Pharmacogenetics of dolutegravir plasma exposure among Southern Africans living with HIV 00439

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BACKGROUND

- Dolutegravir (DTG) is a component of preferred antiretroviral therapy (ART) regimens in low- and middle-income countries.
- Data are lacking regarding DTG pharmacogenetics in Africa.
- The understanding of functional polymorphisms is important as it may aid in the optimizing of ART among Africans.

OBJECTIVE

The goal of the present study was to characterize genetic associations with dolutegravir exposure among ART-naïve Southern Africans who participated in the ADVANCE clinical trial.

METHODS

- The ADVANCE randomized ART-naïve individuals into 3 study arms: 1) DTG + TAF + FTC; 2) DTG + TDF + FTC; or 3) efavirenz + TDF + FTC.
- Genome-wide genotyping followed by imputation was performed.
- A population pharmacokinetic model was developed for DTG using non-linear mixed-effects modelling.
- Linear regression models examined associations with unexplained variability in DTG area under the concentration-time curve (AUC_{VAR}) and clearance (CL_{BSV}).
- Analyses focused on known functional polymorphisms and the *UGT1A* gene locus. We also explored associations genome-wide.
- As a positive control, we used associations between *UGT1A* locus polymorphisms and screening bilirubin concentrations.

RESULTS

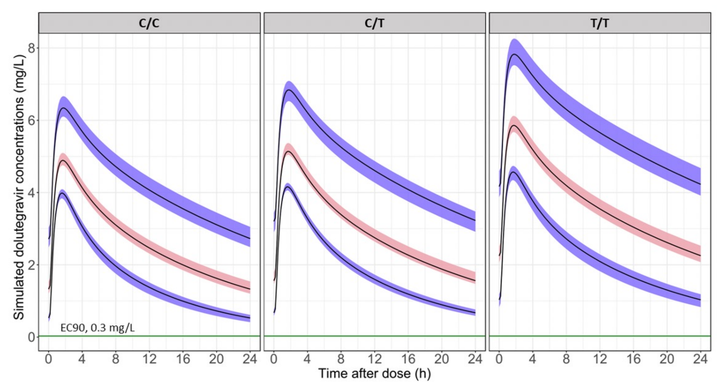
- 284 ADVANCE participants were evaluable for DTG associations.
- All were Black Africans and 62% were females.
- Eight known functional polymorphisms were available for analyses.
- *UGT1A1* rs887829 was significantly associated with AUC_{VAR} (P = 1.8 x 10^{-4}), which withstood correction for multiple testing **(Table 1)**.
- After adjusting for rs887829, *UGT1A* rs28899168 (minor allele frequency (MAF) = 0.15) was independently associated with lower bilirubin (P = 7.7 x 10^{-8}) and with lower DTG AUC_{VAR} (P = 0.02).
- DTG exposure was highest with rs887829 T/T **(Figure 1).**
- rs887829 T/T and C/T were associated with 25.9% (95% CI 37.2% to 11.7%) and 10.8% (21.7% to -3.0%) decreased DTG clearance, respectively.

We characterised genetic associations with between-individual variability in DTG exposure in Southern Africans. The *UGT1A1* rs887829 T allele was significantly associated with unexplained variability in DTG AUC (AUC_{VAR}). rs887829 T/T and C/T were associated with 25.9% and 10.8% decreased DTG clearance, respectively. A second novel *UGT1A* polymorphism (rs28899168) was independently associated with somewhat lower DTG AUC_{VAR}.

Table 1: Associations with SNPs selected *a priori* with AUC_{VAR}

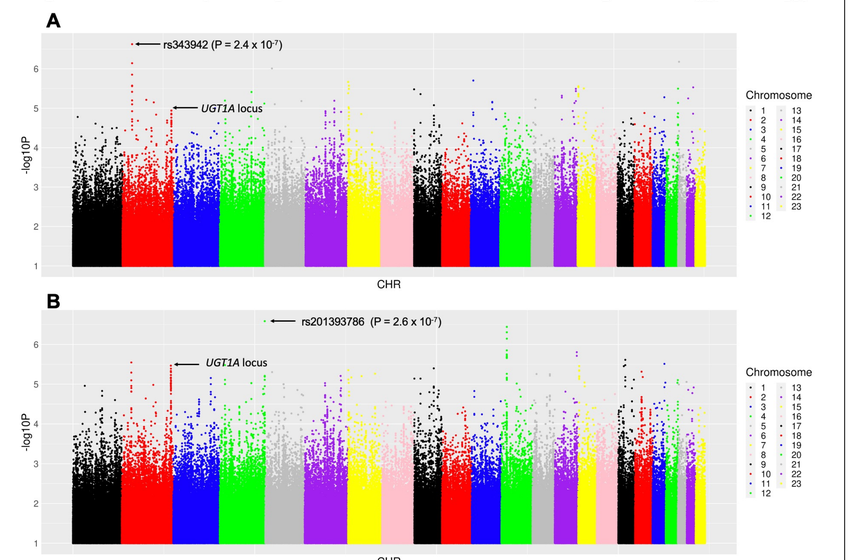
Polymorphism	Gene	MAF	Beta	P value
rs887829	*UGT1A*	0.41	0.14	1.8 x 10^{-4}
rs2472677	*NR1I2*	0.36	0.05	0.2
rs776746	*CYP3A5*	0.19	0.04	0.44
rs3842	*ABCB1*	0.28	-0.02	0.59
rs1045642	*ABCB1*	0.12	-0.03	0.66
rs1128503	*ABCB1*	0.08	0.02	0.8
rs1523130	*NR1I2*	0.06	-0.01	0.9
rs2231137	*ABCG2*	0.06	-0.01	0.94

Figure 1: Simulated dolutegravir concentration-time profiles



Simulations are made with the final dolutegravir model and based on 1200 typical individuals categorized either as C/C, C/T or T/T for *UGT1A1* rs887829. For each panel, the solid black line in the middle represents the median simulated concentration, the lines below and above represent the 5th and 95th percentiles of the simulated concentrations, respectively. The shaded areas represent the 95% confidence interval for the same percentiles.

Figure 2: Manhattan plots of genome-wide associations with dolutegravir AUC_{VAR} and CL_{BSV}



Panel A: Associations with dolutegravir AUC_{VAR}. The lowest P-value was *CAMKMT* rs343942 (P = 2.4 x 10-7).
Panel B: Associations with dolutegravir CL_{BSV}. The lowest P-value was *LOC105377607* rs201393786 (P = 2.6 x 10^{-7})
UGT1A locus highest peak
Threshold of significance is P < 5.0 x10^{-8}

- In genome-wide analyses for AUC_{VAR} and CL_{BSV} associations, none withstood correction for multiple testing **(Figure 2).**

CONCLUSIONS

- Among Southern African participants in the ADVANCE trial, *UGT1A1* rs887829 was associated with DTG AUC_{VAR}, consistent with findings in other populations.
- We identified a novel association of rs28899168 in the *UGT1A* locus with somewhat lower DTG AUC_{VAR}. This warrants replication in independent cohorts.
- This study enhances understanding of DTG pharmacogenetics in Africa, which is important given its widespread prescribing on this continent.

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