UGT1A1 Genotype Predicts Bilirubin-related Discontinuation of Atazanavir/Ritonavir

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Abstract #515

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ABSTRACT

Background: Some patients are not prescribed atazanavir over concern about possible jaundice. Atazanavir-associated hyperbilirubinemia correlates with *UGT1A1* rs887829 genotype. We examined bilirubin-related discontinuation of atazanavir through 96 weeks in participants from AIDS Clinical Trials Group study A5257.
Methods: Discriminatory properties of *UGT1A1* T/T genotype for predicting bilirubin-related atazanavir discontinuation through 96 weeks after antiretroviral initiation were estimated.
Results: Genetic analyses involved 1450 participants, including 481 who initiated randomized atazanavir/ritonavir. Positive predictive values of rs887829 T/T for bilirubin-related discontinuation of atazanavir were 20% in Black, 60% in White, and 29% in Hispanic participants; negative predictive values were 97%, 95%, and 97%, respectively.
Conclusions: Bilirubin-related discontinuation of atazanavir was rare in participants not homozygous for rs887829 T/T, regardless of race/ethnicity. We hypothesize that the higher rate of discontinuation among White participants homozygous for rs887829 T/T may reflect differences in physical manifestations of icterus by race/ethnicity. Selective avoidance of atazanavir initiation among individuals with T/T genotypes would markedly reduce the likelihood of bilirubin-related discontinuation of atazanavir.

BACKGROUND

- The once-daily HIV-1 protease inhibitor atazanavir with low-dose ritonavir as a pharmacokinetic enhancer (ATV/r) is generally safe and effective as a first-line regimen for HIV-1 infection.
- Prescribing ATV/r, however, could lead to hyperbilirubinemia and jaundice-related atazanavir discontinuations in some patients.
- Polymorphisms in *UGT1A1* have been associated with inter-individual differences in plasma indirect bilirubin concentrations (i.e. Gilbert syndrome).
- Previous reported associations between *UGT1A1* genotype and atazanavir discontinuation have been inconsistent (ACTG A5202 [1] and Swiss HIV Cohort Study [2]).
- In ACTG study A5257, participants were randomized to receive ATV/r, darunavir/ritonavir (DRV/r), or raltegravir (RAL), all with concomitant tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). While the three regimens had equivalent virologic response rates over 96 weeks, treatment with ATV/r was inferior to both the DRV/r and RAL [3].
- We examined whether *UGT1A1* genotype, baseline indirect bilirubin, and/or baseline hemoglobin were associated with bilirubin-related ATV/r discontinuation and whether associations differed by race/ethnicity group, and compared tolerability of regimens containing ATV/r versus DRV/r or RAL stratified by *UGT1A1* genotype.

METHODS

Study Participants
- Protocol A5257 was a phase III prospective randomized open-label trial comparing three non-nucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for initial treatment of HIV-1.
- 1,809 participants in A5257 were randomized to ATV/r (605), DRV/r (601) and RAL (603).
- Consent for genetic testing was obtained via ACTG protocol A5128.
- Analysis by *UGT1A1* genotype included 481 (ATV/r), 491 (DRV/r) and 478 (RAL) individuals who were White, Black or Hispanic. Among 481 in the ATV/r arm, 438 had *UGT1A1* genotype, baseline indirect bilirubin, and baseline hemoglobin data.

Genetic polymorphisms
- Genotypes for rs887829 (*UGT1A1* genotype) were available from Illumina HumanCore Exome Chip data generated by Vanderbilt Technologies for Advanced Genomics (VANTAGE), and provided results for 523,486 polymorphisms with call rates ≥99%.
- Genetic data management and association analyses were performed with PLINK version 1.07.
- Clustering of samples by genetic ancestry (African American, European, or Hispanic) was done by multidimensional scaling (MDS) implemented in PLINK.

Statistical Analyses
- The target population was Black, White, or Hispanic participants who initiated randomized treatment in A5257, and had genotype data available.
- Primary endpoint for the analysis was time to bilirubin-related ATV/r discontinuation by 96 weeks.
- Bilirubin-related events were defined a priori as those reported as being due to jaundice, elevated bilirubin, or hyperpigmentation.
- Cumulative incidence of bilirubin-related ATV/r discontinuation was estimated using a competing risks framework and compared across *UGT1A1* genotypes using Gray's test. Cox proportional hazard models were used to estimate relative hazards of bilirubin-related ATV/r discontinuation by *UGT1A1* genotype with and without adjusting for baseline indirect bilirubin and baseline hemoglobin.
- The cumulative incidence of tolerability failure over 96 weeks was estimated by *UGT1A1* genotype with pairwise differences compared between randomized ATV/r, DRV/r, and RAL via 97.5% confidence intervals (CI).
- Discriminatory properties (positive and negative predictive values) of *UGT1A1* T/T genotype for predicting bilirubin-related ATV/r discontinuation through 96 weeks after antiretroviral initiation (binary outcome) were estimated with exact 95% CI.
- All analyses were performed using SAS 9.2 without adjusting for multiple comparisons.

RESULTS

Table 1. Baseline characteristics of study participants on ATV/r

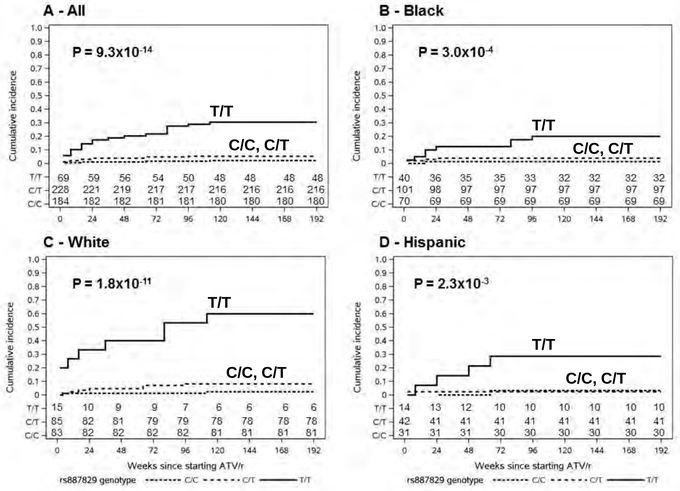
Drug discontinuation analyses (N = 481)		
Race/ethnicity		
Black, n (%)		211 (44%)
UGT1A1	C/C	70 (33%)
	C/T	101 (48%)
	T/T	40 (19%)
White, n (%)		183 (38%)
UGT1A1	C/C	83 (45%)
	C/T	85 (46%)
	T/T	15 (8%)
Hispanic, n (%)		87 (18%)
UGT1A1	C/C	31 (36%)
	C/T	42 (48%)
	T/T	14 (16%)
Female, n (%)		112 (23%)
BMI[a] in kg/m^2, median (IQR[b])		25 (23-29)
Age in years, median (IQR)		38 (29-45)
Bilirubin in mg/dL, median (IQR)		0.4 (0.2 – 0.6)[c]
Hemoglobin in g/dL, median (IQR)		13.9 (12.4 – 14.9)[c]

[a] BMI, body mass index
[b] IQR, interquartile range
[c] Based on 438 participants with baseline covariates

Associations with bilirubin-related ATV/r discontinuation
- Among the 481 evaluable participants, 146 (30%) prematurely discontinued ATV/r (29%, 30%, and 34% among Black, White, and Hispanic participants, respectively).
- Among 146 who prematurely discontinued in the ATV/r arm, discontinuation was bilirubin-related in 37 (25%), including 13 (21%) of 62 Black, 18 (33%) of 54 White, and 6 (20%) of 30 Hispanic participants.
- Other frequently reported reasons for ATV/r discontinuation were non-adherence (n=35) and gastrointestinal toxicity (n=21).
- Among all 481 participants, there was an 8% likelihood of bilirubin-related ATV/r discontinuation (6%, 10%, and 7% among Black, White, and Hispanic participants, respectively).

Figure 1. Cumulative incidence of time to bilirubin-related ATV/r discontinuation stratified by UGT1A1 genotype

- The *UGT1A1* genotype was associated with time to bilirubin-related ATV/r discontinuation in Black (p=3.0x10^{-4}), White (p=1.8x10^{-11}) and Hispanic (p=2.3x10^{-3}) participants (**Figure 1**).
- Participants with T/T genotype had higher cumulative incidence of bilirubin-related ATV/r discontinuation compared to non-T/T genotypes regardless of race/ethnicity; the magnitude of the effect varied by race/ethnicity (p<0.0001).



Discriminative properties of bilirubin-related ATV/r discontinuation
- Among *UGT1A1* T/T participants, the probabilities of bilirubin-related ATV/r discontinuation (i.e., positive predictive value; PPV) were 20% in blacks, 60% in whites and 29% in Hispanics.
- Among participants with non-T/T *UGT1A1* genotypes, the probability of not experiencing bilirubin-related ATV/r discontinuation (i.e., negative predictive value; NPV) ranged from 95% to 97%.
- The positive predictive value of baseline indirect bilirubin >0.4 mg/dL and the combination of *UGT1A1* T/T genotype and baseline indirect bilirubin >0.4 mg/dL for bilirubin-related ATV/r discontinuation by 96 weeks stratified by race/ethnicity are shown in **Table 2**.
- By prescribing ATV/r to *UGT1A1* non-T/T genotype participants who are at low risk for bilirubin-related ATV/r discontinuation, percentages of participants who would not be prescribed ATV/r are shown in **Table 2**.

Table 2. Positive and negative predictive values of UGT1A1 rs887829 and baseline bilirubin for bilirubin-related ATV/r discontinuation

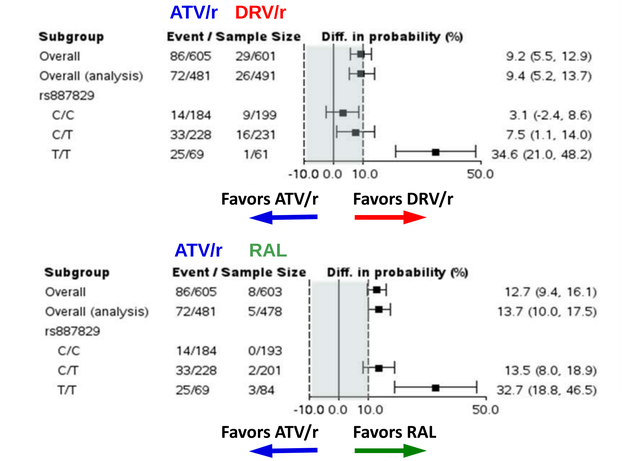
	Positive Predictive Value[a] [# subjects positive test] (95% CI)		Negative Predictive Value[b] [# subjects negative test] (95% CI)		% not prescribed ATV/r if screened
***UGT1A1* T/T genotype**					
Black	[40]	20% (9% - 36%)	[171]	97% (93% - 99%)	19.0%
White	[15]	60% (32% - 84%)	[168]	95% (90% - 98%)	8.2%
Hispanic	[14]	29% (8% - 58%)	[73]	97% (90% - 100%)	16.1%
Baseline bilirubin					
Black	[59]	14% (6% - 25%)	[139]	96% (92% - 99%)	29.8%
White	[78]	18% (10% - 28%)	[94]	96% (89% - 99%)	45.3%
Hispanic	[24]	13% (3% - 32%)	[44]	98% (88% - 100%)	35.3%
***UGT1A1* genotype and baseline bilirubin**					
Black	[22]	23% (8% - 45%)	[123]	98% (94% - 100%)	37.9%
White	[12]	75% (43% - 95%)	[91]	96% (89% - 99%)	47.1%
Hispanic	[5]	40% (5% - 85%)	[39]	97% (87% - 100%)	42.6%

[a] **Positive test:**
T/T genotype or baseline bilirubin > 0.4 mg/dL or T/T genotype and baseline bilirubin > 0.4 mg/dL

[b] **Negative test:**
non-T/T genotype or baseline bilirubin ≤ 0.4 mg/dL or non-T/T genotype and baseline bilirubin ≤ 0.4 mg/dL

Comparisons between randomized treatment arms
- ATV/r vs. DRV/r: estimated difference in 96-week cumulative incidence of all-cause tolerability failure was within the pre-specified A5257 equivalence boundary for participants with *UGT1A1* C/C, and was close to this boundary among participants with *UGT1A1* C/T.
- ATV/r vs. RAL: ATV/r was inferior to RAL from the estimated difference in 96-week cumulative incidence of all-cause tolerability failure regardless of *UGT1A1* genotype.

Figure 2. Pairwise treatment differences in cumulative probability of tolerability failure by week 96



SUMMARY

- In A5257, *UGT1A1* T/T genotype increased likelihood of bilirubin-associated ATV/r discontinuation. Likelihood of bilirubin-associated ATV/r discontinuation was least in Black, intermediate in Hispanic, and greatest in White participants. We speculate that differential rates of discontinuation may reflect differences in physical manifestations of icterus by race/ethnicity.
- Among A5257 participants with non-T/T *UGT1A1* genotypes, tolerability failure in ATV/r was almost within the equivalence boundary compared to DRV/r but was inferior to RAL.
- Knowledge of *UGT1A1* genotype would allow ATV/r to be prescribed to the substantial subset of individuals at relatively low risk for bilirubin-related ATV/r discontinuation.
- In settings where differential drug costs encourage prescribing of ATV/r based regiments, patient care may benefit from screening for *UGT1A1* genotyping, with avoidance of ATV/r in the select subset of patients at greatest risk for bilirubin-related discontinuation.

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