavirenz–levonorgestrel PBPK model

Box-and-whisker plot analysis revealed similar symmetry of data distribution in both the PBPK-simulated log_{10} C_{ss} values and observed *in vivo* clinical log_{10} C_{ss} values for both levonorgestrel

and efavirenz at 12 weeks (Figure 1a and c) and 24 weeks (Figure 1b and d), respectively. At 24 weeks, median $\log_{10}$ levonorgestrel simulated and observed plasma concentrations were 2.39 and 2.43 pg/mL, respectively (Figure 1b), whilst median $\log_{10}$ efavirenz simulated and observed plasma concentrations at 24 weeks were 3.39 and 3.42 ng/mL, respectively (Figure 1d).

To further examine the comparability of the observed *in vivo* clinical efavirenz plasma concentrations and PBPK model-simulated efavirenz plasma concentrations, the GMRs of simulated-to-observed efavirenz plasma concentrations following administration of 600 mg of efavirenz once daily were calculated (Table 2). The GMRs of simulated-to-observed efavirenz plasma concentrations were similar, ranging from 0.84 to 1.27 (Table 2). Statistical analysis of PBPK-simulated and clinically observed levonorgestrel and efavirenz exposures at weeks 12 and 24 showed no significant differences ($P > 0.05$).

Linear regression analysis also supported that the effect of efavirenz on levonorgestrel concentrations was similar when comparing PBPK-simulated data and clinical data.[13] Specifically, considering $\log_{10}$ concentrations, at week 12, the constant (90% CI) was equal to 2.685 (2.587–2.784) and β was equal to − 0.395 (−0.583 to − 0.207) for *in vivo* clinical data versus 2.538 (2.48–2.595) and −0.242 (−0.340 to − 0.144) for the simulated DDI. At week 24, the constant was equal to (90% CI) 2.657 (2.570–2.744) and β was equal to − 0.461 (−0.617 to − 0.304) for *in vivo* clinical data versus 2.527 (2.470–2.583) and −0.241 (−0.339 to − 0.143) for the simulated DDI.

Prediction of the effects of efavirenz dose reduction from 600 to 400 mg once daily on levonorgestrel plasma concentrations

Using the PBPK model, levonorgestrel plasma concentrations were simulated at 1, 4, 12, 24, 36 and 48 weeks in virtual individuals receiving 150 mg levonorgestrel implants without ART (control group) and in virtual individuals receiving 150 mg levonorgestrel implants in combination with either standard-dose (600 mg) efavirenz or reduced-dose (400 mg) efavirenz once daily (Figure 2 and Table 3). In virtual individuals receiving 150 mg levonorgestrel implants without ART, the simulated levonorgestrel C_{ss} at 48 weeks was 578 pg/mL, whereas in simulated individuals receiving 150 mg levonorgestrel implants plus 600 mg of efavirenz, the

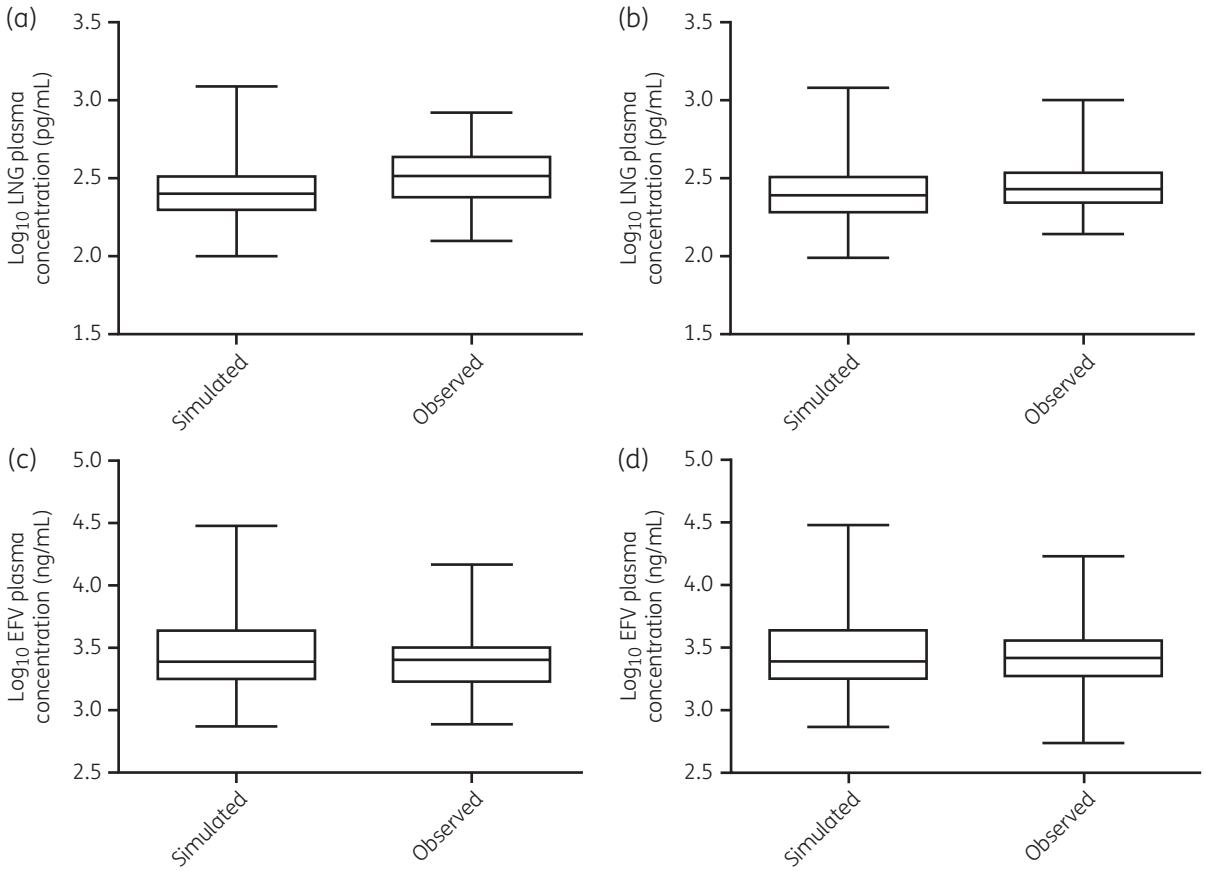

Figure 1. Comparison of PBPK-model-simulated plasma concentrations and clinical plasma concentrations of levonorgestrel and efavirenz. Box and whisker plots showing $\log_{10}$ PBPK-model-simulated levonorgestrel plasma concentrations and observed[a] levonorgestrel plasma concentrations obtained at (a) 12 weeks and (b) 24 weeks post-implant-placement and $\log_{10}$ PBPK-model-simulated and observed[b] efavirenz plasma concentrations obtained at (c) 12 weeks and (d) 24 weeks after placement of the levonorgestrel implants. One hundred virtual individuals were used for the PBPK model simulations, whilst clinical samples were collected from 20 individual patients in each case. [a]Observed *in vivo* levonorgestrel plasma concentrations are as published by Scarsi *et al.*[13] [b]Previously unpublished observed *in vivo* efavirenz plasma concentrations collected 12–14 h after efavirenz dose.[13] Whiskers = minimum and maximum values. EFV, efavirenz; LNG, levonorgestrel.

simulated levonorgestrel C_{ss} at 48 weeks was 245 pg/mL [GMR (90% CI) 0.42 (0.38–0.47); Table 3]. These simulated data are consistent with *in vivo* data in HIV-infected women receiving 150 mg levonorgestrel implants plus 600 mg of efavirenz when compared with individuals receiving 150 mg levonorgestrel implants without ART [GMR (90% CI) 0.43 (0.42–0.44)].[13] In virtual individuals receiving 150 mg levonorgestrel implants together with 400 mg of efavirenz, the simulated levonorgestrel C_{ss} at 48 weeks was 281 pg/mL [GMR (90% CI) 0.49 (0.43–0.55); Table 3]; this represented a +6% ($P = 0.1$) relative increase in simulated levonorgestrel plasma concentrations compared with the control group when standard-dose levonorgestrel was administered with 400 mg of efavirenz, as opposed to when standard-dose levonorgestrel was administered with 600 mg of efavirenz.

Table 2. Comparison of *in silico* and *in vivo* efavirenz plasma concentrations

Week	*In silico*-simulated efavirenz (ng/mL)[a]	*In vivo*-observed efavirenz (ng/mL)[b]	GMR simulated efavirenz: observed efavirenz[c]
1	2402 (2218–2601)	2850 (2186–3718)	0.84 (0.68–1.05)
4	2931 (2605–3299)	2707 (2099–3489)	1.08 (0.81–1.45)
12	2995 (2643–3395)	2709 (2095–3503)	1.11 (0.81–1.50)
24	2998 (2644–3400)	2863 (2174–3771)	1.05 (0.77–1.43)
36	2998 (2644–3400)	2913 (2076–4087)	1.03 (0.73–1.45)
48	2998 (2644–3400)	2362 (1701–3281)	1.27 (0.92–1.76)

In vivo efavirenz plasma concentration 12–14 h post-dose was measured at 1, 4, 12, 24, 36 and 48 weeks post-insertion of a standard-dose (150 mg) levonorgestrel implant in 20 HIV-positive women receiving 600 mg of efavirenz once daily. These data were compared with *in silico* PBPK-simulated efavirenz (600 mg once daily) concentrations generated in a similar group of 100 virtual individuals.

[a]Data are presented as geometric means of simulated efavirenz plasma concentrations with 90% CI calculated from 100 virtual individuals.

[b]Data are presented as geometric means of *in vivo* efavirenz plasma concentrations with 90% CI calculated from 20 HIV-positive women (previously unpublished data collected as part of Scarsi *et al.*[13]).

[c]Data are presented as GMRs with 90% CI.

Comparing the PBPK-simulated effects of increased-dose levonorgestrel when coadministered with 600 or 400 mg of efavirenz

A PBPK simulation of the effects of coadministering 600 mg of efavirenz with increased-dose (300 mg) levonorgestrel implants in 100 virtual individuals yielded simulated levonorgestrel plasma concentrations of 607 pg/mL at 1 week post-implant-placement, gradually decreasing to 500 pg/mL at 48 weeks post-implant-placement (Table 3 and Figure 3). Compared with the control group (150 mg levonorgestrel implants without efavirenz), the GMR (90% CI) of simulated levonorgestrel concentrations from 300 mg levonorgestrel implants plus 600 mg of efavirenz was 0.86 (0.77–0.97) at 48 weeks post-implant-placement (Table 3). Similar simulations conducted in 12 groups of 25 virtual individuals resulted in geometric mean levonorgestrel plasma concentrations (90% CI) ranging from 516 (449–592) pg/mL to 728 (599–884) pg/mL at 1 week post-implant-placement and ranging from 443 (375–523) pg/mL to 591 (505–691) pg/mL at 48 weeks post-implant-placement.

When a daily dose of 400 mg of efavirenz was applied in the PBPK model in combination with 300 mg levonorgestrel implants, simulated levonorgestrel plasma concentrations in 100 virtual individuals were 724 pg/mL at week 1 and 593 pg/mL at 48 weeks post-implant-placement (Table 3 and Figure 3). Compared with the control group, the GMR (90% CI) of simulated levonorgestrel concentrations from 300 mg levonorgestrel implants in combination with 400 mg of efavirenz once daily was 1.03 (0.91–1.16) at 48 weeks post-implant-placement (Table 3). By comparison, when PBPK simulations were conducted in smaller numbers of virtual patients (12 groups of 25 patients), coadministration of 400 mg of efavirenz with increased-dose (300 mg) levonorgestrel implants yielded geometric mean levonorgestrel plasma concentrations (90% CI) ranging

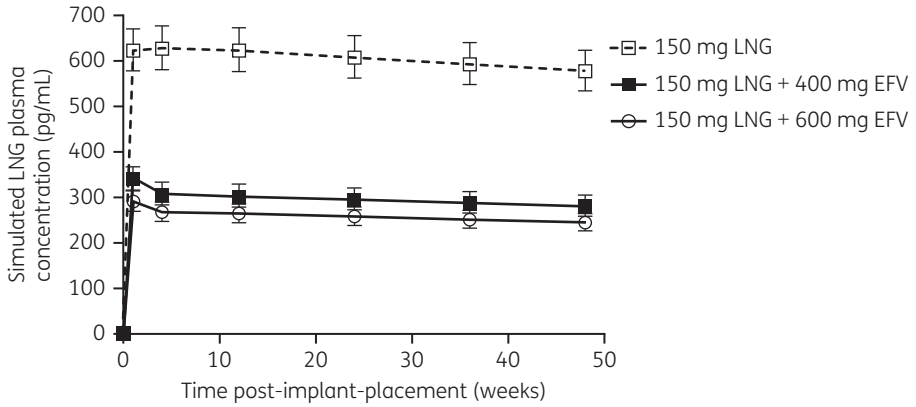

Figure 2. Geometric mean of PBPK-simulated standard-dose levonorgestrel plasma concentrations in 100 virtual individuals measured over 48 weeks after placement of 150 mg levonorgestrel implants in combination with standard- and reduced-dose efavirenz. The geometric mean of the PBPK-simulated levonorgestrel plasma concentrations is shown at 1, 4, 12, 24, 36 and 48 weeks following placement of: standard-dose levonorgestrel implants (150 mg) alone (broken line, open squares); standard-dose levonorgestrel implants together with 600 mg of efavirenz once daily (continuous line, open circles); or standard-dose levonorgestrel implants together with 400 mg of efavirenz once daily (continuous line, filled squares). Error bars = 90% CI. EFV, efavirenz; LNG, levonorgestrel.

Table 3. *In silico* levonorgestrel plasma concentrations measured over 48 weeks following the administration of standard- and increased-dose levonorgestrel implants in combination with standard- and reduced-dose efavirenz

	Week 1	Week 4	Week 24	Week 48
LNG 150 mg subdermal implant (standard dose)[a]				
LNG 150 mg alone (control group) (pg/mL)	623 (579–671)	628 (581–678)	608 (563–657)	578 (535–624)
LNG 150 mg + EFV 600 mg (pg/mL)	291 (270–314)	268 (248–290)	258 (239–279)	245 (226–265)
LNG 150 mg + EFV 400 mg (pg/mL)	341 (317–368)	308 (284–334)	296 (273–321)	281 (259–305)
Standard-dose LNG GMR (90% CI) between groups[b]				
EFV 600 mg versus control group	0.47 (0.42–0.52)	0.43 (0.38–0.48)	0.42 (0.38–0.47)	0.42 (0.38–0.47)
EFV 400 mg versus control group	0.55 (0.49–0.61)	0.49 (0.44–0.55)	0.49 (0.43–0.55)	0.49 (0.43–0.55)
LNG 300 mg subdermal implant (increased dose)[a]				
LNG 300 mg + EFV 600 mg (pg/mL)	607 (559–660)	547 (501–598)	527 (482–576)	500 (458–546)
LNG 300 mg + EFV 400 mg (pg/mL)	724 (664–789)	651 (594–713)	625 (569–686)	593 (541–651)
Increased-dose LNG GMR (90% CI) between groups[b]				
EFV 600 mg versus control group	0.97 (0.87–1.09)	0.87 (0.77–0.98)	0.87 (0.77–0.97)	0.86 (0.77–0.97)
EFV 400 mg versus control group	1.16 (1.04–1.30)	1.04 (0.92–1.17)	1.03 (0.91–1.16)	1.03 (0.91–1.16)

EFV, efavirenz; LNG, levonorgestrel.
PBPK-simulated levonorgestrel plasma concentrations generated over 48 weeks post-insertion at week 0 of levonorgestrel implants in virtual individuals administered standard-dose levonorgestrel implants (150 mg) alone (control group) or with either standard-dose levonorgestrel implants (150 mg) or increased-dose levonorgestrel implants (300 mg) in combination with either 600 mg of efavirenz once daily or 400 mg of efavirenz once daily. One hundred virtual individuals were simulated per group. GMRs were compared between each respective combined efavirenz–levonorgestrel group and the 150 mg levonorgestrel control group in each case.
[a]Data are presented as geometric means of simulated levonorgestrel plasma concentrations with 90% CI.
[b]Data are presented as GMRs with 90% CI.

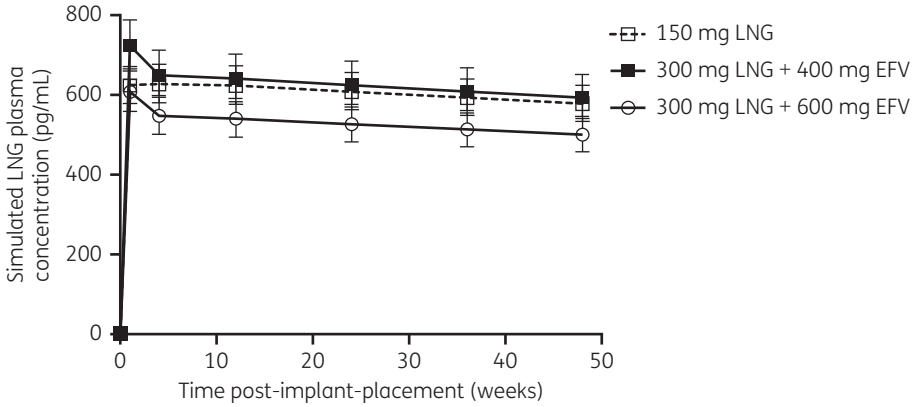

Figure 3. Geometric mean of PBPK-simulated increased-dose levonorgestrel plasma concentrations in 100 virtual individuals measured over 48 weeks after placement of 300 mg levonorgestrel implants in combination with standard- and reduced-dose efavirenz. The geometric mean of PBPK-simulated levonorgestrel plasma concentrations is shown at 1, 4, 12, 24, 36 and 48 weeks following placement of: standard-dose levonorgestrel implants (150 mg) alone (broken line, open squares); increased-dose levonorgestrel implants (300 mg) together with 600 mg of efavirenz once daily (continuous line, open circles); or increased-dose levonorgestrel implants together with 400 mg of efavirenz once daily (continuous line, filled squares). Error bars = 90% CI. EFV, efavirenz; LNG, levonorgestrel.

from 620 (532–724) pg/mL to 837 (700–1001) pg/mL at 1 week post-implant-placement and ranging from 507 (428–600) pg/mL to 680 (557–830) pg/mL at 48 weeks post-implant-placement.

Discussion

Previous work demonstrated that levonorgestrel plasma concentrations decreased 47% when 150 mg levonorgestrel subdermal implants were administered with efavirenz-based ART,[13] which resulted in contraceptive failure and unintended pregnancies in some patients.[13] The presented PBPK model showed that reducing the daily dose of efavirenz from 600 to 400 mg did not significantly alter the efavirenz–levonorgestrel DDI (Figure 2 and Table 3), suggesting that reduced-dose (400 mg) efavirenz may not fully mitigate the risk of contraceptive failure when combined with standard-dose (150 mg) levonorgestrel implants. An encouraging finding of the present study was that an increase in levonorgestrel dosing to 300 mg, in combination with either 600 or 400 mg of

efavirenz, was sufficient to raise simulated levonorgestrel plasma concentrations within the qualified PBPK model to levels comparable to those observed when standard-dose levonorgestrel implants were administered alone, without efavirenz (Figure 3 and Table 3; GMR between 0.8 and 1.25[42,43]). Given the close association between PBPK model-simulated levonorgestrel plasma concentrations and *in vivo* clinically observed levonorgestrel concentrations, coadministration of increased-dose (300 mg) levonorgestrel implants together with either 600 or 400 mg of efavirenz warrants clinical investigation.

Prior work has described a dose-dependent induction of hepatic CYP3A4 activity in human volunteers receiving efavirenz *in vivo*;[35] furthermore, *in vitro* studies conducted in primary human hepatocytes have shown that efavirenz can induce both CYP3A4 expression and CYP3A4 activity in a concentration-dependent manner.[44] These data suggest a hypothesis whereby a dose reduction of efavirenz from 600 to 400 mg may result in fewer clinically significant DDIs with CYP3A4 substrates, such as levonorgestrel. However, the present study showed that simulated levonorgestrel plasma concentrations were similar between simulated patients receiving either efavirenz dose, thus suggesting that an efavirenz dose reduction from 600 to 400 mg, may not be sufficient to overcome efavirenz-induced DDIs with CYP3A4 substrates *in vivo*. It is hereby proposed that this is likely due to the potency of efavirenz as a CYP3A4 inducer, which has previously been reported to be comparable, *in vitro*, to that of the induction potential of the well-documented CYP3A4 inducer rifampicin.[44]

The present efavirenz–levonorgestrel PBPK model was designed to take into account the known differential metabolism of efavirenz as influenced by *CYP2B6* polymorphisms[39] to predict the resultant effects upon levonorgestrel plasma concentrations. Clinically observed efavirenz plasma concentrations and PBPK model-simulated efavirenz concentrations showed a high degree of similarity (Figure 1 and Table 2), whilst the usefulness of the PBPK model as a tool to predict DDIs between levonorgestrel and efavirenz was further exemplified by linear regression analysis, which indicated no significant differences between the PBPK-simulated data and published clinical data. However, simulations conducted in a reduced number of virtual individuals, similar to the patient numbers typically evaluated in clinical pharmacokinetic evaluations,[13,41] resulted in more variable simulated levonorgestrel plasma concentrations when compared with efavirenz–levonorgestrel DDI predictions based on 100 virtual individuals. Taken together, it is suggested that the interindividual variability in the extent of efavirenz–levonorgestrel DDI may influence clinical pharmacokinetic evaluations of this interaction and, further, the clinical recommendations regarding the coadministration of efavirenz and levonorgestrel.

Subdermal hormonal implants are among the most effective methods of contraception available worldwide, with an expected failure rate of <1% during the first year of use.[16,45] Therefore, women choosing a contraceptive implant for family planning expect near-perfect effectiveness, and a DDI that reduces this effectiveness must be clearly described to patients in order to allow an informed choice of contraceptive method to be made. In recent years, an increase in the provision of implantable LARCs in sub-Saharan Africa has occured (>9-fold between 2008 and 2012).[46] With price reductions, the provision of and accessibility to hormone-releasing implantable contraceptives in LMICs is likely to continue to increase over the coming years.[47] Despite the recent inclusion of dolutegravir-based ART in the WHO guidelines, efavirenz is expected to remain in ∼50% of first-line ART regimens in LMICs for the next decade.[48] Therefore, further characterization of the DDI between efavirenz and levonorgestrel is of great importance in the effort to prevent unintended pregnancy and mother-to-child transmission of HIV and to improve the overall health of women residing in LMICs.[16]

The presented PBPK model represents a useful strategy to aid in predicting the likely outcome of clinical pharmacological approaches to overcome detrimental DDIs. However, whilst PBPK models are increasingly accepted by drug regulatory agencies,[24] cautious interpretation of the presented data is nevertheless required, due to the fact that *in vitro*-to-*in vivo* extrapolation is both challenging and has several limitations.[49,50] With respect to the current PBPK model, further customization may be necessary to reflect pharmacogenetic differences when conducting prospective efavirenz–levonorgestrel DDI studies in populations of distinct ethnicities. In addition, the current model does not consider the relative contribution that transporters and non-CYP metabolic enzymes may have in efavirenz and levonorgestrel disposition. Finally, the potential effect of efavirenz and levonorgestrel upon drug transporter activity in the subcutaneous tissue immediately proximal to levonorgestrel implants is not currently known, but may have a role in the absorption and distribution of levonorgestrel. In order to address these limitations, further studies aimed at elucidating the mechanisms of levonorgestrel metabolism will be necessary.

Given the clinical significance of DDIs that occur between efavirenz-based ART and hormone-based contraceptives, future work should aim to investigate DDIs between efavirenz and other progestin-based implants.[15] For example, administering efavirenz-based ART in women using etonogestrel implants has been shown to reduce etonogestrel plasma concentrations by 82%.[17,51] Furthermore, contraceptive failure of etonogestrel-releasing implants has been reported in HIV-positive women concurrently treated with efavirenz-based ART. Therefore, developing a similar PBPK model-based approach to that described here in order to evaluate dose-adjustment strategies for coadministering such implants with efavirenz or other ARVs would be warranted.

In conclusion, this study provides insight into the extent of the DDI between levonorgestrel and efavirenz, yielding information to inform optimization of dosing strategies for combining efavirenz-based ART with levonorgestrel implants. The model predicted that levonorgestrel dose escalation in combination with either 600 or 400 mg of efavirenz has the potential to maintain levonorgestrel plasma concentrations (GMR between 0.8 and 1.25) compared with women using standard-dose levonorgestrel implant without ART;[42,43] a relatively smaller virtual sample size, however, yielded more variable findings. One clinical study investigating the effects of coadministering 600 mg of efavirenz in combination with increased-dose (300 mg) levonorgestrel implants is currently underway (NIH, NCT02722421[41]). Finally, this qualified *in silico* model will serve as a useful basis from which other ARV–hormonal contraceptive DDIs may be investigated.

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Disclaimer

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