Pharmacogenetics of Efavirenz, Rifampin and Isoniazid Interactions with Levonorgestrel Emergency Contraception during Treatment of HIV and Tuberculosis (TB)

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BACKGROUND

- Among women with HIV or TB, unintended pregnancies are associated with poor maternal and neonatal outcomes.
- Emergency contraception is safe and effective when given as a single dose soon after sex.
- Rifampin (RIF) and efavirenz (EFV) lower plasma levonorgestrel (LNG) levels, while isoniazid (INH) increases levels of some drugs.
- In ACTG study A5375, double-dose LNG (3 mg rather than standard 1.5 mg) compensated for the lowering effects of EFV and RIF-INH on plasma LNG exposure over 8 hours post-dose ($AUC_{0\text{-}8h}$), while LNG exposure was not affected in the dolutegravir (DTG) control group [PMID 36641094].

OBJECTIVE

- To determine whether, in study A5375, SNPs that increase plasma EFV and INH levels affect drug-drug interactions after an oral dose of LNG.

METHODS

- A5375 was a phase II, open label trial to determine effects of steady-state EFV, INH-RIF, or DTG on single-dose plasma LNG pharmacokinetics in cisgender women (NCT03819114).
- Participants were at least 16 years of age and either living with HIV (without TB) and receiving EFV- or DTG-based ART, or treated for TB (without HIV) with INH-RIF.
- Women on EFV were randomized 1:2 to Group A (LNG 1.5 mg) or group B (LNG 3.0 mg); women on DTG were assigned to control group C (LNG 1.5 mg); women on INH-RIF were assigned to group D (LNG 3 mg).
- Participants received a single dose of LNG on day 0, with serial plasma samples collected from pre-dose to 48 hours post dose.
- To characterize metabolizer/acetylator status, we genotyped *CYP2B6* (rs3745274, rs28399499, rs4803419), *NAT2* (rs1801279, rs1801280, rs1799930, rs1799931), and *UGT1A1* (rs887829).
- Associations were assessed by linear regression models and included screening body mass index (BMI) and age as covariates.

RESULTS

- Study A5375 enrolled 122 women in Botswana, Brazil, Kenya, Malawi, South Africa, Thailand, and the United States.
- Of the 122 women, 118 (97%) were evaluable for genetic associations
- Participant characteristics at baseline are shown in **Table 1.**

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Among women who received single-dose LNG while also receiving either EFV or RIF-INH in ACTG study A5375, *CYP2B6* poor metabolizer genotypes made the EFV-LNG interaction more difficult to overcome with double-dose (3 mg) LNG. It is reasonable to recommend double-dose LNG for all women receiving EFV, understanding that *CYP2B6* poor metabolizers may still have lower LNG exposure. *NAT2* slow acetylator genotypes attenuate the RIF-INH interaction with LNG, but double-dose LNG is still appropriate.

Table 1. Baselines characteristics of the 118 participants

	INH-RIF (n=34)	EFV-LNG 1.5 (n=17)	EFV-LNG 3.0 (n=35)	DTG (n=32)
Age in years, median (IQR)	24.5 (20.8 – 35.3)	42 (34.5 - 45)	36 (29 - 42)	34 (29 - 40)
Race/Ethnicity; n (%)				
Black	30 (88.2)	7 (41.2)	12 (34.3)	24 (75)
Asian	2 (5.9)	9 (52.9)	20 (57.1)	2 (6.3)
Latina	2 (5.9)	1 (5.9)	3 (8.6)	4 (12.5)
Other	-	-	-	2 (1.8)
BMI in kg/m^2, 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)
CYP2B6, n (%)				
normal	11 (34.4)	3 (17.7)	12 (34.3)	12 (37.5)
intermediate	14 (43.8)	11 (64.7)	18 (51.4)	9 (28.1)
poor	7 (21.9)	3 (17.7)	5 (14.3)	11 (34.4)
NAT2, n (%)				
rapid	4 (11.8)	2 (11.8)	3 (8.6)	5 (15.6)
intermediate	15 (44.1)	9 (52.9)	21 (60)	13 (40.6)
slow	15 (44.1)	6 (35.3)	11 (31.4)	14 (43.8)
UGT1A1, n (%)				
normal	11 (34.4)	8 (47.1)	19 (54.3)	5 (15.6)
intermediate	14 (43.8)	9 (52.9)	14 (40)	22 (68.8)
poor	7 (21.9)	-	2 (5.7)	5 (15.6)

Associations of *CYP2B6* with LNG CL/F in the EFV group

- *CYP2B6* genotype was significantly associated with log LNG clearance (CL/F), with poor metabolizers having the most rapid clearance (**Table 2**, left).
- Adjusted GMR of CL/F in *CYP2B6* poor vs normal metabolizers was 2.09 (90% CI: 1.47, 3.19); in intermediate vs normal was 0.97 (90% CI: 0.71, 1.33).
- Unadjusted log LNG CL/F values are shown in **Figure 1** (left section).

Associations of *NAT2* with LNG CL/F in the INH-RIF group

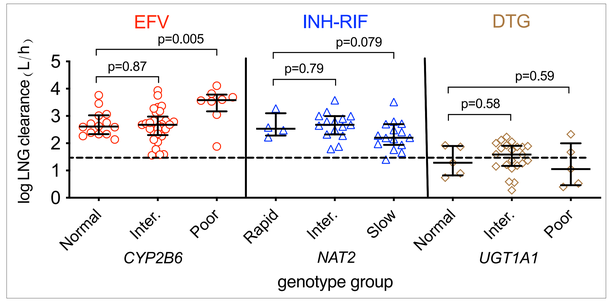
- *NAT2* genotype was associated with log LNG CL/F, with slow acetylators having the slowest clearance (**Table 2**, middle columns).
- Adjusted GMR of CL/F in slow vs rapid acetylators was 0.60 (90% CI: 0.38, 0.97); in intermediate vs rapid was 0.93 (90% CI: 0.59, 1.47).
- Unadjusted log LNG CL/F values are shown in **Figure 1** (middle section).

Table 2. Multivariable models of log LNG clearance

Efavirenz group log clearance β coeff., P-value (n = 52)		Isoniazid-Rifampin group log clearance β coeff., P-value (n = 34)		Dolutegravir group log clearance β coeff., P-value (n = 32)	
CYP2B6 genotype[a]		*NAT2*[a]		*UGT1A1*[a]	
intermediate	-0.03, 0.87	intermediate	-0.074, 0.79	intermediate	0.15, 0.58
poor	0.74, 0.005	slow	-0.50, 0.079	poor	-0.19, 0.59
BMI (per 1 kg/m^2)	0.035, 0.017	BMI	0.0001, 0.99	BMI	0.033, 0.028
Age (per year)	0.002, 0.87	Age	-0.022, 0.038	Age	-0.001, 0.93
LNG dose (per 1 mg)	0.051, 0.67		-		-

[a] reference is normal metabolizers for *CYP2B6* and *UGT1A1*, and rapid acetylators for *NAT2*

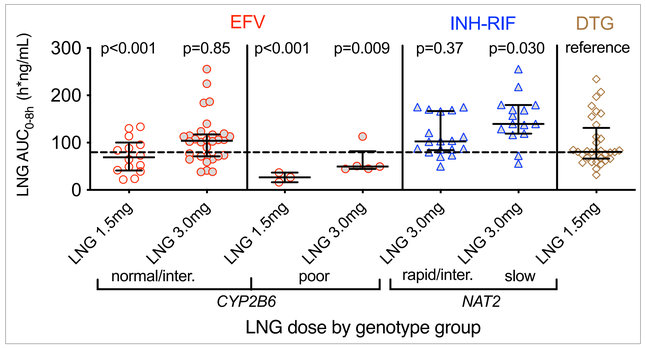
Figure 1. Relationships between genotypes and log LNG CL/F



Error bars indicate median and IQR. Markers are unadjusted for BMI or age. The dashed line indicates median log LNG CL/F (1.47) in the DTG control group. P-values are from multivariable linear regression. Inter = intermediate

- **LNG $AUC_{0\text{-}8h}$ values compared to DTG controls**
- In *CYP2B6* normal/intermediate metabolizers in the EFV group, LNG 3 mg yielded $AUC_{0\text{-}8h}$ values comparable to controls (adjusted GMR 0.98; 90% CI: 0.83, 1.16).
- In *CYP2B6* poor metabolizers in the EFV group, LNG 3 mg yielded $AUC_{0\text{-}8h}$ 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 $AUC_{0\text{-}8h}$ values are shown in **Figure 2**.
- In *NAT2* slow acetylators in the INH-RIF group, LNG 3 mg yielded LNG $AUC_{0\text{-}8h}$ higher than in controls (adjusted GMR 1.36; 90% CI: 1.08, 1.71). Unadjusted $AUC_{0\text{-}8h}$ values are shown in **Figure 2**.

Figure 2. Relationships between genotypes and LNG $AUC_{0\text{-}8h}$



Error bars indicate median and IQR. Markers are unadjusted for BMI or age. The dashed line indicates median $AUC_{0\text{-}8h}$ in the DTG control group. P-values from multivariable linear regression are shown. Clear and grey shaded markers represent 1.5 mg or 3 mg doses of LNG, respectively. Inter = intermediate.

CONCLUSIONS

- *CYP2B6* poor metabolizer genotypes exacerbate the EFV-LNG interaction, likely by increased CYP3A induction with higher EFV exposure, making the interaction more difficult to overcome.
- It is reasonable to recommend double-dose LNG (3 mg) for all women receiving EFV, understanding that *CYP2B6* poor metabolizers will have lower C_{max} and $AUC_{0\text{-}8h}$ values.
- *NAT2* slow acetylator genotypes attenuate the RIF-NIH interaction, likely by increased CYP3A inhibition with higher INH exposure.