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Pharmacogenetics of plasma dolutegravir exposure during 1-month rifapentine/isoniazid treatment of latent tuberculosis

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In Advancing Clinical Therapeutics Globally protocol A5372, a pharmacokinetic study of dolutegravir with 1-month of daily rifapentine/isoniazid, twice-daily dolutegravir offset the induction effects of rifapentine on plasma dolutegravir trough concentrations (C_{trough}). Here, we characterize the impact on dolutegravir C_{trough} of *UGT1A1*, *AADAC*, and *NAT2* polymorphisms that affect dolutegravir, rifapentine, and isoniazid, respectively. People with HIV receiving dolutegravir-based antiretroviral therapy with an indication to treat latent tuberculosis underwent pharmacokinetic sampling during dolutegravir 50 mg once daily alone, and on day 28 of dolutegravir 50 mg twice daily with rifapentine/isoniazid. Multivariable linear regression models characterized genetic associations with dolutegravir C_{trough}. Among 30 participants evaluable for genetic associations, median (Q1, Q3) day 0 dolutegravir C_{trough} was 1745 (1099, 2694) ng/ml, and day 28 was 2146 (1412, 2484) ng/ml. Day 28 C_{trough} was higher with *UGT1A1* rs887829 TT [geometric mean ratio (GMR) = 1.65; 90% confidence interval (CI): 0.97–2.78] and CT (GMR = 1.38; 90% CI: 1.02–1.86) than with CC, and was higher with *AADAC* rs1803155 GG (GMR = 1.79; 90% CI: 1.09–2.93) and AG (GMR = 1.48; 90% CI: 1.14–1.90) than with AA. Median day 28 C_{trough} ranged from 1205 (1063, 1897) ng/ml with 4 total *UGT1A1* and *AADAC* risk alleles, to 3882 and 3717 ng/ml with only one risk allele. Individuals with concomitant *AADAC* slow metabolizer and *UGT1A1* normal metabolizer genotypes may be at greater risk for clinically significant drug–drug interactions between rifapentine/isoniazid and dolutegravir. *Pharmacogenetics and Genomics* 35: 140–144 Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

People with HIV (PWH) are at increased risk of progressing from latent tuberculosis infection (TBI) to active tuberculosis [1]. While isoniazid monotherapy for 6–12 months has historically been used for tuberculosis preventive therapy [2], shorter rifapentine-containing regimens have proven effective. In the BRIEF-TB trial, 4 weeks of daily rifapentine/isoniazid (600 mg/300 mg), the '1HP' regimen, was noninferior to 9 months of daily isoniazid in PWH on efavirenz- or nevirapine-based antiretroviral therapy [3].

Rifapentine induces many hepatic drug-metabolizing enzymes, which decrease plasma exposure of HIV integrase strand transfer inhibitors (INSTI). Isoniazid inhibits several cytochrome P450 (CYP) isoforms [4], which may increase plasma exposure of substrate drugs. The INSTI dolutegravir (50 mg once daily), a component of the WHO-recommended first-line regimen [5], is primarily metabolized by UDP glucosyltransferase (UGT) 1A1 [6]. Frequent genetic variants predict greater plasma exposure of these drugs, including dolutegravir with the *UGT1A1* Gilbert polymorphism [7,8], rifapentine with the *AADAC* rs1803155 A allele [9], and isoniazid with *NAT2* polymorphisms [4,10,11].

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Dolutegravir trough concentration (C_{trough}) is the pharmacokinetic parameter that best predicts virologic response [12,13]. In Advancing Clinical Therapeutics Globally (ACTG) study A5372 (NCT 04272242), dolutegravir C_{trough} values were modestly greater with twice-daily dolutegravir plus 1HP than with once-daily dolutegravir alone [14]. Here, we characterize the pharmacogenetics of dolutegravir C_{trough} in A5372.

Methods

Study design

Study A5372 investigated pharmacokinetic interactions at 4 weeks between 1HP and twice-daily dolutegravir among PWH with TBI [13]. Approvals were obtained from the Ethics Committee for each site, and participants gave written informed consent. Participants were receiving dolutegravir-containing antiretroviral therapy, which included two nucleos[t]ides, for at least 28 days before entry. All participants received 1HP, which comprised 28 once-daily doses of rifapentine/isoniazid (600 mg/300 mg). All participants completed 1HP within 30 days. Adherence was assessed by patient self-report.

Pharmacokinetic sampling

On day 0 (dolutegravir 50 mg once daily without 1HP), serial pharmacokinetic sampling included C_{trough} at 24 h ± 15 min postdose. On day 1, dolutegravir was increased to 50 mg twice daily. Daily rifapentine/isoniazid was prescribed from day 1 to day 28. On day 28 (−2 to +14 day window), repeat serial sampling included C_{trough} at 12 h ± 15 min postdose. Three consecutive days of adherent dosing was required before sampling.

Genetics polymorphisms

Human DNA extracted from blood was genotyped for *UGT1A1* (rs887829) [7,8], *AADAC* (rs1803155) [9], and *NAT2* (rs1799930, rs1799931, rs1801279, and rs1801280) [4,10,11] at VANTAGE (Vanderbilt Technology for Advanced Genomics) using Taqman (ThermoFisher Scientific, Waltham, Massachusetts, USA).

Statistical analysis

Associations of dolutegravir C_{trough} were assessed by linear regression models using STATA version 17.0 (StataCorp, College Station, Texas, USA), adjusting for screening BMI, which was retained in the model by default. Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) summarized between-group comparisons. Antilogs of GMR and confidence bounds are reported.

For *UGT1A1* rs887829, CC, CT, and TT were classified as normal, intermediate, and poor metabolizers, respectively. For *AADAC* rs1803155, GG, AG, and AA were classified as normal, intermediate, and poor metabolizers, respectively. For *NAT2*, acetylator groups were defined based on rs1801280 (*NAT2*5*), rs1799930 (*NAT2*6*), rs1799931 (*NAT2*7*), and rs1801279 (*NAT2*14*) as described elsewhere [15]. We did not correct for multiple comparisons. Two-sided statistical tests were used. *P*-values <0.05 were considered statistically significant. Trough concentrations were natural log-transformed.

Results

Participant characteristics

Thirty-two A5372 participants completed 28 doses of rifapentine and isoniazid and with complete pharmacokinetic sampling, and 30 were evaluable for pharmacogenetics. Participants' characteristics are shown in Table 1.

UGT1A1 rs887829 and dolutegravir C_{trough}

At day 0 (before starting rifapentine/isoniazid), *UGT1A1* rs887829 was associated with dolutegravir C_{trough}. Compared with rs887829 CC normal metabolizers, day 0 C_{trough} was higher in CT intermediate metabolizers (GMR = 1.51; 90% CI: 1.10–2.07), and in TT poor metabolizers (GMR = 1.90; 90% CI: 1.09–3.28). At day 28 (with rifapentine/isoniazid), *UGT1A1* rs887829 was still associated with dolutegravir C_{trough}, although the GMR values were somewhat less than at day 0. Compared with rs887829 CC normal metabolizers, day 28 C_{trough} was higher in CT intermediate metabolizers (GMR = 1.38; 90% CI: 1.02–1.86), and in TT poor metabolizers (GMR = 1.65; 90% CI: 0.97–2.78). Relationships between *UGT1A1* genotype and dolutegravir C_{trough} are shown in Fig. 1a.

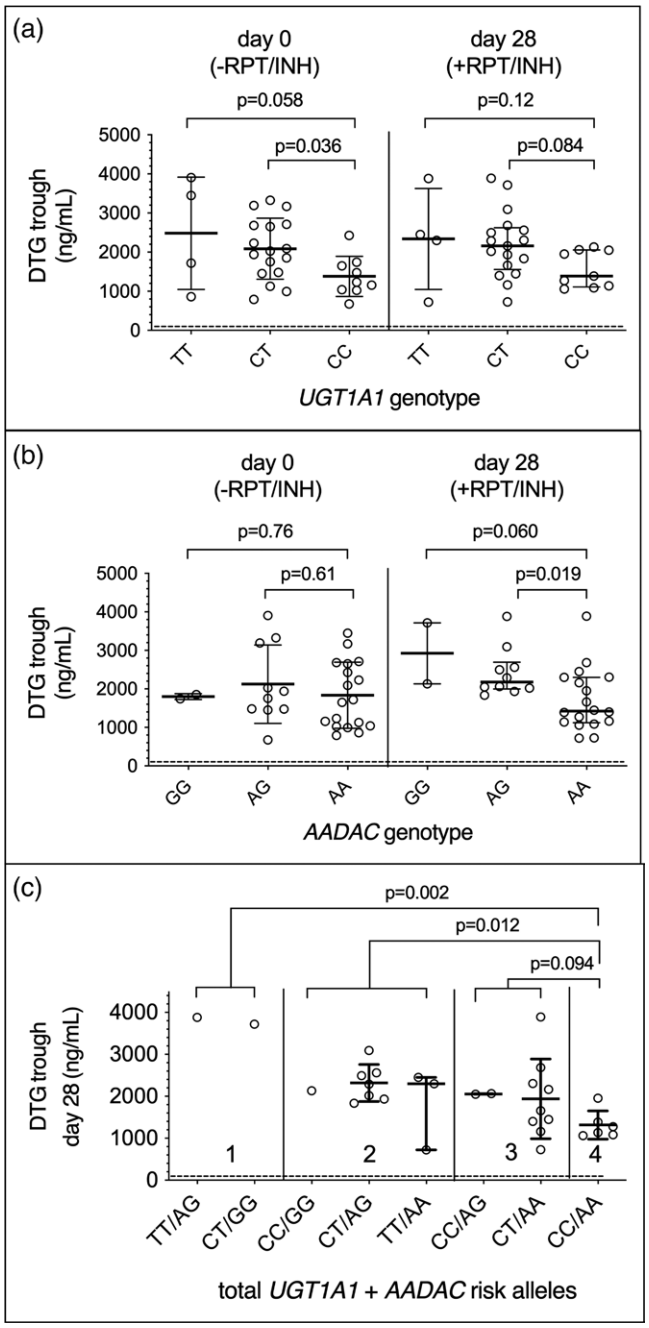
AADAC rs1803155 and *dolutegravir* C_{trough}

At day 0, there was no association between *AADAC* rs1803155 and dolutegravir C_{trough}. Compared with *rs1803155* AA poor metabolizers (more frequent than normal genotype, so used as the reference group), day 0 C_{trough} was similar in AG intermediate metabolizers

Table 1 Baseline characteristics of A5372 participants evaluable for genetic associations

	Total (*n* = 30)
Age in years, median (range)	41 (21–57)
Sex (cis-gender)	
Female; *n* (%)	11 (37)
Male; *n* (%)	19 (63)
Race/Ethnicity; *n* (%)	
Asian	8 (27)
Black or African American	19 (63)
White	3 (10)
BMI in kg/m², median (range)	24.0 (18.6–41.0)
Weight in kg, median (range)	65.4 (43–115.8)
UGT1A1 rs887829 metabolizer; *n* (%)	
Normal, CC	9 (30)
Intermediate, CT	17 (57)
Poor, TT	4 (13)
AADAC rs1803155 metabolizer; *n* (%)	
Normal, GG	2 (7)
Intermediate, AG	10 (33)
Poor, AA	18 (60)
NAT2 acetylator; *n* (%)	
Rapid	3 (10)
Intermediate	15 (50)
Slow	12 (40)

Fig. 1



Relationships of *UGT1A1* and *AADAC* genotypes with dolutegravir C_{trough} at days 0 and 28. (a) Left side – relationship of *UGT1A1* rs887829 with dolutegravir C_{trough} at day 0 (dolutegravir 50 mg once daily, without rifapentine and isoniazid). Right side – relationship of *UGT1A1* rs887829 with dolutegravir C_{trough} at day 28 (dolutegravir 50 mg twice daily, with once daily rifapentine 600 mg and isoniazid 300 mg). (b) Left side – relationship of *AADAC* rs1803155 with dolutegravir C_{trough} at day 0. Right side – relationship of *AADAC* rs1803155 with dolutegravir C_{trough} at day 28. (c) Risk alleles for lower dolutegravir C_{trough} were defined as *AADAC* rs1803155 A, and UGT1A1 rs887829 C. Numbers 1–4 above the X axis indicate the total number of risk alleles. The rs887829 C/T and rs1803155 A/G genotype combinations are indicated below the X-axis. Error bars indicate the median and interquartile range. Marker positions are unadjusted for BMI. The horizontal dashed line indicates the *in vitro*, protein-adjusted dolutegravir IC_{90} for wild-type HIV-1 of 64 ng/ml [13]. *P*-values from multivariable linear regression models are adjusted for BMI. DTG, dolutegravir; INH, isoniazid; RPT, rifapentine.

(GMR = 1.11; 90% CI: 0.82–1.52), and in GG normal metabolizers (GMR = 1.11; 90% CI: 0.61–2.02). In contrast, at day 28, *AADAC* rs1803155 was associated with dolutegravir C_{trough}. Compared with *rs1803155* AA poor metabolizers, day 28 C_{trough} was higher in AG intermediate metabolizers (GMR = 1.48; 90% CI: 1.14–1.90), and in GG normal metabolizers (GMR = 1.79; 90% CI: 1.09–2.93). Relationships between *AADAC rs1803155* genotype and dolutegravir C_{trough} are shown in Fig. 1b. Results of multivariable models that include *UGT1A1* rs887829, *AADAC* rs1803155, and BMI are presented in Table 2.

NAT2 acetylator status and dolutegravir C_{trough}

At days 0 and 28, in multivariable models that adjusted for *UGT1A1* rs887829, *AADAC* rs1803155, and screening BMI, there was no association between *NAT2* acetylator status and dolutegravir C_{trough} (Supplemental Material, Supplemental digital content 1, *http://links.lww.com/FPC/B510*). Compared with *NAT2* slow acetylators, day 28 C_{trough} was similar in intermediate acetylators (GMR = 0.91; 90% CI: 0.70–1.19), and in rapid acetylators (GMR = 0.86; 90% CI: 0.55–1.35).

Total number of AADAC and UGT1A1 risk alleles and day 28 C_{trough}

There was an ordinal relationship between number of risk alleles for lower dolutegravir C_{trough} values (i.e. *UGT1A1* rs887829 C and *AADAC* rs1803155 A alleles) and day 28 C_{trough} (Fig. 1c). Among the six participants with four risk alleles (i.e. rs887829 CC normal dolutegravir metabolism, and rs1803155 AA poor rifapentine metabolism), median day 28 C_{trough} was 1205 ng/ml [interquartile range (IQR): 1079, 1530 ng/ml]. In contrast, the two participants with only one risk allele had day 28 C_{trough} values of 3882 ng/ml and 3717 ng/ml. Participants with two or three risk alleles had intermediate C_{trough} values of 2290 ng/ml (IQR: 1936, 2495 ng/ml) and 2049 ng/ml (IQR: 1400, 2305 ng/ml), respectively.

Discussion

Among A5372 participants [14], *UGT1A1* rs887829 and *AADAC* rs1803155 were independently associated with day 28 dolutegravir C_{trough}. The *UGT1A1* association was expected based on previous reports [7,8,16]. For example, among 284 South Africans in the ADVANCE trial, rs887829 C/T and T/T were associated with 10.8% and 25.9% slower dolutegravir clearance, respectively, compared with C/C [8]. The rs887829 T allele is in strong linkage with *UGT1A1*28*, the Gilbert trait allele (a promoter TA_n dinucleotide) that confers decreased gene expression [17].

Dolutegravir is not a substrate for arylacetamide deacetylase (AADAC), which is encoded by *AADAC*. Rifapentine is an AADAC substrate [18], and the *AADAC* rs1803155 A allele has been associated with slower rifapentine clearance [9]. Among individuals carrying *AADAC* rs1803155 A alleles, higher plasma rifapentine

Table 2 Multivariable models of dolutegravir C_{trough} associations with genotype and body mass index

	Day 0 β coeff. (90% CI) *P*-value ($n = 30$)		Day 28 β coeff. (90% CI) *P*-value ($n = 30$)	
	UGT1A1	*UGT1A1* & *AADAC*	*UGT1A1*	*UGT1A1* & *AADAC*
UGT1A1 genotype[a]				
Intermediate	0.41 (0.094–0.73) 0.036	0.40 (0.063–0.73) 0.053	0.32 (0.016–0.62) 0.084	0.27 (–0.005 to 0.55) 0.11
Poor	0.64 (0.090–1.19) 0.058	0.64 (0.068–1.21) 0.068	0.50 (–0.025 to 1.023) 0.12	0.49 (0.021–0.96) 0.086
AADAC genotype[b]				
Intermediate	-	0.10 (–0.22 to 0.41) 0.61	-	0.39 (0.12–0.65) 0.019
Normal	-	0.11 (–0.50 to 0.72) 0.76	-	0.58 (0.078–1.089) 0.060
BMI (per 1 kg/m^2)	–0.016 (–0.047 to 0.015) 0.39	–0.015 (–0.048 to 0.019) 0.46	–0.023 (–0.053 to 0.007) 0.20	–0.016 (–0.044 to 0.010) 0.32
Intercept	7.54 (6.77–8.31) <0.001	7.47 (6.46–8.31) <0.001	7.85 (7.12–8.58) <0.001	7.55 (6.86–8.24) <0.001

CI, confidence interval.
[a]The reference group for *UGT1A1* is normal metabolizer.
[b]The reference group for *AADAC* is poor metabolizer.

concentrations likely cause greater induction of hepatic drug-metabolizing enzymes, which may explain the lower plasma dolutegravir C_{trough}.

Isoniazid inhibits CYP3A4, CYP2A6, CYP1A2, and CYP2C19 [4], and *NAT2* slow acetylators have higher plasma isoniazid concentrations. We found no association between *NAT2* slow acetylators and higher dolutegravir C_{trough} values. Strong enzyme induction by rifapentine may dominate isoniazid's modest inhibitory effect, despite higher isoniazid concentrations, or hepatic enzymes inhibited by isoniazid may not be important for dolutegravir.

Dolutegravir C_{trough} was better predicted by *UGT1A1* and *AADAC* risk alleles together than each separately. Median dolutegravir C_{trough} concentrations were approximately three-fold lower among individual with four risk alleles than among the two participants with a single risk allele. Dolutegravir C_{trough} concentrations were intermediate among individuals with two or three risk alleles. Both the *AADAC* rs1803155 A allele and UGT1A1 rs887829 C allele are frequent worldwide [19], such that approximately 17% of Africans, and 15–30% of people worldwide have four risk alleles, and are anticipated to have the lowest dolutegravir C_{trough} concentrations when taking once-daily dolutegravir and rifapentine. It is reassuring that, even with four risk alleles, C_{trough} values with dolutegravir 50 mg twice daily were well above 64 ng/ml, the *in vitro*, protein-adjusted IC_{90} for wild-type HIV-1 [20]. While not addressed in the present study, as we consider dosing dolutegravir 50 mg once daily with 1HP, one wonders whether individuals with four risk alleles are also at risk for lower dolutegravir C_{trough} concentrations if prescribed dolutegravir 50 mg once daily with 1HP. Because induction of hepatic enzymes by rifapentine takes about 2 weeks to reach full effect, dolutegravir C_{trough} would only be low during the latter weeks of 1HP. Also, because dolutegravir slowly dissociates from intracellular integrase-DNA complexes [21], antiviral activity may persist despite dolutegravir C_{trough} falling below the IC_{90}.

In summary, among PWH receiving dolutegravir 50 mg twice daily with daily rifapentine/isoniazid, *AADAC* and *UGT1A1* polymorphisms were associated with dolutegravir C_{trough}. This is not clinically relevant with twice-daily dosing but may be important to study in evaluations of once-daily dolutegravir with rifapentine. This study reinforces the importance of evaluating pharmacogenetic effects on drug–drug interactions.

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Conflicts of interest

A.F.L. has contracts for clinical research unrelated to this work from Gilead, ViiV, and Merck; consulting fees from ViiV. A.A. reports grants from Gilead, ViiV, Roche, GSK, and MSD unrelated to this work. S.S. reports grants from ViiV unrelated to the present work. For the remaining authors, there are no conflicts of interest.

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