

# Pharmacogenetic interactions of efavirenz or rifampin and isoniazid with levonorgestrel emergency contraception during treatment of HIV or tuberculosis

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**Objective** In AIDS Clinical Trials Group study A5375, a pharmacokinetic trial of levonorgestrel emergency contraception, double-dose levonorgestrel (3 mg, versus standard dose 1.5 mg) offset the induction effects of efavirenz or rifampin on plasma levonorgestrel exposure over 8 h post-dose ( $AUC_{0-8h}$ ). We characterized the pharmacogenetics of these interactions.

**Methods** Cisgender women receiving efavirenz- or dolutegravir-based HIV therapy, or on isoniazid-rifampin for tuberculosis, were followed after a single oral dose of levonorgestrel. Linear regression models, adjusted for BMI and age, characterized associations of *CYP2B6* and *NAT2* genotypes (which affect plasma efavirenz and isoniazid exposure, respectively) with levonorgestrel pharmacokinetic parameters.

**Results** Of 118 evaluable participants, 17 received efavirenz/levonorgestrel 1.5 mg, 35 efavirenz/levonorgestrel 3 mg, 34 isoniazid-rifampin/levonorgestrel 3 mg, and 32 (control group) dolutegravir/levonorgestrel 1.5 mg. There were 73 Black and 33 Asian participants. Regardless of genotype, women on efavirenz and isoniazid-rifampin had higher levonorgestrel clearance. In the efavirenz/levonorgestrel 3 mg group, *CYP2B6* normal/intermediate metabolizers had levonorgestrel  $AUC_{0-8h}$  values similar to controls, while *CYP2B6* poor metabolizers had  $AUC_{0-8h}$  values of 40% lower than controls. In the isoniazid-rifampin group, *NAT2* rapid/intermediate acetylators had levonorgestrel  $AUC_{0-8h}$  values similar to controls, while *NAT2* slow acetylators had  $AUC_{0-8h}$  values 36% higher than controls.

**Conclusion** *CYP2B6* poor metabolizer genotypes exacerbate the efavirenz-levonorgestrel interaction, likely by increased *CYP3A* induction with higher efavirenz exposure, making the interaction more difficult to overcome. *NAT2* slow acetylator genotypes attenuate the rifampin-levonorgestrel interaction, likely by increased *CYP3A* inhibition with higher isoniazid exposure. *Pharmacogenetics and Genomics* 33: 126–135 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.

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**Keywords:** *CYP2B6*; efavirenz; emergency contraception; HIV therapy; isoniazid; levonorgestrel; *NAT2*; pharmacogenetics; rifampin; tuberculosis

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## Introduction

Tuberculosis and HIV (HIV-1) are leading causes of infection-related deaths worldwide [1]. Women comprise the majority of persons with HIV worldwide [2]. Among

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women with HIV or tuberculosis, unintended pregnancies are associated with poor maternal and neonatal outcomes [3]. Emergency contraception is safe and effective when used as a single dose soon after sex [4], such that the WHO recommends access to emergency contraception, when needed, to prevent unintended pregnancy [5].

Isoniazid and rifampin are cornerstone medications for treating drug-sensitive tuberculosis, while efavirenz is recommended by the WHO for individuals of childbearing potential as an alternative to dolutegravir in first-line antiretroviral therapy (ART) [6]. Rifampin and efavirenz induce cytochrome (CYP) P450 enzymes that metabolize levonorgestrel [7,8], reducing plasma concentrations and compromising the efficacy of some hormonal contraceptives [9,10], and limiting family planning options. Isoniazid inhibits CYP3A4, CYP2A6, CYP1A2 and CYP2C19 [11], which may increase plasma exposure of drugs metabolized by these isoforms [12]. Dolutegravir is not expected to affect hormonal contraceptive plasma exposure.

Genetic polymorphisms predict increased plasma isoniazid and efavirenz exposure. Isoniazid is metabolized by N-acetyltransferase 2 (NAT2) [13], and *NAT2* loss-of-function alleles are frequent [13–15]. One or two copies of such alleles confer intermediate or slow acetylator phenotypes, respectively, and progressively greater isoniazid exposure [13–15]. Increased plasma efavirenz exposure is predicted by frequent *CYP2B6* polymorphisms [16].

Study A5375 of the AIDS Clinical Trials Group (ACTG) evaluated the pharmacokinetics and safety of dose-adjusted levonorgestrel emergency contraception in combination with efavirenz-based ART or rifampicin-containing tuberculosis therapy [17]. The trial showed that double-dose levonorgestrel (3 mg rather than standard 1.5 mg dose) effectively compensated for the lowering effects of efavirenz and rifampin-isoniazid on plasma levonorgestrel exposure over 8 h post-dose ( $AUC_{0-8h}$ ). The present analyses examined whether genetic polymorphisms that impact plasma efavirenz and isoniazid exposure affect drug-drug interactions following an oral dose of levonorgestrel.

## Methods

### Study population

A5375 (NCT03819114) was a phase II, open-label, partially randomized trial to determine the effects of steady-state efavirenz, isoniazid-rifampin, or dolutegravir on single-dose plasma levonorgestrel pharmacokinetics. Participants were post-menarcheal women at least 16 years of age, that were either living with HIV (without tuberculosis) and receiving either efavirenz- or dolutegravir-based ART or were being treated for tuberculosis (without HIV) with isoniazid and rifampin. Participants were excluded if pregnant, within 6 weeks post-partum, or breastfeeding an infant less than 6 months of age, had received levonorgestrel or other hormonal contraceptives

within the prior 30 days, norethisterone enanthate within the prior 60 days, or depo-medroxyprogesterone within the prior 90 days. Institutional review boards of participating institutions approved the study, and participants provided written informed consent.

### Procedures

A description of A5375 procedures and primary results are provided elsewhere [17]. Women with HIV and receiving efavirenz-based ART were randomized 1:2 to Group A (efavirenz/levonorgestrel 1.5 mg) or group B (efavirenz/levonorgestrel 3.0 mg). Women living with HIV and receiving dolutegravir-based ART were assigned to control group C (dolutegravir/levonorgestrel 1.5 mg). Women being treated for tuberculosis with isoniazid-rifampin were assigned to group D (isoniazid-rifampin/levonorgestrel 3 mg). Participants received a single dose of levonorgestrel on day 0, with or within 2 h of food consumption. Plasma was collected pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 and 48 h post-dose. Drug concentrations were quantified by validated, quality-controlled, liquid chromatography-tandem mass spectrometry [18–20]. The coefficient of variation of each analyte was less than 15%, and assays met Food and Drug Administration guidance on bioanalytical method validation [21]. Adherence to ART and tuberculosis medications was assessed using a self-report questionnaire [22]. Standard noncompartmental techniques were used to determine pharmacokinetic parameters using Phoenix WinNonLin (Certara) software.

### Genetic polymorphisms

Human DNA extracted from whole blood was used to genotype three *CYP2B6* polymorphisms (rs3745274, rs28399499, rs4803419) that predict increased plasma efavirenz exposure [16], four *NAT2* polymorphisms (rs1801279, rs1801280, rs1799930, rs1799931) that predict increased plasma isoniazid exposure [13–15], one *UGT1A1* polymorphism (rs887829) that predicts increased plasma dolutegravir exposure [23,24], and two *SLCO1B1* polymorphisms (rs4149032, rs4149056), the former associated in one study with reduced plasma rifampin exposure [25], and the latter with reduced transporter function that impacts statins and other drugs [26]. Genotyping was done in VANTAGE (Vanderbilt Technology for Advanced Genomics) using Taqman (ThermoFisher Scientific, Massachusetts, USA). Genotyping efficiency was 100% for all polymorphisms in all participants except for one individual in whom rs4149032 was indeterminate. All were in Hardy-Weinberg equilibrium ( $P > 0.05$ ).

### Statistical analysis

Primary analyses focused on associations of levonorgestrel clearance with *CYP2B6* in the efavirenz arms, and *NAT2* in the isoniazid-rifampin arm. We also considered *UGT1A1* in the dolutegravir arm and *SLCO1B1* in each arm. Associations were assessed by linear regression

models using STATA version 17.0 (StataCorp, College Station, Texas, USA). For *CYP2B6* and *UGT1A1*, intermediate and poor metabolizer groups were pairwise evaluated in relation to the reference normal metabolizer group, and intermediate and slow acetylator groups in relation to the reference rapid acetylator group for *NAT2*. We secondarily assessed associations of levonorgestrel  $AUC_{0-8h}$ . Covariates included screening BMI and age. For associations with levonorgestrel clearance among efavirenz recipients, the 1.5 mg and 3 mg levonorgestrel dose groups were combined, with levonorgestrel dose included as a covariate, despite A5375 showing that clearance in these groups did not differ by dose [17]. Analyses were repeated within subgroups based on self-identified race. Geometric mean ratios (GMR) summarized between-group comparisons. The 90% confidence interval (CI) of the GMR was calculated using the pooled variance of the difference and log transformation of pharmacokinetic parameters. Anti-logs of GMR and confidence bounds are reported. Some analyses used the dolutegravir arm as a control, as A5375 showed no apparent interaction between dolutegravir and levonorgestrel [17].

We defined *CYP2B6* metabolizer groups based on combinations of three polymorphisms, *CYP2B6* 516G→T (rs3745274), 983T→C (rs28399499), and 15582C→T (rs4803419) as follows: normal metabolizer (1 : 15582CC-516GG-983TT or 2 : 15582CT-516GG-983TT); intermediate metabolizer (3 : 15582TT-516GG-983TT; 4 : 15582CC-516GT-983TT; 5 : 15582CC-516GG-983CT; 6 : 15582CT-516GT-983TT; or 7 : 15582CT-516GG-983CT); and poor metabolizer (8 : 15582CC-516TT-983TT; 9 : 15582CC-516GT-983CT; 10 : 15582CC-516GG-983CC) [16]. For *NAT2*, acetylator groups were defined based on combinations of rs1801280 (*NAT2\*5*), rs1799930 (*NAT2\*6*), rs1799931 (*NAT2\*7*), and rs1801279 (*NAT2\*14*), as slow if homozygous for the variant allele at any locus (i.e. AA, CC, AA, AA, respectively), or heterozygous at 2 or more loci; intermediate if heterozygous at a single locus; or rapid if no variant allele at any locus. For *UGT1A1* rs887829, participants with CC, CT, and TT genotypes were classified as normal, intermediate, and slow metabolizers, respectively. We did not correct for multiple comparisons, given strong a priori evidence of the pharmacokinetic impact of the polymorphisms on efavirenz and isoniazid. Two-sided statistical tests were used. Clearance and  $AUC_{0-8h}$  were natural log transformed.

## Results

### Participant characteristics

A5375 enrolled 122 cisgender women across seven countries, of whom 118 (97%) were evaluable for genetic associations. Among 52 women in the efavirenz groups, 8 (15.4%) were *CYP2B6* poor metabolizers.

Among 34 women in the isoniazid-rifampin group, 15 (44.1%) were *NAT2* slow acetylators. The median age was lowest in the isoniazid-rifampin group. Median screening BMI was lowest in the isoniazid-rifampin group and efavirenz/levonorgestrel 1.5 mg group, and highest in the dolutegravir group. The baseline characteristics of participants are shown in Table 1.

### Genetic associations with levonorgestrel clearance in the efavirenz group

In multivariable analyses among all 52 women in the efavirenz group, *CYP2B6* genotype was significantly associated with log levonorgestrel clearance, with *CYP2B6* poor metabolizers having the most rapid clearance. Model results are shown in Table 2. This association was driven by *CYP2B6* poor metabolizers. The adjusted GMR of clearance in poor versus normal metabolizers was 2.09 (90% CI: 1.47–3.19), and in intermediate versus normal metabolizers was 0.97 (90% CI: 0.71–1.33). Unadjusted log clearance values are shown in Fig. 1 (left section). In multivariable analyses that controlled for *CYP2B6* genotype, there was not evidence of association of *SLCO1B1* rs4149056 and rs4149032 with levonorgestrel clearance ( $P > 0.05$  for each).

In multivariable analyses that included only the 29 Asian women in the efavirenz group, *CYP2B6* genotype was also significantly associated with levonorgestrel clearance, again driven by *CYP2B6* poor metabolizers. Among Asian women, the adjusted GMR of clearance in poor versus normal metabolizers was 2.77 (90% CI: 1.96–3.91), and in intermediate versus normal metabolizers was 0.88 (90% CI: 0.68–1.15).

In multivariable analyses that included only the 19 Black women in the efavirenz group, *CYP2B6* poor metabolizers also had the most rapid levonorgestrel clearance, but this was not statistically significant. Among Black women, the adjusted GMR of clearance in poor versus normal metabolizers was 1.96 (90% CI: 0.89–4.31), and in intermediate versus normal metabolizers was 1.76 (90% CI: 0.89–3.48).

### Genetic associations with levonorgestrel clearance in the isoniazid-rifampin group

In multivariable analyses among the 34 women in the isoniazid-rifampin group, *NAT2* genotype was associated with log levonorgestrel clearance, with *NAT2* slow acetylators having the slowest clearance. Model results are shown in Table 2. This was driven by *NAT2* slow acetylators. The adjusted GMR of clearance in slow versus rapid acetylators was 0.60 (90% CI: 0.38–0.97), and in intermediate versus rapid acetylators was 0.93 (90% CI: 0.59–1.47). Unadjusted log clearance values are shown in Fig. 1 (middle section). In multivariable analyses that controlled for *NAT2* acetylator status, there was no evidence of association between *SLCO1B1* rs4149056 and

**Table 1** Baseline characteristics of A5375 participants included in genetic association analyses

	INH-RIF <sup>a</sup> (n = 34)	EFV-LNG 1.5 <sup>b</sup> (n = 17)	EFV-LNG 3.0 <sup>c</sup> (n = 35)	DTG <sup>d</sup> (n = 32)	Total (n = 118)
Age in years, median (IQR <sup>e</sup> )	24.5 (20.8–35.3)	42 (34.5–45)	36 (29–42)	34 (29–40)	34 (26.8–41.3)
Race/ethnicity, n (%)					
Black	30 (88.2)	7 (41.2)	12 (34.3)	24 (75)	73 (61.9)
Asian	2 (5.9)	9 (52.9)	20 (57.1)	2 (6.3)	33 (28.0)
Latina	2 (5.9)	1 (5.9)	3 (8.6)	4 (12.5)	10 (8.5)
White	-	-	-	1 (0.9)	1 (0.9)
Multiple	-	-	-	1 (0.9)	1 (0.9)
Country; n (%)					
Botswana	2 (5.9)	-	-	-	2 (1.7)
Brazil	2 (5.9)	1 (5.9)	3 (8.6)	4 (12.5)	10 (8.5)
Kenya	4 (11.8)	-	-	-	4 (3.4)
Malawi	6 (17.7)	-	-	10 (31.3)	16 (13.6)
South Africa	18 (52.9)	7 (41.2)	12 (34.3)	2 (6.3)	39 (33.1)
Thailand	2 (5.9)	9 (52.9)	20 (57.1)	2 (6.3)	33 (28.0)
USA	-	-	-	14 (43.8)	14 (11.9)
BMI <sup>e</sup> in kg/m <sup>2</sup> , median (range)	21.5 (19.7–24.6)	20.3 (18.3–27.6)	23.5 (20.5–26.6)	25.3 (21.6–28.5)	23.2 (20.0–26.3)
<i>CYP2B6</i> metabolizer, n (%)					
Normal	11 (34.4)	3 (17.7)	12 (34.3)	12 (37.5)	38 (32.8)
Intermediate	14 (43.8)	11 (64.7)	18 (51.4)	9 (28.1)	52 (44.8)
Poor	7 (21.9)	3 (17.7)	5 (14.3)	11 (34.4)	26 (22.4)
<i>NAT2</i> acetylator, n (%)					
Rapid	4 (11.8)	2 (11.8)	3 (8.6)	5 (15.6)	14 (11.9)
Intermediate	15 (44.1)	9 (52.9)	21 (60)	13 (40.6)	58 (49.2)
Slow	15 (44.1)	6 (35.3)	11 (31.4)	14 (43.8)	46 (39.0)
<i>UGT1A1</i> metabolizer, n (%)					
Normal	11 (34.4)	8 (47.1)	19 (54.3)	5 (15.6)	43 (37.1)
Intermediate	14 (43.8)	9 (52.9)	14 (40)	22 (68.8)	59 (50.1)
Poor	7 (21.9)	-	2 (5.7)	5 (15.6)	14 (12.1)
<i>SLCO1B1</i> rs4149032, n (%)					
CC	3 (9.4)	3 (17.7)	8 (22.9)	5 (16.1)	19 (16.4)
CT	14 (43.8)	3 (17.7)	14 (40.0)	12 (38.7)	43 (37.1)
TT	15 (46.9)	11 (64.7)	13 (37.1)	14 (45.2)	53 (45.7)
<i>SLCO1B1</i> rs4149056, n (%)					
CT	5 (15.6)	1 (5.9)	5 (14.3)	1 (3.1)	12 (10.3)
TT	27 (84.4)	16 (94.1)	30 (85.7)	31 (96.9)	104 (89.7)

<sup>a</sup>INH-RIF, isoniazid-rifampin with 3 mg levonorgestrel (LNG) dose.<sup>b</sup>EFV-LNG 1.5, efavirenz with 1.5 mg LNG dose.<sup>c</sup>EFV-LNG 3.0, efavirenz with 3 mg LNG dose.<sup>d</sup>DTG, dolutegravir with 1.5 mg LNG dose.<sup>e</sup>IQR, interquartile range.**Table 2** Multivariable models of log levonorgestrel clearance associations with genotype, sex, BMI, and levonorgestrel dose.

	Efavirenz group log clearance $\beta$ coeff., <i>P</i> -value (n = 52)	Isoniazid-Rifampin group log clearance $\beta$ coeff., <i>P</i> -value (n = 34)	Dolutegravir group log clearance $\beta$ coeff., <i>P</i> -value (n = 32)
<i>CYP2B6</i> genotype <sup>a</sup>		<i>NAT2</i> genotype <sup>a</sup>	<i>UGT1A1</i> genotype <sup>a</sup>
Intermediate	-0.03 to 0.87	Intermediate	Intermediate
Poor	0.74 to 0.005	Slow	Poor
BMI <sup>b</sup>	0.035 to 0.017	BMI	BMI
Age <sup>c</sup>	0.002 to 0.87	Age	Age
Levonorgestrel dose <sup>d</sup>	0.051 to 0.67		

<sup>a</sup>The reference group is normal metabolizer for *CYP2B6* and *UGT1A1*, and rapid acetylator for *NAT2*.<sup>b</sup>Per 1 kg/m<sup>2</sup><sup>c</sup>Per year.<sup>d</sup>Per mg increase in levonorgestrel dose.

rs4149032 with levonorgestrel clearance ( $P > 0.05$  for each).

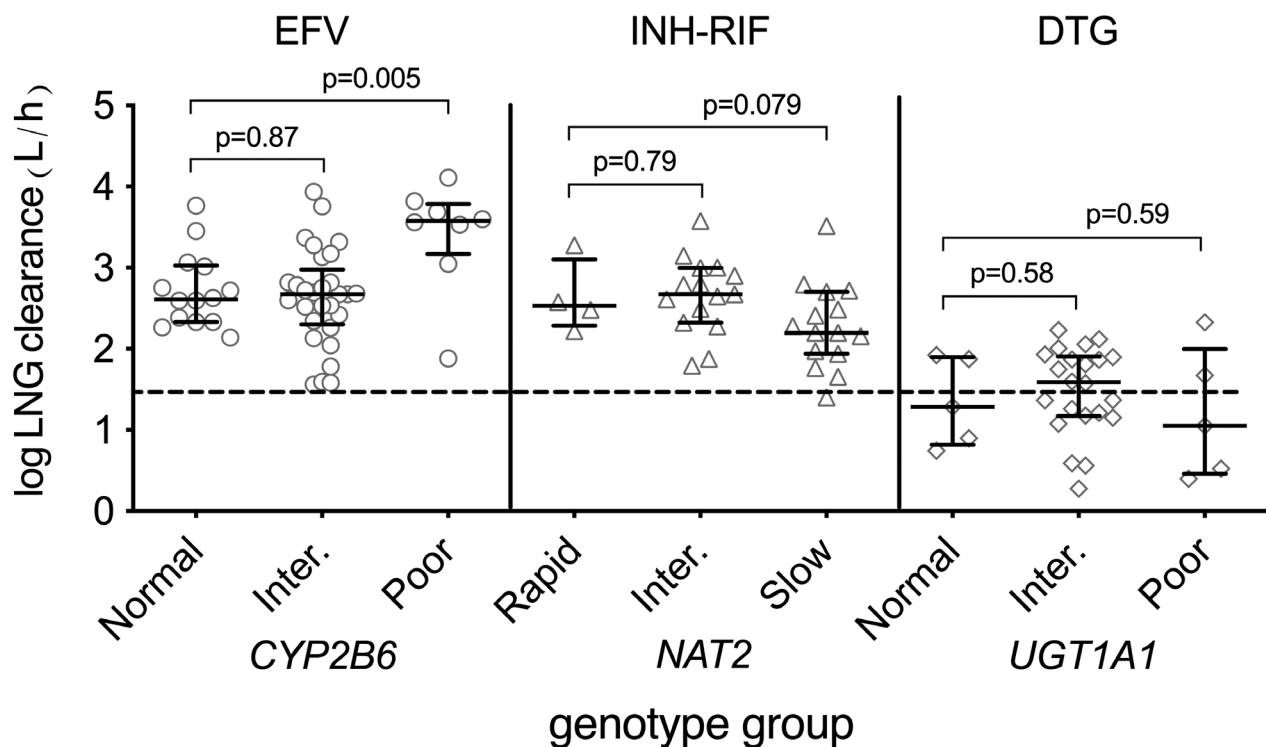
In multivariable analyses that included only the 30 Black women in the isoniazid-rifampin group, *NAT2* acetylator status was also significantly associated with levonorgestrel clearance, again driven by *NAT2* slow acetylators. Among Black women, the adjusted GMR of clearance in slow versus rapid acetylators was 0.56 (90% CI: 0.35–0.88), and in intermediate versus rapid acetylators was 0.88 (90% CI: 0.57–1.37).

### Genetic associations with levonorgestrel clearance in the dolutegravir control group

In multivariable analyses among all 32 women in the dolutegravir group, there was no evidence of association between *UGT1A1* genotype and levonorgestrel clearance. Model results are shown in Table 2. The adjusted GMR of clearance in TT versus CC was 1.01 (90% CI: 0.63–1.65), and in CT versus CC was 0.85 (90% CI: 0.59–1.24). Unadjusted log clearance values are shown in Fig. 1



Fig. 1



Relationships between human genetic variants and log levonorgestrel clearance among women in A5375. Left panel: relationship of *CYP2B6* metabolizer group with plasma levonorgestrel clearance in women with HIV on efavirenz, who received a single 1.5 mg or 3 mg oral dose of levonorgestrel. Middle panel: relationship of *NAT2* acetylator group with plasma levonorgestrel clearance in women being treated for tuberculosis with isoniazid and rifampin, and who received a single 3 mg oral dose of levonorgestrel. Right panel: relationship of *UGT1A1* genotype with plasma levonorgestrel clearance in women with HIV on dolutegravir, who received a single 1.5 mg oral dose of levonorgestrel. Error bars indicate the median and interquartile range. The markers are unadjusted for BMI or age. The dashed line indicates median log levonorgestrel clearance (1.47) in the dolutegravir control group. *P* values from multivariable linear regression are shown. DTG, dolutegravir; EFV, efavirenz; INH, isoniazid; Inter, intermediate; LNG, levonorgestrel; RIF, rifampin.

(right section). In multivariable analyses that controlled for *UGT1A1* genotype, there was no evidence of association between *SLCO1B1* rs4149056 and rs4149032 with levonorgestrel clearance ( $P > 0.05$  for each).

#### Genetic associations with plasma levonorgestrel

##### AUC<sub>0-8h</sub>

Genetic association with plasma levonorgestrel AUC<sub>0-8h</sub> were generally consistent with those for clearance. In multivariable analyses among the 17 women in the efavirenz/levonorgestrel 1.5 mg group, *CYP2B6* genotype was significantly associated with log AUC<sub>0-8h</sub>, with *CYP2B6* poor metabolizers having the lowest AUC. In these 17 women, the adjusted GMR of AUC<sub>0-8h</sub> in poor versus normal metabolizers was 0.43 (90% CI: 0.27–0.69), and in intermediate versus normal metabolizers was 1.30 (90% CI: 0.88–1.91). Similarly, among the 35 women in the efavirenz/levonorgestrel 3 mg group, there was a relationship between AUC<sub>0-8h</sub> and *CYP2B6* genotype. In these 35 women, the adjusted GMR of AUC<sub>0-8h</sub> in poor versus normal metabolizers was 0.59 (90% CI: 0.39–0.88), and in intermediate versus normal metabolizers was 0.95 (90% CI: 0.72–1.27).

Among the 34 women in the rifampin-isoniazid group, *NAT2* slow acetylators had the highest levonorgestrel AUC<sub>0-8h</sub> values, but this was not significantly significant. The adjusted GMR of AUC<sub>0-8h</sub> in slow versus normal acetylators was 1.31 (90% CI: 0.93–1.86), and in intermediate versus normal acetylators was 1.01 (90% CI: 0.72–1.42). Among the 32 women in the dolutegravir group, a relationship between AUC<sub>0-8h</sub> and *UGT1A1* genotype was not observed, nor in analyses that controlled for rs887829, *SLCO1B1* rs4149056 and rs4149032 ( $P > 0.05$  for each).

Within each study arm and metabolizer/acetylator group, we considered AUC<sub>0-8h</sub> values in relation to dolutegravir controls, adjusting for BMI and age. Because levonorgestrel clearance in the efavirenz group was similar in *CYP2B6* normal and intermediate metabolizers, we combined these groups for AUC<sub>0-8h</sub> analyses. Among *CYP2B6* normal and intermediate metabolizers in the efavirenz group, levonorgestrel 1.5 mg yielded a lower levonorgestrel AUC<sub>0-8h</sub> values than in controls (adjusted GMR 0.58; 90% CI: 0.46–0.72), while levonorgestrel 3 mg yielded AUC<sub>0-8h</sub> values comparable to controls (adjusted GMR 0.98; 90% CI: 0.83–1.16). In contrast,

among *CYP2B6* poor metabolizers in the efavirenz group, levonorgestrel 1.5 mg yielded  $AUC_{0-8h}$  markedly lower than in controls (adjusted GMR 0.23; 90% CI: 0.15, 0.33); Levonorgestrel 3 mg also yielded  $AUC_{0-8h}$  lower than in controls (adjusted GMR 0.60; 90% CI: 0.44–0.82), and  $C_{max}$  values 23% lower than in controls (adjusted GMR 0.77; 90% CI: 0.55–1.06). Unadjusted  $AUC_{0-8h}$  values are shown in Fig. 2.

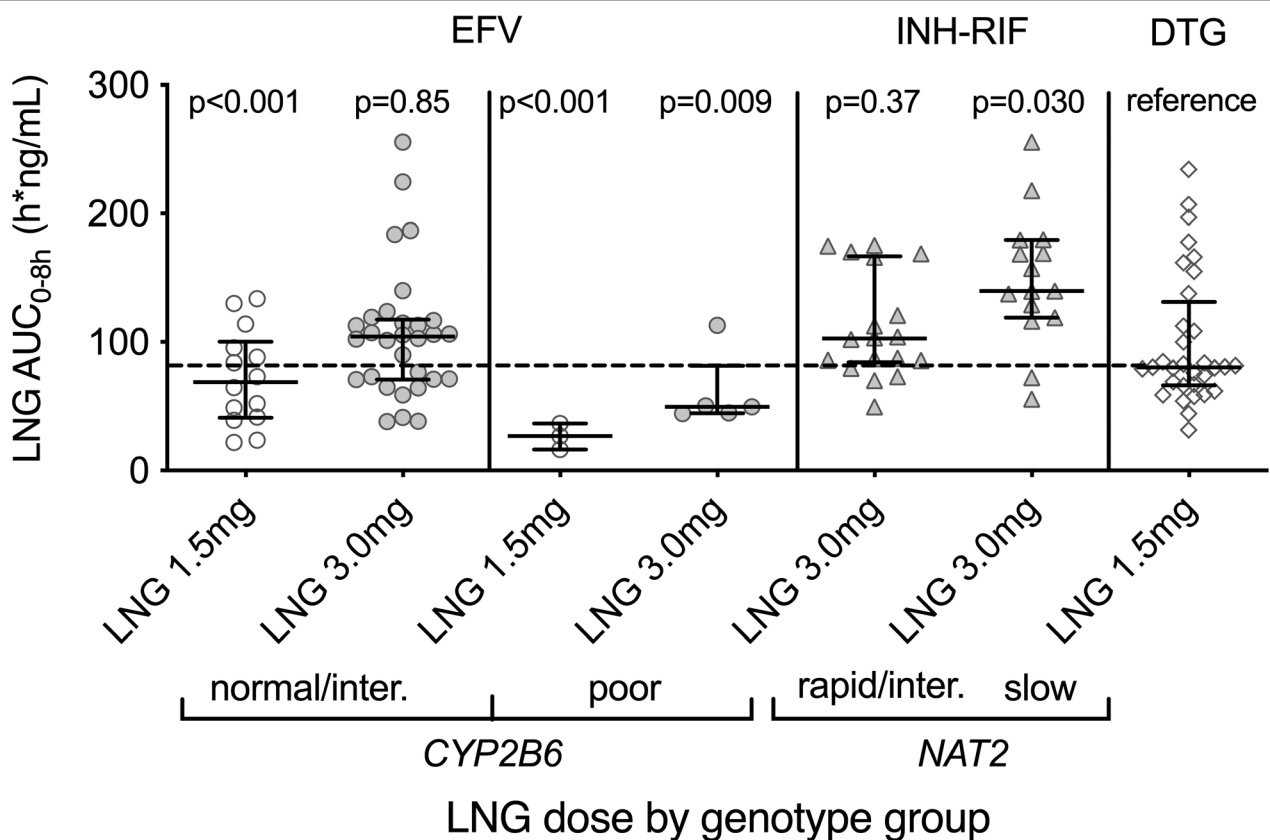
Levonorgestrel clearance in the isoniazid-rifampin group was similar in *NAT2* rapid and intermediate acetylators. We therefore combined these groups for evaluation of  $AUC_{0-8h}$  compared to the control group and adjusted for BMI and age. Among *NAT2* rapid and intermediate acetylators in the isoniazid-rifampin group, levonorgestrel 3 mg yielded levonorgestrel  $AUC_{0-8h}$  values comparable to controls (adjusted GMR 1.10; 90% CI: 0.92–1.32). In contrast, among *NAT2* slow acetylators in

the isoniazid-rifampin group, levonorgestrel 3 mg yielded higher levonorgestrel  $AUC_{0-8h}$  values than in controls (adjusted GMR 1.36; 90% CI: 1.08–1.71). Unadjusted  $AUC_{0-8h}$  values are shown in Fig. 2.

## Discussion

Primary analyses from A5375 showed that, among women who received a single dose of levonorgestrel, those on efavirenz-based ART exhibited much faster plasma levonorgestrel clearance compared to a dolutegravir control group, and that doubling the levonorgestrel dose from 1.5 mg to 3.0 mg yielded levonorgestrel  $AUC_{0-8h}$  values comparable to controls [17]. The present analyses show that effects of double-dose levonorgestrel to compensate for efavirenz-induced levonorgestrel clearance differ by *CYP2B6* genotype. Among *CYP2B6* normal and intermediate metabolizers in the efavirenz group, levonorgestrel 1.5 mg yielded levonorgestrel  $AUC_{0-8h}$  approximately

Fig. 2



Relationships between human genetic variants and levonorgestrel  $AUC_{0-8h}$  among women in A5375. Left panel: relationship between levonorgestrel dose and levonorgestrel  $AUC_{0-8h}$  among *CYP2B6* normal and intermediate metabolizers in women with HIV on efavirenz, and who received a single 1.5 mg or 3 mg oral dose of levonorgestrel. Panel second from left: relationship between levonorgestrel dose and levonorgestrel  $AUC_{0-8h}$  among *CYP2B6* poor metabolizers in women with HIV on efavirenz, and who received a single 1.5 mg or 3 mg oral dose of levonorgestrel. Panel second from right: relationship between *NAT2* genotype and levonorgestrel  $AUC_{0-8h}$  among women with tuberculosis on isoniazid and rifampin, and who received a single 3 mg oral dose of levonorgestrel. Right panel: levonorgestrel  $AUC_{0-8h}$  in women with HIV on dolutegravir, and who received a single 1.5 mg oral dose of levonorgestrel. Error bars indicate the median and interquartile range. Clear and gray shaded markers represent 1.5 mg or 3 mg doses of levonorgestrel, respectively. The markers are unadjusted for BMI or age. The horizontal dashed line indicates a median  $AUC_{0-8h}$  in the dolutegravir control group. *P* values from multivariable linear regression are shown. DTG, dolutegravir, EFV, efavirenz, INH, isoniazid, Inter, intermediate, inter, intermediate, LNG, levonorgestrel, RIF, rifampin.

42% lower than in controls, and among *CYP2B6* poor metabolizers approximately 77% lower than in controls. With double-dose levonorgestrel, among *CYP2B6* normal and intermediate metabolizers in the efavirenz group, levonorgestrel 3 mg yielded levonorgestrel  $AUC_{0-8h}$  similar to controls, yet among *CYP2B6* poor metabolizers, levonorgestrel  $AUC_{0-8h}$  remained approximately 40% lower than in controls. These results indicate that among *CYP2B6* poor metabolizers receiving efavirenz, a levonorgestrel dose greater than 3 mg might be needed to achieve  $AUC_{0-8h}$  values comparable to controls. As  $C_{max}$  is suggested to be associated with emergency contraceptive effectiveness [27], it is reassuring that levonorgestrel 3 mg yielded  $C_{max}$  values only 23% lower than in controls among *CYP2B6* poor metabolizers in the efavirenz group. However, caution is still warranted, as the pharmacokinetic-pharmacodynamic relationship has not been established.

The pharmacogenetic interaction with efavirenz in this study is complex. In *CYP2B6* poor metabolizers, plasma efavirenz exposure is much greater than it is in normal and intermediate metabolizers [16]. The resultant induction of *CYP3A4* expression by efavirenz is therefore expected to be greater in poor metabolizers than in normal and intermediate metabolizers, and levonorgestrel clearance by *CYP3A4* increased to a greater extent in poor metabolizers. This explains why double-dose levonorgestrel in these *CYP2B6* poor metabolizers yields  $AUC_{0-8h}$  values that remain lower than in controls, while double-dose levonorgestrel in normal and intermediate metabolizers yields a similar  $AUC_{0-8h}$  compared to controls.

Associations of *CYP2B6* genotype with levonorgestrel clearance and  $AUC_{0-8h}$  among efavirenz recipients were not unexpected. Many contraceptive hormones including levonorgestrel are metabolized by *CYP3A* isoforms, and greater efavirenz exposure has been shown to increase rates of plasma clearance of some hormonal contraceptives [9,10]. Among women receiving efavirenz-based ART who then received a levonorgestrel-releasing contraceptive implant, *CYP2B6* poor metabolizers had more rapid levonorgestrel clearance and lower  $AUC$  values [28]. In ACTG study A5316, efavirenz reduced plasma concentrations of etonogestrel and ethinyl estradiol, given as a vaginal ring [9], with *CYP2B6* poor metabolizers having the greatest reductions [29]. However, study findings have not been consistent. In ACTG study A5093, which compared pharmacokinetics of depot-medroxyprogesterone acetate (DMPA) and selected ART regimens among women with HIV found no difference in MPA  $AUC$ ,  $C_{max}$  or clearance based on *CYP2B6* genotype [30,31]. Findings were similarly negative in pharmacogenetic analyses from ACTG study A5338, which studied the pharmacokinetics of DMPA among women with HIV receiving efavirenz-based ART and rifampicin plus isoniazid for tuberculosis co-infection [32]. Another study

demonstrated higher plasma MPA  $AUC$  values among women receiving efavirenz-based ART than women not on ART [33].

Primary analyses from A5375 showed that, among pre-menopausal women who received a single dose of levonorgestrel, those on isoniazid-rifampin therapy for tuberculosis exhibited much faster levonorgestrel clearance compared to dolutegravir controls, and that a levonorgestrel 3.0 mg double-dose yielded levonorgestrel  $AUC_{0-8h}$  values somewhat greater than in controls [17]. The present analyses show that effects of double-dose levonorgestrel to compensate for rifampin-induced levonorgestrel clearance, in the presence of the *CYP3A4* inhibitor isoniazid, differ by *NAT2* genotype. Among *NAT2* normal and intermediate acetylators who received levonorgestrel 3 mg,  $AUC_{0-8h}$  was approximately 10% greater than in controls, but among slow acetylators was approximately 36% greater than in controls. Since such levels should provide effective contraception, and because the risk of toxicity following a single dose is low, double-dose levonorgestrel for all women receiving concomitant isoniazid and rifampin is appropriate regardless of *NAT2* genotype.

The pharmacogenetic interaction with isoniazid and rifampin in this study is complex. Rifampin potently induces *CYP3A4* expression [7], while isoniazid is a mechanism-based inhibitor of *CYP3A4* [11]. In individuals receiving both isoniazid and rifampin, induction by rifampin typically dominates the inhibitory effect of isoniazid. In *NAT2* normal and intermediate acetylators, plasma isoniazid exposure is relatively low, so isoniazid minimally counteracts the inductive effect of rifampin, and levonorgestrel clearance by *CYP3A4* is greatly increased. Double-dose levonorgestrel in these individuals therefore yields  $AUC_{0-8h}$  values only slightly higher than in controls. In *NAT2* poor metabolizers, plasma isoniazid exposure is greater, so the inhibitory effect of isoniazid on *CYP3A4* is greater, which more effectively attenuates the inductive effect of rifampin on levonorgestrel clearance. Double-dose levonorgestrel in these women therefore yields median  $AUC_{0-8h}$  values considerably greater than in controls.

The association of *NAT2* genotype with levonorgestrel clearance and  $AUC_{0-8h}$  was not unexpected. An analogous situation occurs in some patients receiving tuberculosis therapy that includes isoniazid with rifampin, who paradoxically experience increased plasma efavirenz exposure in the presence of *CYP2B6* and *NAT2* loss-of-function polymorphisms [34–36]. In ACTG trial A5279, which studied rifapentine plus isoniazid for preventing tuberculosis in patients living with HIV [37], *NAT2* slow acetylators had higher plasma concentrations not only of efavirenz, but also of rifapentine, its 25-desacetyl rifapentine metabolite, and nevirapine [12], reflecting greater inhibition of *CYP* isoforms that metabolize these drugs.

The present trial enrolled women of various ancestries. In subgroup analyses, results generally reflected those in the total group. Among 29 Asian women in the efavirenz group, *CYP2B6* genotype was significantly associated with levonorgestrel clearance, while among 30 Black women in the isoniazid-rifampin group, *NAT2* acetylator status was significantly associated with levonorgestrel clearance. The lack of significant association between *CYP2B6* genotype and levonorgestrel clearance among 19 Black women in the efavirenz group may be due to a small sample size. There were too few women in other subgroups to analyze.

Because treatment assignment was not by randomization (except for 1.5 versus 3 mg of levonorgestrel among those taking efavirenz), there were anticipated differences in some baseline characteristics between trial arms (Table 1), including BMI as was reported in the A5375 primary manuscript [17]. Therefore, all comparisons adjusted for BMI, which affects levonorgestrel concentrations during emergency contraception [38,39].

We found no associations between *UGT1A1* genotype and levonorgestrel clearance in the dolutegravir group. This was expected, since A5375 primary analyses showed that dolutegravir did not alter levonorgestrel pharmacokinetics in comparison to a historical control [17]. Similarly, we did not find associations between *SLCO1B1* genotype and levonorgestrel clearance. A single study from South Africa associated *SLCO1B1* rs4149032 with rifampin clearance [25]. The infrequency of *SLCO1B1* rs4149056 may have precluded finding associations.

Regarding potential clinical implications for women on efavirenz, while *CYP2B6* poor metabolizers who received a levonorgestrel dose of 3 mg did not achieve  $AUC_{0-8h}$  comparable to controls, we are reassured that  $C_{max}$  values were closer to those in controls. In our total sample, 22.4% of women were *CYP2B6* poor metabolizers, reflecting that these genotypes are frequent with Asian and African ancestry [40]. Lacking future data, and because results of *CYP2B6* genotyping would almost certainly not be available in clinical practice prior to emergency contraception, it is reasonable to recommend double-dose levonorgestrel (3 mg) for all women receiving efavirenz, understanding that some women will have lower  $C_{max}$  and  $AUC_{0-8h}$  values.

The present analysis had limitations. Because A5375 was only partially randomized, pharmacokinetic differences between groups may be affected by factors not captured in our analyses. Because of the modest sample size, we could only study frequent polymorphisms with large effect sizes. Because A5375 did not study rifampin without isoniazid, we cannot know what levonorgestrel exposure would be in such women, although it would almost certainly be lower than with isoniazid-rifampin.

In summary, among cisgender women with HIV and receiving efavirenz-based ART, the pharmacokinetic effect of doubling the levonorgestrel dose for emergency contraception varies by *CYP2B6* genotype. Similarly, among women being treated for tuberculosis with isoniazid and rifampin, the effect of doubling the levonorgestrel dose varies by *NAT2* genotype. This analysis reinforces the importance of evaluating pharmacogenetics effects on drug-drug interactions.

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### Conflicts of interest

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