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The Effect of Gene Variants on Levonorgestrel Pharmacokinetics when Combined with Antiretroviral Therapy containing Efavirenz or Nevirapine

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Author responsibility

The corresponding author accepts final responsibility and confirms access to all data in the study.

Conflict of interest/Disclosure

Megan Neary, Kimberly Scarsi have no conflict of interest/disclosures.

Author contributions:

M.N., M.S., A.O., and K.S. wrote the manuscript; M.L., K.D., C.M., P.B., D.B., A.O., and K.S. designed the research; M.N., M.L., A.O., K.D., C.M., P.B., D.B., and K.S. performed the research, M.N. analyzed the data; M.S. and A.O. contributed new reagents/ analytical tools.

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Abstract

Reduced levonorgestrel concentrations from the levonorgestrel contraceptive implant was previously seen when given concomitantly with efavirenz. We sought to assess whether single nucleotide polymorphisms (SNPs) in genes involved in efavirenz and nevirapine metabolism were linked to these changes in levonorgestrel concentration. SNPs in *CYP2B6*, *CYP2A6*, *NR1I2* and *NR1I3* were analysed. Associations of participant demographics and genotype with levonorgestrel pharmacokinetics were evaluated in HIV-positive women using the levonorgestrel implant plus efavirenz- or nevirapine-based ART, in comparison to ART-naïve women using multivariate linear regression. Efavirenz group: *CYP2B6* 516G>T was associated with lower levonorgestrel $\log_{10}$ C_{max} and $\log_{10}$ AUC. *CYP2B6* 15582C>T was associated with lower $\log_{10}$ AUC. Nevirapine group: *CYP2B6* 516G>T was associated with higher $\log_{10}$ C_{max} and lower $\log_{10}$ C_{min}. Pharmacogenetic variations influenced subdermal levonorgestrel pharmacokinetics in HIV-positive women, indicating that the magnitude of the interaction with non-nucleoside reverse transcriptase inhibitors (NNRTIs) is influenced by host genetics.

Keywords

Levonorgestrel; Efavirenz; Nevirapine; Pharmacokinetics; Pharmacogenetics; HIV; CYP2A6; CYP2B6; NR1I2; NR1I3; Single nucleotide polymorphisms

Introduction

Hormonal contraceptives and antiretroviral therapy (ART) are critical components of healthcare for the estimated 17 million women living with HIV and are key pillars in the effort to globally reduce mother-to-child HIV transmission.(1–3) The subdermal levonorgestrel (LNG) implant is a highly effective and desirable method of contraception.(4, 5) LNG is released from the implant initially at 100mcg/day, decreasing to 40mcg/day within one year and to 30mcg/day within three years, providing relatively stable daily drug concentrations.(6) Notably, the use of contraceptive implants is rapidly expanding in low- and middle-income countries.(7) In these same settings, the World Health Organization (WHO) recommends ART-containing two nucleos(t)ide reverse transcriptase inhibitors (NRTI) in combination with efavirenz (EFV) as a first-line regimen for HIV treatment.(8) The use of EFV-based ART in women of childbearing potential has expanded in the past decade, first following characterization of the lower than expected level of fetal risk during in-utero EFV exposure (9–11), and subsequently due to recent WHO recommendations for universal use of ART irrespective of CD4+ cell count.(12) Considered an alternate first-line option, nevirapine (NVP), is still used by many women in low- and middle-income countries.(8) In light of this, identifying safe and efficacious combinations of both therapies with hormonal contraceptives in HIV-positive women is a critical public health priority.

We previously described a significant drug-drug interaction between the LNG implant and EFV-based ART in HIV-positive Ugandan women, which resulted in 47% lower LNG

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concentrations compared to control participants, and a high rate of unintended pregnancy, in women receiving EFV-based ART [3 (15%) of 20 participants].(13) Induction of CYP3A4- and CYP3A5-mediated metabolism of LNG is the proposed mechanism of the observed interaction with EFV. No pharmacokinetic interaction or unintended pregnancies were observed in women receiving NVP-based ART within the same study. These findings are supported by a retrospective cohort study of Kenyan women that found a three-fold higher adjusted pregnancy incidence in HIV-positive women receiving the implant plus EFV-based ART compared to those receiving NVP-based ART.(14)

LNG, EFV and NVP are substrates of cytochrome P450 (CYP) enzymes; LNG is metabolized by CYP3A4 and CYP3A5, (15) EFV is metabolized by CYP2B6 with minor contributions from CYP2A6, CYP3A4, and UGT2B7, (16, 17) while NVP is metabolized by CYP2B6, CYP3A4 and partially by CYP2D6 (18, 19). The nuclear receptors NR1I2 and NR1I3 are known to regulate the expression and activity of several CYPs, including CYP2B6 and CYP3A4. Multiple SNPs in both *NR1I2* and *NR1I3* genes have been linked to variation in expression of CYP3A4 and CYP2B6 (20–22), which may alter the pharmacokinetics (PK) of substrate drugs. Activation of NR1I2 and NR1I3 results in up regulation of target CYPs and alters the PK of their substrates. Both phenomenon' have been demonstrated for EFV and NVP. (23, 24) *CYP2B6* 516G>T has previously been associated with higher EFV and NVP plasma concentrations. (25–31) Notably, several polymorphisms associated with EFV and NVP PK are found more commonly within African populations compared to Caucasians or Asians.(1, 28, 32–35)

The primary objective of this secondary study analysis was to ascertain the contributory effect of SNPs in key genes of interest in LNG, EFV, and NVP metabolism (*CYP2B6*, *CYP2A6*, *NR1I2* and *NR1I3)* on plasma LNG PK when the subdermal implant is given in combination with EFV- or NVP-based ART (EFV and NVP groups, respectively) in HIV-positive women. The control group of the primary study was not included in this pharmacogenetics analysis because the purpose of the study was to investigate the genetic basis for the interaction between NNRTIs and LNG. Since these SNPs have been shown to influence non-nucleoside reverse transcriptase inhibitors (NNRTI) PK, our underlying hypothesis was that there would be consequences of different NNRTI concentrations for the degree of CYP3A induction, and therefore a genetic basis for the subsequent magnitude of the interaction with LNG.

Results

All women in the EFV and NVP group from the primary study were included in this analysis (n=40). (13) Patient characteristics and genotype frequencies are summarized in Table 1. The median (interquartile range [IQR]) age and weight of all patients was 31 years (29–34 years) and 59kg (53–68kg). All SNPs were in Hardy-Weinberg equilibrium, except *CYP2B6* 15582C>T (rs4803419) (X^2=20.62, P=<0.001) and *NR1I3* 540C>T (rs2307424) (X^2=12.36, P=<0.001), which compromises their interpretation. Univariate and multiple regression analysis for LNG PK parameters based on EFV and NVP groups are presented in Table 2. All regression results can be found in Supplementary Table 1.

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Levonorgestrel, efavirenz and nevirapine pharmacokinetics

LNG C_{max}, T_{max}, C_{min}, and $AUC_{0–24week}$ are summarized by study group and SNP in Table 3. EFV $C_{12–14h}$ (mg/L) was 76% higher in homozygous *CYP2B6* 516 TT participants compared to those who were homozygous for the G allele. Within the NVP group NVP $C_{11–13h}$ (mg/L) was 5% lower in heterozygous *CYP2B6* 516 CT participants compared to homozygotes for the G allele.

Efavirenz group

All patients in the EFV group (n=20) received EFV 600mg daily plus 2 NRTIs for a median (IQR) of 10.5 months (6.3–37.8) prior to study entry. After multivariate analysis, *CYP2B6* 516G>T (rs3745274) was associated with lower $\log_{10}$ LNG C_{max} (β=−0.209, *P*=0.021) and $\log_{10}$ LNG $AUC_{0–24weeks}$ (β=−0.132, *P*=0.023). This meant that LNG C_{max} median values were 692.8, 402.4 and 200.6 pg/mL in the GG, GT and TT genotype groups, respectively (71% difference between homozygote groups) and LNG $AUC_{0–24weeks}$ median values were 10,114.6, 6311.8 and 3622.1 pg*wk/mL in the GG, GT and TT genotype groups, respectively (64% difference between homozygote groups). *CYP2B6* 15582C>T (rs4803419) was associated with lower $\log_{10}$ LNG $AUC_{0–24weeks}$ (β=−0.163, *P*=0.021), resulting in LNG $AUC_{0–24weeks}$ median values of 10,114.6 and 7754.4 pg*wk/mL in the CC and CT genotype groups, respectively (23% difference between groups). Figure 1 illustrates the LNG $AUC_{0–24weeks}$ within the EFV group according to these genotypes. In addition to these genetic associations, age was inversely associated with $\log_{10}$ LNG $AUC_{0–24weeks}$ (β=−0.018 per 1 year, *P*=0.039) (Table 2).

Consistent with previous reports, through univariate linear regression analysis, *CYP2B6* 516G>T was associated with higher EFV concentration (β=0.269, *P*=0.011), meaning that $C_{12–14h}$ values were 2.1, 2.6 and 8.7 mg/L in GG, GT and TT genotype groups, respectively (76% difference between homozygote groups). Additionally, higher EFV $C_{12–14h}$ ($\log_{10}$ mg/L) was associated with lower LNG $\log_{10}$ $AUC_{0–24week}$ (β=−0.030, *P*=0.003).

Nevirapine group

Patients in the NVP group (n=20) received NVP 200mg twice daily plus 2 NRTIs for a median (IQR) of 30.5 months (13.5–80.3) prior to study entry. *CYP2B6* 516G>T (rs3745274) was associated with higher $\log_{10}$ LNG C_{max} (β=0.103, *P*=0.034) and $\log_{10}$ LNG C_{min} (β=0.115, *P*=0.048). Resulting in LNG C_{max} median values of 1310.8 and 1449.5 pg/mL in the GG and GT genotype groups, respectively (10% difference between homozygote groups) and LNG C_{min} median values of 553.7 and 562.6 pg/mL in the GG and GT genotype groups (2% difference between groups). *NR1I2* 63396C>T was associated with delayed LNG T_{max} (β=1.623, *P*=0.003) with a median value of 1.0, 1.0 and 6.5 weeks in the CC, CT and TT genotype groups. Additionally, $\log_{10}$ weight (β=−15.910, *P*=0.002) and albumin concentration at baseline (β=−0.340, *P*=0.003) were associated with shorter LNG T_{max}. Log_{10} SHBG was associated with higher $\log_{10}$ LNG $AUC_{0–24weeks}$ (β=0.484, *P*=0.004), $\log_{10}$ LNG C_{min} (β=0.522, *P*=0.011) and $\log_{10}$ LNG C_{max} (β=0.469, *P*=0.007). Age was associated with higher $\log_{10}$ LNG C_{max} (β=0.013, *P*=0.044) (Table 2).

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No other genetic associations were observed in any of the groups; however, the sample size was insufficient to robustly assess the *CYP2B6* 983T>C variant (rs28399499).

Pharmacodynamic outcome in the EFV group

Three women in the EFV group became pregnant between study weeks 36 and 48 (3 (15%) of 20 participants). Pharmacogenetic characteristics of these three patients were as follows for the statistically significant genotypes within the EFV group: One woman was both homozygous TT for *CYP2B6* 516G>T (rs3745274) and heterozygous CT for *CYP2B6* 15582C>T (rs4803419). She was the only patient who possessed both of these genotypes in the study group, and her LNG concentration at the study visit prior to pregnancy (week 36) was 122 pg/mL (LNG $AUC_{0–24weeks}$ 3622 pg*wk/mL). The other two women were heterozygous CT for *CYP2B6* 516G>T and homozygous CC for *CYP2B6* 1582 C>T. They were the only patients in the EFV group who possessed these genotypes, and their LNG concentration prior to pregnancy (week 36) were 299 and 303 pg/mL (LNG $AUC_{0–24weeks}$ 10,115 and 8500 pg*wk/mL), respectively.

Discussion

The impact of this investigation is greatest for women receiving a combination of EFV-based ART with a LNG subdermal implant. Women receiving this drug combination are at risk for suboptimal LNG exposure, which results in a higher rate of contraceptive failures.(13, 14) For women who are heterozygous or homozygous for *CYP2B6* 516G>T or *CYP2B6* 15582C>T, which was associated with lower LNG AUC when combined with EFV, this drug-drug interaction will be more pronounced. This was evidenced by the 3 patients who became pregnant in the EFV group: all possessed at least one of these genotypes and the patient who possessed both significant genotypes had the lowest LNG exposure of any study participant. Importantly, nine additional women in the EFV group were heterozygous for either *CYP2B6* 516G>T or *CYP2B6* 15582C>T, and had LNG exposure (median LNG $AUC_{0–24weeks}$ 6831 pg*wk/mL), consistent with those women who became pregnant, indicating that they were also at risk for contraceptive failure. We hypothesize that high EFV plasma concentrations associated with these SNPs may result in greater EFV induction of *CYP3A4*, resulting in increased LNG metabolism and lower LNG exposure in the patients who were heterozygous or homozygous for *CYP2B6* 516G>T or *CYP2B6* 15582C>T. Further contributing to this effect may be the modest inhibitory effect of LNG on *CYP2B6*. (36, 37) It is possible that LNG may inhibit CYP2B6 activity, resulting in high EFV concentrations and further inhibition of CYP3A4.

Within the NVP group, the significant association between *CYP2B6* 516G>T and higher LNG $\log_{10} C_{max}$ and LNG $\log_{10} C_{min}$ is surprising, given that NVP is an inducer of CYP3A4, the enzyme believed to be primarily responsible for LNG metabolism. In a previous study of three HIV-positive Malawian women receiving 30 μg ethinyl estradiol/300 μg norgestrel (a racemic mixture of LNG and dextronorgestrel) and NVP-based ART, higher LNG exposure was also observed compared to HIV-uninfected women.(38) Notably, two of the three women were heterozygous for *CYP2B6* 516G>T. Furthermore, *CYP2B6* 516G>T has been associated with elevated NVP concentrations in previous studies.(1, 39) Therefore,

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the association between *CYP2B6* 516G>T and LNG PK parameters observed in our study could be attributed to NVP-mediated inhibition of LNG metabolism by CYP3A4, or potential inhibition of CYP3A5. However, this result must be interpreted with caution, given that overall exposure (as measured by AUC) was not associated with the same SNP. Further investigation is required to determine the mechanism underpinning this finding.

We observed an association between *NR1I2* 63396C>T (rs2472677) and delayed LNG T_{max} in patients on NVP, which has the potential to result in suboptimal LNG concentrations. Previously, *NR1I2* 63396C>T (in linkage disequilibrium (LD) with 63704G>A, 63813(CAAA)n/(CA)n, and 65104T>C) has been associated with higher *NR1I2* expression, elevated *CYP3A4* expression, and unboosted atazanavir plasma concentrations.(23, 40, 41) *NR1I2* 63396C>T may be directly or indirectly associated with inducibility of CYP3A4 and hence reduced LNG metabolism. This is supported by observations in primary human hepatocytes where the 63396T allele was associated with higher basal activity but lower rifampicin-mediated inducibility of CYP3A4.(23)

LNG pharmacokinetics demonstrate high inter-individual variability, often attributed to variations in protein binding(42) and bodyweight.(43–45) Although we did not observe a consistent association with weight and LNG PK, this may be related to the lower median body weight of HIV-infected Ugandan women compared to those in other studied populations. LNG is highly protein-bound to sex hormone-binding globulin (SHBG) and albumin. (42) Elevated $\log_{10}$ SHBG concentration has previously been associated with higher serum LNG concentration.(46) However, the observed association of $\log_{10}$ SHBG concentration at baseline with higher LNG $\log_{10}$ C_{max}, LNG $\log_{10}$ C_{min} and LNG $\log_{10}$ $AUC_{0–24weeks}$, and of albumin concentration at baseline with lower T_{max} within the NVP group, may reflect some influence of baseline protein binding on overall LNG exposure.

Limitations of this study include a relatively small sample size, particularly related to *CYP2B6* 15582C>T (rs4803419) and *NR1I3* 540C>T (rs2307424), as both SNPs were not in Hardy Weinberg equilibrium. In addition, the consequences of the T_{max} associations are unclear, but should in any case be interpreted cautiously given the intermittent measurement of LNG PK during the study period.

Our study demonstrates pharmacogenetic associations with LNG PK when administered as a LNG subdermal implant in HIV-positive women receiving EFV- or NVP-based ART. Even with the EFV interaction with LNG, effectiveness of the LNG subdermal implant may still be higher than that for oral contraception due to improved medication adherence.(14, 47) Notwithstanding, any increased risk of pregnancy during contraception is important, given the impact that unintended pregnancy has for women living with HIV. Based upon our findings, screening for SNPs associated with low LNG exposure in patients receiving EFV represents a novel approach to identify women at the highest risk for an unintended pregnancy. Added pharmacogenetic knowledge would allow clinicians to personalize counseling of women on their choice of a contraceptive method based on individualized risks and benefits. Overall, this study highlights the potential role of affordable, accessible and clinically-relevant pharmacogenetic screening in resource-constrained settings. Specifically, future studies with larger populations and a more diverse range of ethnicities,

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should focus upon prospective evaluation of the relationship between pharmacogenetics and the effectiveness of the LNG implant in the presence of EFV-related drug-drug interactions.

Methods

Aim of the study

To assess the association between LNG PK and SNPs in *CYP2B6, CYP2A6, NR1I3* and *NR1I2* in Ugandan HIV-positive women participating in a drug-drug interaction PK study. (13)

Ethical approval

All study procedures followed the Helsinki Declaration of 1975 and were approved by ethics boards at the Joint Clinical Research Centre Kampala, Uganda National Council for Science and Technology, and the University of Nebraska Medical Centre. The study was registered on clinicaltrials.gov (NCT01789879).

Study design and cohort

This was a prospective PK evaluation of HIV-positive Ugandan women receiving EFV-based ART (EFV group, n=20), NVP-based ART (NVP group, n=20), or ART-naïve (n=17). For the pharmacogenetic study, all participants in the EFV and NVP group were included (n=40) and the ART-naïve group was excluded. The two-rod (75mg/rod) LNG sub-dermal implant was inserted in all patients upon study entry. Inclusion criteria for the EFV and NVP groups included prescription of EFV or NVP plus 2 NRTIs for 30 days or longer and a HIV-RNA of <400 copies/mL. (48)

Sample and data collection

Over a total of 48 weeks, a plasma sample was collected at weeks 1, 4, 12, 24, 36 and 48 to assess LNG, NVP and EFV PK. Follow-up was interrupted for 9 subjects between weeks 36–44 after 3 pregnancies were identified in the EFV group. The primary endpoint for the PK analysis was 24 weeks. Timing of blood sample collection for the EFV group was based on EFV mid-dosing interval at 12–14 hours post dose and for the NVP group based on the end dosing interval of 11–13 hours post dose. PK parameters included in this analysis were area under the concentration time curve (AUC) from entry to week 24 ($AUC_{0–24\ weeks}$), maximum concentration (C_{max}), time to C_{max} (T_{max}) and minimum concentration (C_{min}). C_{max} and C_{min} represent the highest and lowest concentrations observed over the entire study period. AUC was calculated using the trapezoidal rule (Phoenix WinNonlin, Certara®). LNG concentrations were analyzed by a validated LC-MS/MS method; EFV and NVP plasma concentrations were determined using HPLC assays with ultraviolet detection as previously outlined by Scarsi *et al.* (13)

Genotyping

Genomic DNA was extracted from whole blood through use of the manufacturers protocol (E.Z.N.A Blood DNA Mini Kit; Omega bio-tek; Norcross, GA). Extracted DNA was quantified using NanoDrop (Thermo Fisher Scientific, Wilmington, DE). Genotyping was

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completed using real-time allelic discrimination polymerase chain reaction (PCR) assay on a DNA Engine Chromo4 system (Bio-Rad Laboratories, Hercules, CA). The PCR protocol followed denaturation at 95°C for 10 minutes, followed by 50 cycles of amplification at 92°C for 15 seconds and annealing at 60°C for 1 minute 30 seconds. Taqman Genotyping Master mix and assays *CYP2B6* 516G>T (rs3745274, catalogue number C___7817765_60), *CYP2B6* 983T>C (rs28399499, catalogue number C__60732328_20), *CYP2B6* 15582C>T (rs4803419, catalogue number C___7817764_10), *CYP2A6* -48A>C (rs28399433, catalogue number C__30634332_10) *CYP2A6*9B* 1836G>T (rs8192726, catalogue number C__29560333_20) *NR1I2* 63396C>T (rs2472677, catalogue number C_2607845), *NR1I3* 540C>T (rs2307424, catalogue number C__25746794_20) and *NR1I3* 1089T>C (rs3003596, catalogue number C__16194070_10) were purchased from Life Technologies (Paisley, Renfrewshire, UK). Opticon Monitor v.3.1 software (Bio-Rad Laboratories) was used to obtain allelic discrimination plots and identify genotypes.

Statistical analysis

Compliance with Hardy Weinberg equilibrium was tested using previously outlined methods.(49) Genotypes were coded for regression analyses as 0=homozygous common allele, 1=heterozygous and 2=homozygous variant allele. Categorical variables were described using relative frequencies, whilst continuous variables were described using median and IQR. The Shapiro-Wilk Test was used to test for normality, with a P value ≤0.05 considered as statistically significant. A univariate analysis through linear enter regression was carried out in order to identify independent variables associated with LNG PK parameters within all patients, the EFV group, and the NVP group. Variables with a P value ≤0.2 for the univariate analysis were carried through to a linear backwards multivariate analysis were a P value ≤0.05 was classed as statistically significant. All statistical analyses were carried out using IBM SPSS Statistics v.22 (IBM Armonk, NY). All charts were produced using GraphPad Prism 6 (GraphPad Software, La Jolla, CA).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study highlights

1. What is the current knowledge on the topic?

Use of the subdermal levonorgestrel implant with efavirenz-based antiretroviral therapy (ART) results in suboptimal concentrations of levonorgestrel, a result that was not observed for patients receiving nevirapine. *CYP2B6, CYP2A6, NR1I3* and *NR1I2* single nucleotide polymorphisms (SNPs) have previously been associated, through multiple studies, with alterations in efavirenz and nevirapine concentrations.

2. What question did this study address?

Are SNPs in genes involved in efavirenz and nevirapine metabolism linked to the reduced LNG concentrations observed from a drug-drug interaction between levonorgestrel and ART?

3. How this might change clinical pharmacology or translation science

This is the first study to demonstrate an association between pharmacogenetic variations in *CYP2B6* and the extent of the drug-drug interaction observed when sub-dermal levonorgestrel was combined with ART. In total, this manuscript adds to the current understanding of the mechanism by which efavirenz- and nevirapine-based ART interacts with the LNG sub-dermal implant.

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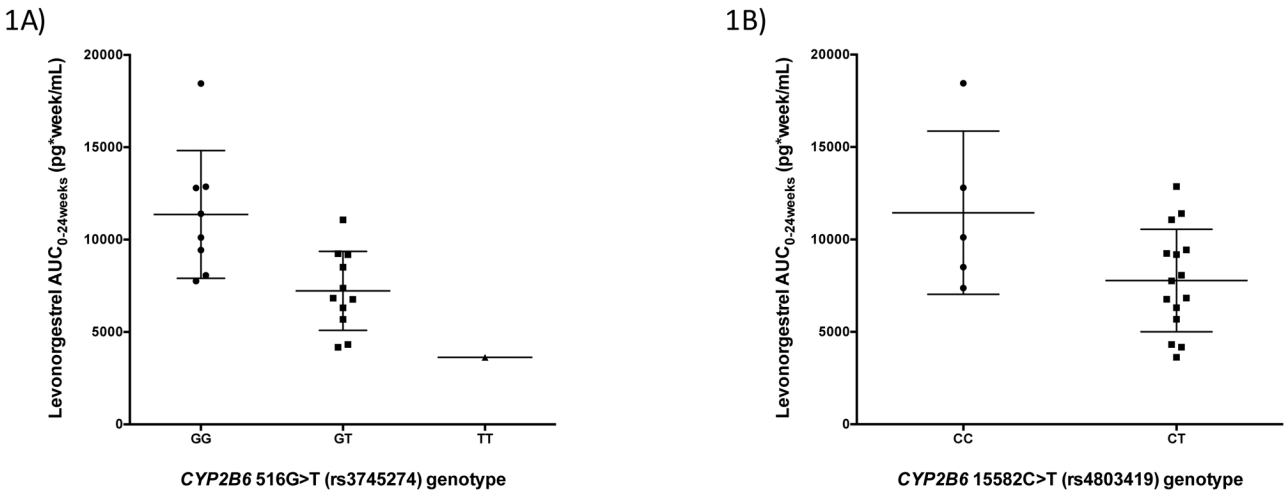

Figure 1. Levonorgestrel $AUC_{0–24weeks}$ within the efavirenz group shown by statistically significant genotype

Levonorgestrel $AUC_{0–24weeks}$ compared by statistically significant genotype.

Data is represented by median (interquartile range) and compared by genotype for each of the single nucleotide polymorphisms (SNPs) significantly associated levonorgestrel $\log_{10}$ $AUC_{0–24weeks}$ found through multivariate analysis (P=0.05) within the efavirenz group.

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Table 1

Characteristics of the study participants at entry

Characteristics	Total (n=40)			Efavirenz group (n=20)			Nevirapine group (n=20)		
Age (years)	31.0 (29.0–34.0)			31.0 (28.3–34.0)			32.5 (31.0–35.8)		
Weight (kg)	59.0 (53.0–68.0)			59.5 (52.3–63.8)			59.5 (54.3–69.8)		
CD4 count (cells/mm^3)	579.0 (464.0–731.0)			556.5 (477.3–663.5)			626.0 (399.8–857.3)		
Albumin concentration at baseline (g/L)	43.7 (41.5–46.5)			43.3 (40.7–45.1)			43.1 (41.8–45.6)		
SHBG at baseline (nmol/L)	105.0 (82.3–136.0)			100.0 (79.4–125.9)			100.0 (100.0–125.9)		
Genotype frequencies									
CYP2B6 516G>T (rs3745274) (%)	GG	GT	TT	GG	GT	TT	GG	GT	TT
	43	55	2	40	55	5	45	55	0
CYP2B6 983T>C (rs28399499) (%)	TT	CT	CC	TT	CT	CC	TT	CT	CC
	80	18	2	85	15	0	75	20	5
CYP2B6 15582C>T (rs4803419) (%)	CC	CT	TT	CC	CT	TT	CC	CT	TT
	28	70	2	25	75	0	30	65	5
*CYP2A6*9B* 1836G>T (rs8192726) (%)	GG	GT	TT	GG	GT	TT	GG	GT	TT
	82	18	0	80	20	0	75	25	0
CYP2A6 48A>C (rs28399433) (%)	AA	AC	CC	AA	AC	CC	AA	AC	CC
	78	22	0	75	25	0	70	30	0
NR1I2 63396C>T (rs2472677) (%)	CC	CT	TT	CC	CT	TT	CC	CT	TT
	63	30	7	65	30	5	60	30	10
NR1I3 540C>T (rs2307424) (%)	CC	CT	TT	CC	CT	TT	CC	CT	TT
	25	75	0	30	70	0	20	80	0
NR1I3 1089T>C (rs3003596) (%)	TT	CT	CC	TT	CT	CC	TT	CT	CC
	35	55	10	30	60	10	40	50	10

Values shown as median (interquartile range) and percentage of population.

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Table 2

Univariate and multivariate linear regression analysis from each study group

Efavirenz group						
$\log_{10}$ C_{max}	**Univariate linear regression**			**Multivariate linear regression**		
	***P* value**	**β value (95% CI)**	**r^2**	***P* value**	**β value (95% CI)**	**r^2**
Age (years)	0.049	−0.027 (−0.01,0.0)	0.199			
***CYP2B6* 516G>T (rs3745274)**	**0.021**	**−0.209 (−0.4,0.0)**	**0.263**	**0.021**	**−0.209 (−0.4,0.0)**	**0.263**
$\log_{10}$ $AUC_{0–24\ weeks}$	*P* value	β (pg/mL) (95% CI)	r^2	*P* value	β (pg/mL) (95% CI)	r^2
Age (years)	**0.028**	**−0.022 (0.0,0.0)**	**0.242**	**0.039**	**−0.018 (−0.0,0.0)**	**0.739**
CD4 ($\log_{10}$cells/mm^3)	0.085	0.520 (−0.1,1.1)	0.156			
***CYP2B6* 516G>T (rs3745274)**	**<0.000**	**−0.216 (−0.3,−0.1)**	**0.512**	**0.023**	**−0.132 (−0.2,0.0)**	**0.739**
***CYP2B6* 15582C>T (rs4803419)**	**0.058**	**−0.172 (−0.3,0.0)**	**0.186**	**0.021**	**−0.163 (−0.3,0.0)**	**0.756**
Nevirapine Group						
$\log_{10}$ C_{max}	Univariate linear regression			Multivariate linear regression		
	P value	β value (95% CI)	r^2	*P* value	β value (95% CI)	r^2
Age (years)	**0.056**	**0.015 (0.0,0.0)**	**0.189**	**0.044**	**0.013 (0.0,0.3)**	**0.569**
Albumin concentration at baseline (g/L)	0.076	0.019 (0.0,0.0)	0.164			
SHBG at baseline ($\log_{10}$ pg/mL)	**0.017**	**0.480 (0.1,0.9)**	**0.280**	**0.007**	**0.469 (0.0,0.8)**	**0.569**
***CYP2B6* 516G>T (rs3745274)**	**0.115**	**0.098 (0.0,0.2)**	**0.133**	**0.034**	**0.103 (0.0,0.2)**	**0.569**
T_{max}	*P* value	β value (95% CI)	r^2	*P* value	β value (95% CI)	r^2
Age (years)	0.043	−0.259 (−0.5,0.0)	0.209			
Weight ($\log_{10}$ kg)	**0.029**	**−16.956 (−31.9,−0.2)**	**0.239**	**0.002**	**−15.910 (−24.9,−6.9)**	**0.771**
CD4 ($\log_{10}$ cells/mm^3)	0.157	−3.489 (−8.5,1.5)	0.108			
Albumin concentration at baseline (g/L)	**0.001**	**−0.499 (−0.8,0.2)**	**0.446**	**0.003**	**−0.340 (−0.5,−0.1)**	**0.771**
***NR1I2* 63396C>T (rs2472677)**	**0.013**	**2.000 (0.5,3.5)**	**0.300**	**0.003**	**1.623 (0.6,2.6)**	**0.771**
$\log_{10}$ C_{min}	*P* value	β value (95% CI)	r^2	*P* value	β value (95% CI)	r^2
Weight ($\log_{10}$kg)	0.168	−0.751 (−1.8,0.3)	0.103			
SHBG at baseline ($\log_{10}$ nmol/L)	**0.022**	**0.496 (0.1,0.9)**	**0.258**	**0.011**	**0.522 (0.1,0.9)**	**0.561**
***CYP2B6* 516G>T (rs3745274)**	**0.118**	**0.104 (0.0,0.2)**	**0.130**	**0.048**	**0.115 (0.0,0.2)**	**0.561**

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Efavirenz group						
$\log_{10}$ C_{max}	**Univariate linear regression**			**Multivariate linear regression**		
	***P* value**	**β value (95% CI)**	**r^2**	***P* value**	**β value (95% CI)**	**r^2**
$\log_{10}$ $AUC_{0–24\ weeks}$	*P* value	β value (95% CI)	r^2	*P* value	β value (95% CI)	r^2
CD4 ($\log_{10}$cells/mm^3)	0.034	−0.282 (−0.5,0.0)	0.227			
SHBG at baseline ($\log_{10}$ pg/mL)	**0.008**	**0.465 (0.1,0.8)**	**0.333**	**0.004**	**0.484 (0.2,0.8)**	**0.457**
CYP2B6 516G>T (rs3745274)	0.179	0.075 (0.0,0.0)	0.098			

Univariate linear regression (*P*=≤0.2) completed, all statistically significant results then carried through to multivariate linear regression analysis (*P*=≤0.05). All statistically significant variables from multivariate linear regression shown in bold type.

β is the regression coefficient and represents incremental change in the $\log_{10}$ LNG pharmacokinetic parameter per unit change in a patient characteristic (e.g. per kg body weight or per allele carried). So if β=0.5 an increase per unit in the patient characteristic results in the $\log_{10}$ LNG pharmacokinetic parameter increasing by a factor of 0.5.

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Table 3

Levonorgestrel (LNG), Efavirenz (EFV) and Nevirapine (NVP) pharmacokinetic parameters shown as median (interquartile range), summarized by associated *CYP2B6, NR1I2* or *CYP2A6* genotype.

LNG C_{max} (pg/mL)	***CYP2B6*** **516G>T (rs3745274)**			***CYP2B6*** **15582C>T (rs4803419)**			***CYP2A6*9B*** **1836G>T (rs8192726)**			***NR1I2*** **63396C>T (rs2472677)**		
	GG	**GT**	**TT**	**CC**	**CT**	**TT**	**GG**	**GT**	**TT**	**CC**	**CT**	**TT**
EFV group	**692.57 (486.82–887.95)**	**402.40 (223.07–1027.65)**	**200.63**	**692.57 (501.09–706.56)**	**486.82 (347.10–775.28)**	-	**486.82 (359.66–706.56)**	**585.19 (223.07–1405.43)**	-	**486.82 (347.10–775.28)**	**463.03 (419.79–1027.65)**	**585.19**
NVP group	**1310.78 (1069.99–2530.06)**	**1449.53 (1053.42–1836.94)**	-	**1097.94 (814.90–2157.00)**	**1449.53 (1069.99–1836.94)**	**1267.16**	**1449.53 (1267.16–1836.94)**	**1097.94 (1069.99–1543.09)**	-	**1436.43 (1054.42–1877.35)**	**1310.78 (1303.20–1818.52)**	**1466.49 (775.98–2157.00)**
LNG T_{max} (wk)												
EFV group	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**4.00**	**1.00 (1.00–1.00)**	**1.00 (1.00–12.00)**	-	**1.00 (1.00–4.00)**	**1.00 (1.00–36.00)**	-	**1.00 (1.00–12.00)**	**1.00 (1.00–1.00)**	**1.00**
NVP group	**1.00 (1.00–1.00)**	**1.00 (1.00–12.00)**	-	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**1.00**	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	-	**1.00 (1.00–1.00)**	**1.00 (1.00–1.00)**	**6.50 (1.00–12.00)**
LNG C_{min} (pg/mL)												
EFV group	**272.21 (189.45–377.85)**	**202.23 (175.86–359.66)**	**121.82**	**298.99 (272.98–307.27)**	**208.13 (188.23–274.21)**	-	**224.66 (188.23–307.27)**	**202.23 (189.45–1405.43)**	-	**223.07 (188.23–359.66)**	**202.23 (189.13–298.99)**	**189.45**
NVP group	**553.65 (365.16–1094.09)**	**562.62 (504.42–807.67)**	-	**504.42 (343.67–713.96)**	**562.38 (512.46–986.40)**	**526.38**	**562.38 (504.42–807.67)**	**724.96 (540.18–986.40)**	-	**540.18 (501.00–956.95)**	**562.62 (562.38–986.40)**	**599.33 (512.46–686.21)**
LNG $AUC_{0–24weeks}$ (pg*wk/mL)												
EFV group	**10114.61 (8069.30–12862.18)**	**6311.80 (6569.71–14937.71)**	**3622.06**	**10114.61 (8499.98–12798.81)**	**7754.35 (5676.92–9435.56)**	-	**7754.35 (6311.80–11399.63)**	**8069.30 (4321.25–11070.02)**	-	**6830.55 (5676.92–11399.63)**	**7754.35 (7371.57–10114.61)**	**8069.30**
NVP group	**19970.24 (15259.29–30339.86)**	**15965.35 (15729.55–26301.13)**	-	**15761.90 (11338.65–22478.35)**	**20167.18 (15729.55–27442.02)**	**19970.24**	**19970.24 (15761.90–26301.13)**	**16948.72 (15258.29–21199.91)**	-	**16948.72 (15729.55–26301.13)**	**16759.11 (15258.29–27442.02)**	**19189.39 (15900.44–22478.35)**
EFV $C_{12–14h}$ (mg/L)	2.06 (1.39–2.61)	2.63 (2.05–6.89)	8.71	2.38 (2.20–2.63)	2.35 (1.75–5.06)	-	2.38 (1.75–3.03)	2.35 (1.99–6.64)	-	2.61 (2.05–6.64)	2.21 (2.01–2.38)	1.62
NVP $C_{11–13h}$ (mg/L)	6.51 (4.40–7.36)	6.16 (5.10–10.03)	-	6.75 (5.85–8.33)	6.10 (4.95–8.34)	8.01	6.10 (5.10–8.42)	6.63 (5.45–7.14)	-	6.75 (4.81–8.42)	6.16 (5.50–6.86)	7.06 (5.85–8.27)

EFV $C_{12–14h}$ (mg/L) and NVP $C_{11–13h}$ (mg/L) determined from individual participant's geometric mean value calculated from concentration measured at study entry, week 1, 4, 12, 24, 36 and 48 and summarized for the group as median (interquartile range).

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