Pharmacogenetics of Early Neuropsychiatric Adverse Events after Switching to DTG in Second-Line ART

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BACKGROUND

- Dolutegravir (DTG) is associated with neuropsychiatric adverse events (NPAEs).
- Data regarding pharmacogenetics of DTG-associated NPAEs are limited.

OBJECTIVE

To characterise genetic associations with early NPAEs in ARTIST clinical trial adult participants, who were switched from tenofovir-emtricitabine-efavirenz to tenofovir-lamivudine-dolutegravir (TLD) and randomised to supplemental 50 mg DTG dose or placebo for the initial 14 days.

METHODS

- Primary outcome was change in sleep quality from baseline to week 2.
- We screened for insomnia using the Insomnia Severity Index, and for psychiatric symptoms using the Brief Symptoms Inventory Anxiety Subscale and the Centre for Epidemiology Studies Depression Scale.
- Plasma DTG trough concentrations were measured at week 2.
- We genotyped polymorphisms relevant to efavirenz disposition [*CYP2B6* (rs3745274 G>T, rs28399499 T>C and rs4803419 C>T), and *CYP2A6* rs28399433 A>C], DTG disposition (*UGT1A1* rs887829 C>T), and DTG toxicity (*SLC22A2* rs316019 C>A).
- Regression analyses were used to determine associations between genetic polymorphisms, worsening sleep quality at week 2, and early DTG exposure.

RESULTS

- 128 participants were evaluable for genetic analyses: 65 in the supplemental DTG arm and 63 in the placebo arm.
- Baseline characteristics were similar between arms (**Table 1**). Genotype frequencies are shown in **Figure 1**.
- At week 2, insomnia events occurred in 8 (12%) in the supplemental DTG arm and 9 (14%) in the placebo arm.
- There were no statistically significant associations between genetic polymorphisms and change in Insomnia Severity Index scores from baseline to week 2 (**Table 2**).
- Three (2%) participants developed clinically significant anxiety and 2 (2%) developed clinically significant depression over 24 weeks.
- There was a trend towards higher DTG exposure in those with *UGT1A1* rs887829 homozygous TT genotype (**Table 3**).
- *CYP2B6* slow efavirenz metaboliser genotype was associated with lower DTG exposure in both arms, but this was only statistically significant in the supplemental DTG arm (**Table 3 and Figure 2**).

Amongst patients who switched from efavirenz to dolutegravir, early insomnia events were common, but these were not associated with known functional polymorphisms. *CYP2B6* slow metaboliser genotype was associated with lower dolutegravir exposure, reflecting prolonged efavirenz induction effect.

Table 1: Baseline characteristics

	TLD + DTG (n = 65)	TLD + Placebo (n = 63)
Age, years	38 (32-45)	38 (33-45)
Female sex	42 (65)	45 (71)
Weight, kg	74 (62-87)	80 (63-96)
CD4 cell count, cells/mm^3	246 (187-334)	250 (154-358)
Viral load, $\log_{10}$ copies/mL	4.12 (3.46-4.69)	4.01 (3.49-4.62)

Data are median (IQR) or n (%)

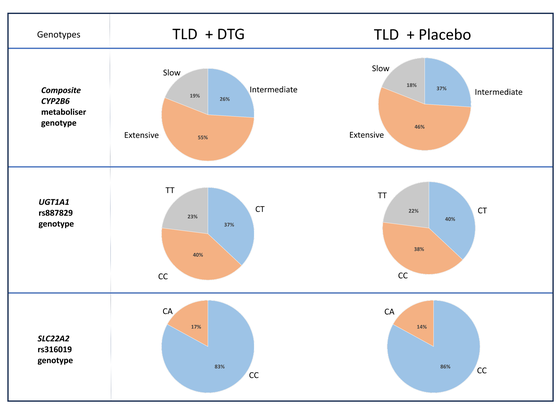

Figure 1: Genotype frequencies for the *CYP2B6, UGT1A1* and *SLC22A2* polymorphisms

Table 2: Multivariable linear regression* to assess association between genetic variants and worsening sleep quality from baseline

	TLD + DTG (n = 65)		TLD + Placebo (n = 62)	
Covariate	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
***SLC22A2* polymorphism**				
CC	referent group			
CA	-0.593 (-1.936 to 0.750)	0.380	-0.530 (-2.478 to 1.417)	0.587
***UGT1A1* polymorphism**				
CC	referent group			
CT	-0.525 (-1.720 to 0.669)	0.382	-0.109 (-1.620 to 1.403)	0.886
TT	-0.312 (-1.655 to 1.031)	0.643	-0.571 (-2.363 to 1.221)	0.526

**Adjusted for sex, age, baseline CD4 count, baseline viral load*

Table 3: Multivariable linear regression* to assess association between genetic variants and DTG trough concentrations at week 2

	TLD + DTG (n = 65)		TLD + Placebo (n = 63)	
Covariate	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
***CYP2B6* metaboliser genotype**				
Extensive	referent group			
Intermediate	-0.650		-0.341	
	(-1.484 to 0.185)	0.124	(-0.774 to 0.092)	0.120
Slow	**-1.457**		-0.296	
	(-2.467 to -0.447)	**0.006**	(-0.865 to 0.272)	0.300
***UGT1A1* polymorphism**				
CC	referent group			
CT	0.202		-0.117	
	(-0.606 to 1.011)	0.618	(-0.560 to 0.325)	0.597
TT	0.841		-0.148	
	(-0.030 to 1.711)	0.058	(-0.683 to 0.388)	0.582

**Adjusted for sex, age, baseline CD4 count, baseline viral load, weight*

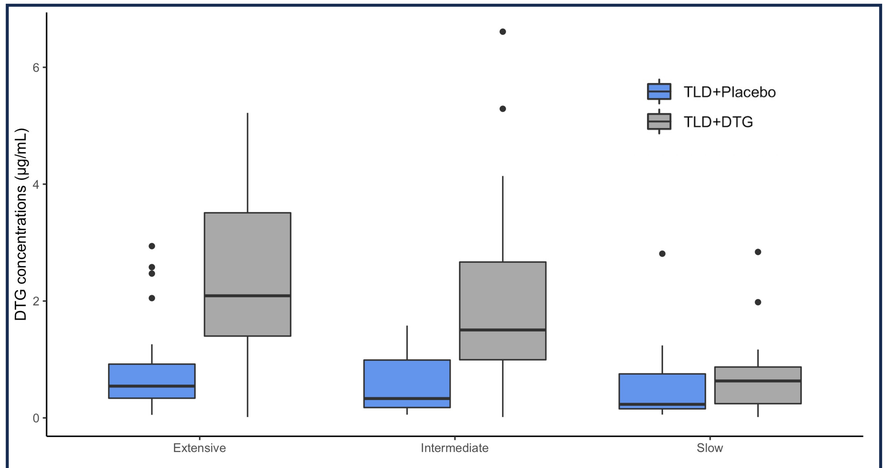

Figure 2: DTG trough concentrations at week 2 by efavirenz metaboliser genotype in the supplemental DTG arm and the placebo arm

CONCLUSIONS

We found a high incidence of insomnia at week 2 among ARTIST participants who switched from efavirenz to DTG and not associated with known functional polymorphisms in *UGT1A1* or *SLC22A2.*

ADDITIONAL KEY INFORMATION

- We have no conflicts of interest to disclose.
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