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ABCG2 rs2231142 and NR1I2 rs2472677 Influence Dolutegravir Concentrations in Plasma

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BACKGROUND

Dolutegravir (DTG) is a preferred agent in most guidelines but concerns are emerging as real life data show higher rates of neuropsychiatric adverse events (NP-AEs) than seen in licensing trials. Supra-therapeutic drug concentrations may predispose to side effects, amongst other factors. An association between the *ABCG2* genetic variant and DTG plasma peak concentrations has been shown, whilst an association between carrying *UGT1A1*6* and/or *UGT1A1*28*, DTG trough concentrations and selected NP-AEs has been made by some and refuted by others.[2-3] The objectives of our study was to investigate the association between pharmacogenetic variants of the following genes linked to DTG transport and metabolism and DTG pharmacokinetic (PK) parameters: *UGT1A1*, *ABCG2*, *NR1I2* and *CYP3A*.

METHODS

- Pooled data from six Phase I and III clinical studies was analyzed in subjects receiving 50 mg DTG once daily (and no interacting co-medications) after formal consent to a pharmacogenetic sub-study.
- Subjects underwent intensive PK sampling and steady-state plasma concentrations were determined using validated LC-MS/MS or UPLC.[4-6]
- Genomic DNA was extracted from whole blood using a spin-column based kit (Omega bio-tek).
- *UGT1A1*6, UGT1A1*27, ABCG2*, *NR1I2* and *CYP3A* were genotyped using PCR-based allelic discrimination Taqman assays. The *UGT1A1* promoter region (*1, *28, *36 and *27) was genotyped using an Agena MassArray iPLEX assay.
- Variables were tested for normal distribution using the Shapiro-Wilkes test and were log_{10} transformed where required.
- Associations between subject characteristics or genotypes and DTG PK parameters ($logC_{min}$, C_{max} and AUC_{0-24}) were determined through univariate and multivariate linear regressions. Univariate linear regressions with a *P* value of ≤0.2 were carried through to multivariate linear regression analysis where a *P* value of ≤0.05 was classed as statistically significant.

RESULTS

- 95 subjects were included (59 HIV-infected and 36 healthy volunteers; 68 men and 27 women). Characteristics and genotypes are summarised in table 1.
- All genotypes were in Hardy-Weinberg equilibrium except for ABCG2 and NR1I2 variants, which still mirrored European genotypic frequency distribution accurately.

	Total N
	95
	Median (IQR)
Age (years)	51 (35-64)
Weight (kg)	76.8 (66.6-84.3
Height (cm)	173 (167-177)
ARV Regimen	**N (%)**
• ABC/FTC/DTG	40 (42)
• TFV/3TC + DTG	19 (20)
• DTG alone	36 (38)
Ethnicity	**N (%)**
• Caucasian	71 (75)
• Black	16 (17)
• Asian	4 (4)
• Mixed race	1 (1)
• Other	3 (3)
Female gender	26 (27)
DTG GM C_{max}	3974 ng/mL
DTG GM C_{min}	1054 ng/mL
DTG GM AUC_{0-24}	51846 hr*ng/mL

	Genotypic frequencies %		
	Normal activity (*1/*1)	Reduced activity (*1/*28 or *1/*37)	Low activity (*28/*28 or *37/*37)
*UGT1A1*28 (rs8175347)*	41	45	14
*UGT1A1*6 (rs4148323)*	*1/*1	*1/*6	*6/*6
*UGT1A1*27 (rs35350960)*	100	64	0
*CYP3A4*22 (rs35599367)*	*1/*1	*1/*27	*27/*27
*CYP3A5*3 (rs776746)*	100	0	0
ABCG2 421 C>A (rs2231142)	GG	GA	AA
ABCG2 34 C>T (rs2231137)	88	6	5
NR1I2 63396 C>T (rs2472677)	TT	TC	CC
NR1I2 44477 A>G (rs1523130)	12	12	77
	CC	CA	AA
	82	17	1
	CC	CT	TT
	0	17	83
	CC	CT	TT
	17	43	40
	TT	CT	CC
	19	39	42

Table 1: Characteristics of participant population. Values shown as median (interquartile range), percentage of population and geometric means (GM) (95% Confidence Interval, 95%CI)

Log_{10} C_{max}	Univariate Linear Regressions			Multivariate Linear Regressions		
	P value	β value (95% CI)	r^2	*P* value	β value (95% CI)	r^2
Log_{10}Height (Log_{10}cm)	0.008	-1.716	0.092	**0.012**	-1.649	0.394
Weight (kg)	0.000	-0.004	0.175	**0.009**	-0.003	0.394
Ethnicity	0.297	0.002	0.015			
ARV regimen	0.019	0.061	0.071	**0.001**	0.074	0.394
***ABCG2* 421 C>A (rs2231142)**	0.111	0.050	0.034	**0.047**	0.053	0.394
***NR1I2* 63396 C>T (rs2472677)**	0.010	0.045	0.086	**0.033**	0.032	0.394
Log_{10} C_{min}	**Univariate Linear Regressions**			**Multivariate Linear Regressions**		
	P value	β value (95% CI)	r^2	*P* value	β value (95% CI)	r^2
*UGT1A1*28 (rs8175347)*	0.153	-0.101	0.027	0.153	-0.101	0.027
AUC_{0-24}	**Univariate Linear Regressions**			**Multivariate Linear Regressions**		
	P value	β value (95% CI)	r^2	*P* value	β value (95% CI)	r^2
Log_{10}Height (Log_{10}cm)	0.025	-184350.5	0.066	0.622	-51210.2	0.329
Weight (kg)	0.009	-348.9	0.088	**0.007**	351.2	0.283
Ethnicity	0.005	814.3	0.1	**0.002**	934.2	0.283
*UGT1A1*28 (rs8175347)*	0.112	4407.3	0.042	0.240	2965.9	0.322
*CYP3A4*22 (rs35599367)*	0.057	5909.5	0.048	0.195	3592.6	0.304
*CYP3A5*3 (rs776746)*	0.140	-3374.7	0.030	0.603	1591.8	0.326
***NR1I2* 63396 C>T (rs2472677)**	0.053	4324.7	0.050	**0.011**	5698.0	0.283

Table 2: Univariate linear regression (*P*=≤0.2) completed, all statistically significant results then carried through to multivariate linear regression analysis (*P*=≤0.05). Statistically significant associations are shown in bold.

	ABCG2 421 C>A (rs2231142)			% difference between wild type and SNP variant	
	CC	CA	AA		
GM (95%CI) C_{max} (ng/mL)	3893 (3659-4126)	4346 (3395-5297)	4994 (n=1)	Heteroz. 12%	Homoz. 28%
	NR1I2 63396 C>T (rs2472677)			% difference between wild type and variant SNP	
	CC	CT	TT		
GM Cmax (95%CI) (ng/mL)	3445 (3095-3836)	3938 (3540-4382)	4278 (3920-4668)	Heteroz. 14%	Homoz. 24%
GM AUC (95%CI) (hr*ng/mL)	42750 (35620-49880)	54138 (48965-59311)	54170 (49473-58867)	Heteroz. 27%	Homoz. 27%

Table 3: Dolutegravir (DTG) pharmacokinetic parameters (GM, 95%CI), summarized by associated genotypic variant.

- *ABCG2* (rs2231142) and *NR1I2* (rs2472677) variants were both independently associated with higher DTG plasma peak concentrations (*P*=0.047, β=0.053 and *P*=0.033, β=0.032), as were ethnicity and accompanying drugs. Weight and height were inversely associated with C_{max}. The *NR1I2* (rs2472677) variant was additionally associated with an increase in total DTG exposure (*P*=0.011, β=5698) (tables 2 and 3, figure 1).
- Importantly, the above genetic associations were persistently observed when the analyses were restricted to Caucasians only.
- Of note our population was 100% homozygous for the UGT1A1*6 and *27 wild types, thus precluding any meaningful analysis for these SNPs.

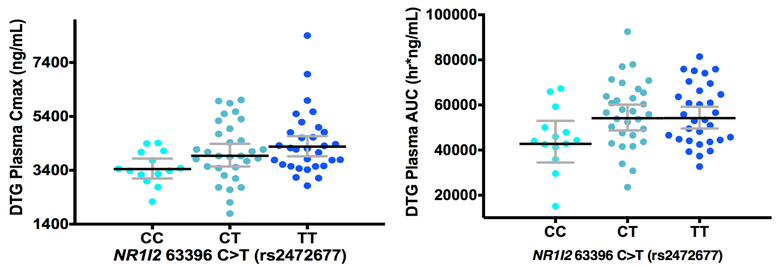

Figure 1: Relationship between NR1I2 63396 C>T genotype and DTG plasma GM (95% CI) Cmax (ng/mL) and AUC (hr*ng/mL)

DISCUSSION

This is the first study to demonstrate that *NR1I2* 63396C>T influences DTG plasma C_{max} and AUC, which could suggest a complex metabolic influence, through the PXR intra-nuclear receptor. Our results also confirm the association between *ABCG2* 421C>A and C_{max} alone, which may signal an impact on DTG absorption. Further research in bigger and more diverse cohorts is warranted to confirm these associations and their mechanisms and to investigate their putative relationship with pharmacodynamics.

References: *1) Tsuchiya et al. 2017. 2) Yagura et al. 2017. 3) Chen et al. 2014 4) Else et al. 2010. 5) Penchala et al. 2016. 6) Wang et al. 2016.*

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