The pharmacokinetics, pharmacogenetics, and toxicity of the interaction between efavirenz and isoniazid

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Background

- People with *CYP2B6 s*low metaboliser genotypes have higher efavirenz concentrations, which are further increased by isoniazid, which inhibits the accessory metabolising enzyme of efavirenz, CYP2A6.
- We hypothesized that higher efavirenz concentrations would be associated with more toxicity (neuropsychiatric, metabolic and hepatic) in *CYP2B6* slow metabolisers on isoniazid and efavirenz-based antiretroviral therapy (ART).

Methods

- We conducted a substudy of participants randomized to the efavirenz arm of the ADVANCE trial (NCT03122262) who received isoniazid and consented to genotyping.
- We compared paired efavirenz concentrations on and off isoniazid and stratified by *CYP2B6* genotype.
- Neuropsychiatric symptoms were screened for using the Modified Mini Screen (MMS).
- We used linear regression to detect associations between *CYP2B6* genotype and efavirenz concentrations on isoniazid; and changes from baseline to week 24 in lipids, alanine aminotransferase (ALT), fasting plasma glucose, sleep quality, and MMS scores.

Results

- We included 176 participants, 168 of whom were classifiable by *CYP2B6* genotype, median age 31 years, 57% female.
- The proportions of *CYP2B6* metaboliser genotypes were: 28% extensive, 45% intermediate, and 27% slow.
- Baseline characteristics were similar between *CYP2B6* metaboliser genotypes, except for weight, which was lower in extensive metabolisers (p = 0.02).
- Efavirenz concentrations on isoniazid were greater than off isoniazid in *CYP2B6* slow and intermediate metabolisers **(Figure 1).**

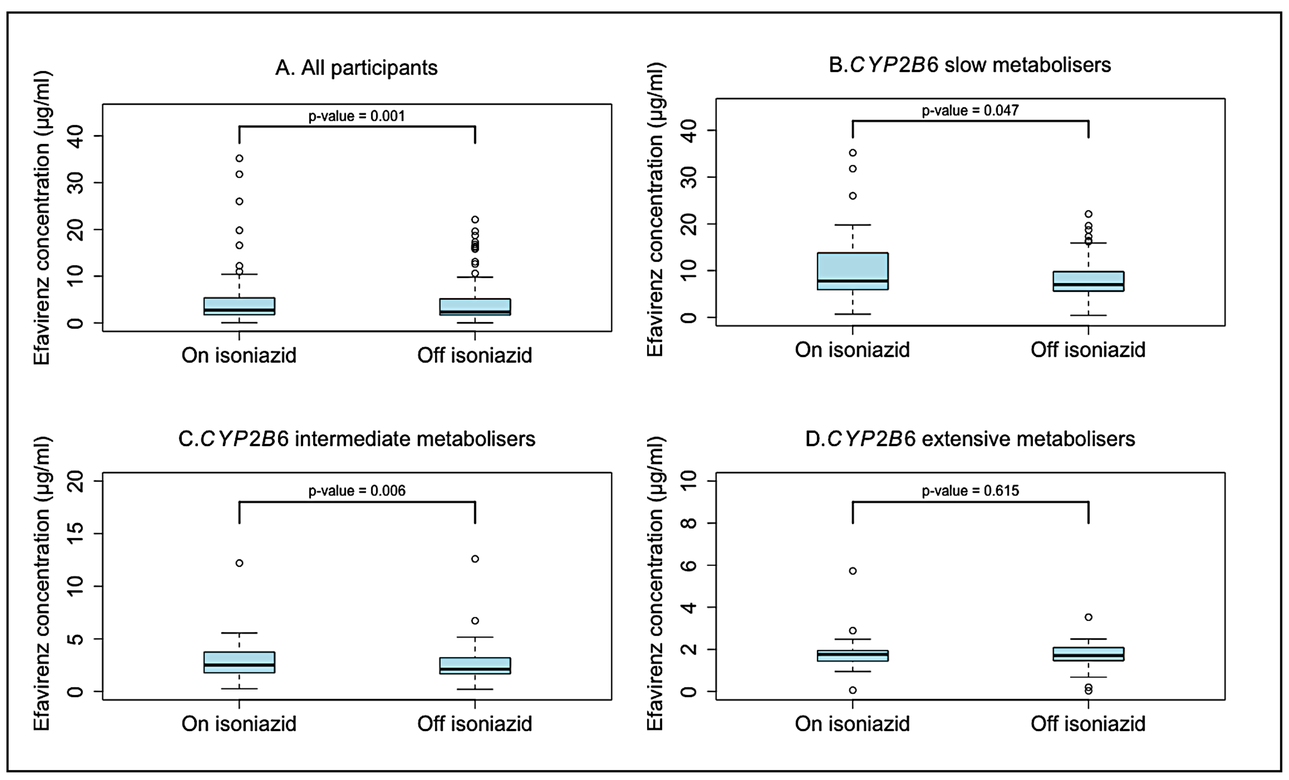

Figure 1. Boxplots of efavirenz concentrations on and off isoniazid
(A) All participants (pseudo-median difference 0.49 µg/mL [95% CI 0.19 to 0.91]),
(B) CYP2B6 slow metabolisers (pseudo-median difference 2.13 µg/mL [95% CI 0.02 to 8.77]),
(C) CYP2B6 intermediate metabolisers (pseudo-median difference 0.52 µg/mL [95% CI 0.16 to 0.89]),and
(D) CYP2B6 extensive metabolisers (pseudo-median difference 0.07 µg/mL [95% CI -0.25 to 0.39]).

- *CYP2B6* slow metabolisers had higher log-transformed efavirenz concentrations on isoniazid than extensive metabolisers (β=1.66 [95% CI 0.98 to 2.34] p < 0.001) after adjustment for baseline weight and other covariates.
- *CYP2B6* slow metabolisers had greater increases in total cholesterol and HDL-cholesterol over 24 weeks than extensive metabolisers **(Table 1).**

Table 1. Multivariable linear regression models for change in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides from baseline to week 24.

Variables	Change in total cholesterol (mmol/L) β (95% CI)	Change in LDL-cholesterol (mmol/L) β (95% CI)	Change in HDL-cholesterol (mmol/L) β (95% CI)	Change in triglycerides (mmol/L) β (95% CI)
***CYP2B6* genotype (Reference: Extensive Metaboliser)**				
Intermediate Metaboliser	0.13 (-0.21 to 0.47)	0.19 (-0.08 to 0.45)	0.06 (-0.06 to 0.18)	-0.76 (-2.59 to 1.07)
Slow Metaboliser	**0.44 (0.01 to 0.86) ***	0.27 (-0.05 to 0.59)	**0.39 (0.21 to 0.57) ***	-1.50 (-4.59 to 1.60)
***CYP2A6* genotype (Reference: Extensive Metaboliser)**				
Intermediate Metaboliser	0.04 (-0.30 to 0.38)	-0.11 (-0.39 to 0.17)	0.17 (-0.01 to 0.35)	-0.23 (-0.95 to 0.49)
Slow Metaboliser	0.23 (-0.39 to 0.85)	0.09 (-0.90 to 1.08)	-0.08 (-0.42 to 0.26)	0.07 (-2.40 to 2.54)
***NAT2* genotype (Reference: Rapid Acetylator)**				
Intermediate Acetylator	0.21 (-0.21 to 0.62)	0.21 (-0.17 to 0.60)	0.02 (-0.20 to 0.25)	0.72 (-1.32 to 2.77)
Slow Acetylator	0.25 (-0.22 to 0.72)	0.07 (-0.31 to 0.45)	0.13 (-0.10 to 0.37)	1.16 (-1.85 to 4.16)
Male Sex (Reference: Female)	-0.26 (-0.56 to 0.03)	**-0.27 (-0.51 to -0.03) ***	**-0.14 (-0.27 to -0.01) ***	0.08 (-0.38 to 0.55)
Age (years)	0.01 (-0.01 to 0.04)	0.01 (-0.01 to 0.03)	0.002 (-0.01 to 0.01)	0.05 (-0.06 to 0.17)
Baseline CD4 count (per 100 cells)	-0.02 (-0.12 to 0.09)	-0.06 (-0.13 to 0.02)	-0.02 (-0.05 to 0.01)	0.26 (-0.30 to 0.83)
Baseline VL (log10 cp/mL)	-0.02 (-0.21 to 0.18)	-0.04 (-0.21 to 0.12)	-0.03 (-0.10 to 0.04)	0.27 (-0.23 to 0.77)
Weight (kg)	-0.003 (-0.01 to 0.01)	0.002 (-0.01 to 0.01)	-0.003 (-0.01 to 0.002)	-0.02 (-0.06 to 0.03)
Baseline value of dependent variable (mmol/L)	**-0.45 (-0.67 to -0.22) ***	**-0.50 (-0.73 to -0.26) ***	**-0.17 (-0.29 to -0.04) ***	1.45 (-2.97 to 5.86)

(*p < 0.05)
Abbreviations: LDL – low-density lipoprotein; HDL – high-density lipoprotein; 95% CI – 95% confidence interval; NAT2 – N-acetyltransferase 2; VL – HIV viral load.

- *CYP2B6* slow metabolisers had greater increases in low-density lipoprotein cholesterol over 24 weeks, but this was not statistically significant (β=0.27 [95% CI -0.05 to 0.59] p = 0.09).
- There was no association between *CYP2B6* genotype and change in ALT, fasting plasma glucose, triglycerides, sleep scores or MMS scores over 24 weeks.

Conclusion

- *CYP2B6* slow metabolisers on isoniazid had greater increases in total cholesterol and HDL-cholesterol.
- We found no association between *CYP2B6* genotype and worsening sleep quality or psychiatric symptoms, hepatotoxicity, or dysglycemia.

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