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Screening for UGT1A1 Genotype in Study A5257 Would Have Markedly Reduced Premature Discontinuation of Atazanavir for Hyperbilirubinemia

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Background. Some patients are not prescribed atazanavir because of concern about possible jaundice. Atazanavir-associated hyperbilirubinemia correlates with UGT1A1 rs887829 genotype. We examined bilirubin-related discontinuation of atazanavir 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 (with 95% confidence intervals [CIs]) were 20% (CI, 9%–36%) in Black, 60% (CI, 32%–84%) in White, and 29% (CI, 8%–58%) in Hispanic participants; negative predictive values were 97% (CI, 93%–99%), 95% (CI, 90%–98%), and 97% (CI, 90%–100%), respectively.

Conclusions. Bilirubin-related discontinuation of atazanavir was rare in participants not homozygous for rs887829 T/T, regardless of race or ethnicity. We hypothesize that the higher rate of discontinuation among White participants homozygous for rs887829 T/T may reflect differences in physical manifestations of jaundice by race and ethnicity. Selective avoidance of atazanavir initiation among individuals with T/T genotypes would markedly reduce the likelihood of bilirubin-related discontinuation of atazanavir while allowing atazanavir to be prescribed to the majority of individuals. This genetic association will also affect atazanavir/cobicistat.

Keywords. atazanavir; HIV; pharmacogenomics; pharmacokinetics; UGT1A1.

The once-daily human immunodeficiency virus (HIV)-1 protease inhibitor atazanavir with low-dose ritonavir as a pharmacokinetic enhancer (atazanavir/ritonavir) is generally safe and effective as a first-line regimen for HIV-1 infection [1–4]. Atazanavir increases plasma indirect bilirubin concentrations by inhibiting uridine diphosphate glucuronosyltransferase (UGT) 1A1-mediated bilirubin glucuronidation [5]. This provides a reliable biomarker of very recent medication adherence [6–8]. Atazanavir-associated indirect hyperbilirubinemia does not indicate hepatic injury [2, 9–11], but some patients discontinue atazanavir due to cosmetic jaundice [3, 12, 13], and many are not prescribed atazanavir to avoid this possibility. Better pretreatment prediction of atazanavir intolerance due to hyperbilirubinemia could reduce jaundice-related atazanavir discontinuations.

Polymorphisms in UGT1A1 are associated with interindividual differences in plasma indirect bilirubin concentrations in the general population (ie, Gilbert’s syndrome). A promoter tandem TA repeat, UGT1A1*28
(TA)$_7$, is associated with reduced UGT1A1 transcription compared with UGT1A1*1 (TA)$_6$ [14, 15]. Among atazanavir recipients, UGT1A1*28 has been strongly associated with unconjugated hyperbilirubinemia [16, 17], as has a C→T single-nucleotide polymorphism (rs887829) in almost complete linkage disequilibrium with UGT1A1*28 [18]. In a genome-wide study involving individuals who had been randomized to atazanavir-containing regimens in AIDS Clinical Trials Group (ACTG) protocol A5202, rs887829 genotype, baseline indirect bilirubin, and baseline hemoglobin were each independently associated with peak on-treatment total bilirubin concentration [18]. However, reported associations between UGT1A1 genotype and atazanavir discontinuation have been inconsistent [17, 19].

In ACTG protocol A5257, participants were randomized to receive atazanavir/r, darunavir/ritonavir (darunavir/r), or raltegravir, all with concomitant tenofovir disoproxil fumarate (TDF)/emtricitabine. The present study examined whether UGT1A1 genotype, baseline indirect bilirubin, and/or baseline hemoglobin were associated with bilirubin-related discontinuation of atazanavir/r in A5257, and whether associations differed by race or ethnic group. We also assessed whether tolerability of regimens containing atazanavir/r compared with darunavir/r or raltegravir differed by UGT1A1 genotype.

**METHODS**

**Study Participants**

Protocol A5257 was a phase III prospective randomized open-label trial comparing 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for initial treatment of HIV-1 infection. Primary results of A5257 were previously published [20]. In brief, A5257 participants enrolled from 2009 to 2011 at research sites in the United States and Puerto Rico were randomized to open-label atazanavir (300 mg) plus ritonavir (100 mg), darunavir (800 mg) plus ritonavir (100 mg), or raltegravir (400 mg), all with concomitant TDF/emtricitabine (300 mg/200 mg). Study medications were once daily except for raltegravir, which was twice daily. Study evaluations were performed before entry, at entry, at weeks 4, 8, 16 and 24, 36, and 48, and every 16 weeks thereafter until the last enrolled subject was followed for 96 weeks. Bilirubin and hemoglobin were assayed individually as per standard procedures at each clinical research site. Participants with asymptomatic hyperbilirubinemia were allowed to continue atazanavir/r if the site investigator felt that the hyperbilirubinemia was not clinically relevant.

**Identifying Genetic Polymorphisms**

Consent for genetic analyses was obtained under ACTG protocol A5128 [21]. The Vanderbilt University Institutional Review Board and the ACTG approved this use of DNA. Genotypes for rs887829 (hereafter called UGT1A1 genotype) were available from Illumina HumanCore Exome Chip data generated by Vanderbilt Technologies for Advanced Genomics, and these genotypes provided results for 523,486 polymorphisms with call rates ≥99%. Laboratory personnel blinded to clinical data performed genotyping. Genetic data management and association analyses were performed with PLINK version 1.07 [22]. Samples that clustered to African American, European, or Hispanic genetic ancestry are hereafter called Black, White, and Hispanic, respectively. Clustering of samples was done by multidimensional scaling (MDS) implemented in PLINK.

**Statistical Analyses**

The target population for this study was Black, White, or Hispanic participants who initiated randomized treatment in A5257 and had genotype data available. Primary endpoints for the analysis were time to bilirubin-related discontinuation of atazanavir/r by 96 weeks. Attribution of reasons for discontinuation of randomized treatment, including details of toxicity or adverse events and participant-initiated discontinuations that were due to low-grade adverse events, was based on site report. Bilirubin-related events were defined a priori as those reported as being due to jaundice, elevated bilirubin, or hyperpigmentation. Inconsistent or unclear information was reconciled by site query.

Cumulative incidence of bilirubin-related discontinuation of atazanavir/r 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 discontinuation of atazanavir/r by UGT1A1 genotype with and without adjusting for baseline indirect bilirubin and baseline hemoglobin. Mirroring the primary A5257 analyses, the cumulative incidence of tolerability failure over 96 weeks was estimated by UGT1A1 genotype with pairwise differences compared between randomized atazanavir/r, darunavir/r, and raltegravir via 97.5% confidence intervals (CIs) [20]. Discriminatory properties (positive predictive value [PPV] and negative predictive value [NPV]) of UGT1A1 T/T genotype for predicting bilirubin-related atazanavir/r discontinuation through 96 weeks after antiretroviral initiation (binary outcome) were estimated with exact 95% CIs. All analyses were performed using SAS 9.2 without adjusting for multiple comparisons.

All analyses were done separately by self-identified race or ethnicity. To minimize potential errors due to race or ethnicity misclassification, sensitivity analyses were performed based on inferred ancestry using genome-wide data with exclusion of samples that did not cluster with African American, European, or Hispanic populations.

**RESULTS**

**Study Participants**

Among 605 participants randomized to the atazanavir/r-containing arm in A5257, 600 initiated the regimen and had
available treatment discontinuation data. Among these 600 participants, 493 participants had genotype data available, 481 of whom were self-identified as Black non-Hispanic, White non-Hispanic, or Hispanic. Derivation of the study population is shown in Figure 1. Baseline characteristics and genotype frequencies of study participants from the atazanavir/r arm are shown in Table 1. Among the 481 participants, median age was 38 years, median body mass index was 25 kg/m², and 23% were female, consistent with the full study population. Frequency of UGT1A1 T/T genotype varied by race or ethnicity (19% in Black, 8% in White, 16% in Hispanic participants). Genotype data were unavailable on 107 participants because they either did not consent to genetic testing or because genotyping was unsuccessful.

Associations With Bilirubin-Related Atazanavir/r Discontinuation

Among the 481 evaluable participants, 146 (30%) prematurely discontinued atazanavir/r (29%, 30%, and 34% among Black, White, and Hispanic participants, respectively). Among these 146 participants, most atazanavir/r discontinuations were not bilirubin-related, regardless of race or ethnicity; discontinuation was considered bilirubin-related in 37 (25%), including 13 (21%) of 62 Black participants, 18 (33%) of 54 White participants, and 6 (20%) of 30 Hispanic participants. Among all 481 participants, there was an 8% likelihood of bilirubin-related discontinuation of atazanavir/r (6%, 10%, and 7% among Black, White, and Hispanic participants, respectively). Other frequently reported reasons of atazanavir/r discontinuation were nonadherence (n = 35) and gastrointestinal toxicity (n = 21).

Table 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>UGT1A1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black, n (%)</td>
<td>211 (44%)</td>
</tr>
<tr>
<td>C/C</td>
<td>70 (33%)</td>
</tr>
<tr>
<td>C/T</td>
<td>101 (48%)</td>
</tr>
<tr>
<td>T/T</td>
<td>40 (19%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>183 (38%)</td>
</tr>
<tr>
<td>C/C</td>
<td>83 (45%)</td>
</tr>
<tr>
<td>C/T</td>
<td>85 (46%)</td>
</tr>
<tr>
<td>T/T</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>87 (18%)</td>
</tr>
<tr>
<td>C/C</td>
<td>31 (36%)</td>
</tr>
<tr>
<td>C/T</td>
<td>42 (48%)</td>
</tr>
<tr>
<td>T/T</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>Female</td>
<td>112 (23%)</td>
</tr>
<tr>
<td>Median BMI in kg/m² (IQR)</td>
<td>25 (23–29)</td>
</tr>
<tr>
<td>Median age in years (IQR)</td>
<td>38 (29–45)</td>
</tr>
<tr>
<td>Median baseline bilirubin mg/dL (IQR)</td>
<td>0.4 (0.2–0.6)</td>
</tr>
<tr>
<td>Median baseline hemoglobin g/dL (IQR)</td>
<td>13.9 (12.4–14.9)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IQR, interquartile range.

a Based on 438 participants with baseline covariates.

The UGT1A1 genotype was associated with time to bilirubin-related discontinuation of atazanavir/r in Black (P = 3.0 × 10⁻⁴), White (P = 1.8 × 10⁻¹¹), and Hispanic (P = 2.3 × 10⁻³) participants (Figure 2). Participants with T/T genotype had higher cumulative incidence of bilirubin-related atazanavir/r discontinuation compared with non-TT genotypes regardless of race or ethnicity by visual inspection; the magnitude of the effect varied by race or ethnicity (P < .0001). In Cox proportional hazards models stratified by race/ethnicity, and that included baseline indirect bilirubin and baseline hemoglobin, only UGT1A1 T/T genotype was independently associated with bilirubin-related atazanavir/r discontinuation, with a hazard ratio that ranged from 10 in Black participants to 24 in White participants (Table 2).

Discriminative Properties of Bilirubin-Related Discontinuation of Atazanavir

Positive and NPVs of UGT1A1 genotype and/or baseline indirect bilirubin for bilirubin-related discontinuation of atazanavir/r by 96 weeks are presented in Table 3. Among participants with UGT1A1 T/T genotypes, the probabilities of bilirubin-related discontinuation of atazanavir/r (ie, PPV) were 20% in Blacks, 60% in Whites, and 29% in Hispanics. Among participants with non-TT UGT1A1 genotypes, the
probability of not experiencing bilirubin-related discontinuation of atazanavir/r (ie, NPV) ranged from 95% to 97%.

The PPV of baseline indirect bilirubin >0.4 mg/dL (threshold based on the median value) for bilirubin-related discontinuation of atazanavir/r by 96 weeks stratified by race or ethnicity ranged from 13% to 18%, whereas the NPV ranged from 96% to 98%. Considering the combination of UGT1A1 T/T genotype and baseline indirect bilirubin >0.4 mg/dL, by race or ethnicity, the PPV ranged from 23% to 75%, and the NPV ranged from 94% to 97%.

Comparisons Between Randomized Treatment Arms
In A5257, primary treatment arm comparisons for all-cause tolerability failure over 96 weeks showed atazanavir/r to be inferior to both darunavir/r and raltegravir [20]. We repeated these analyses, within subgroups defined by UGT1A1 genotype. Comparing atazanavir/r and darunavir/r arms, among participants with UGT1A1 C/C, the estimated difference in 96-week cumulative incidence of all-cause tolerability failure was within the prespecified A5257 equivalence boundary, and among participants with UGT1A1 C/T was close to this boundary. In contrast, the estimated differences in 96-week cumulative incidence of tolerability failure with 97.5% CIs demonstrated inferiority for atazanavir/r compared with raltegravir regardless of UGT1A1 genotype (Figure 3).

Sensitivity Analyses
Sensitivity analyses were performed based on inferred ancestry using genome-wide data. These analyses censored 28 participants who, by MDS plot, did not cluster into distinct subgroups. Results and conclusions were unchanged in sensitivity analyses after removal of outliers (data not shown).

DISCUSSION
The present study showed that, among 481 participants who initiated atazanavir/r in A5257, the likelihood of bilirubin-related discontinuation of atazanavir/r was low among participants...
with UGT1A1 non-T/T genotypes (i.e., C/C or C/T) regardless of race or ethnicity, and this was substantially higher among participants with UGT1A1 T/T genotype regardless of race or ethnicity and was particularly high among White participants. These findings indicate that avoidance of atazanavir prescribing to individuals with UGT1A1 T/T genotypes would have reduced by approximately one-half the likelihood of bilirubin-related discontinuation of atazanavir, regardless of race or ethnicity. This approach would have still allowed atazanavir/r to be prescribed to the large percentage of individuals (81% of Black participants, 92% of White participants, and 84% of Hispanic participants) who are at low risk for bilirubin-related discontinuation.

We also examined the ability of baseline indirect bilirubin to predict bilirubin-related discontinuation of atazanavir among 438 participants who initiated atazanavir/r and had available baseline indirect bilirubin, regardless of genotype. Selective avoidance of atazanavir/r in individuals with baseline indirect bilirubin >0.4 mg/dL would have also reduced by approximately one-half the likelihood of bilirubin-related discontinuation of atazanavir, regardless of race or ethnicity, but would have allowed atazanavir/r to be prescribed to only 70% of Black participants, 55% of White participants, and 65% of Hispanic participants.

Finally, we examined the predictive utility of UGT1A1 genotype and baseline indirect bilirubin in combination. With both UGT1A1 T/T genotype and baseline indirect bilirubin >0.4 mg/dL, the likelihood of bilirubin-related discontinuation of atazanavir/r was modestly higher compared with considering baseline indirect bilirubin or UGT1A1 genotype alone. Prescribing atazanavir/r only to individuals who both lacked UGT1A1 T/T and had baseline indirect bilirubin ≤0.4 mg/dL would have also reduced by approximately one-half the likelihood of bilirubin-related discontinuation of atazanavir, regardless of race or ethnicity, but would have allowed atazanavir/r to be prescribed to only 62% of Black participants, 53% of White participants, and 57% of Hispanic participants.

Overall, the reductions in bilirubin-related discontinuation were similar in all race and ethnic groups whether by screening
for low risk based on baseline indirect bilirubin < 0.4, based on non-TT UGT1A1 genotype, or considering both. However, considering just UGT1A1 genotype would allow atazanavir/r prescribing a substantially greater percentage of participants. In particular, among White participants, 92% could be prescribed to atazanavir/r if screened using UGT1A1 genotype compared with only 55% if screened using baseline indirect bilirubin.

With UGT1A1 T/T homozygosity, the likelihood of bilirubin-related atazanavir/r discontinuation was least in Black participants, intermediate in Hispanic participants, and greatest in White participants. We speculate that the extent to which jaundice becomes visible differs depending on skin color and/or ancestry.

Two previous studies that analyzed associations between UGT1A1 genotype used all-cause discontinuation of atazanavir/r as the outcome of interest. In an observational study involving 121 Swiss HIV Cohort Study participants (80% Caucasian) who had received atazanavir/r, carriage of UGT1A1 low expresser alleles (*28/*28 or *28/*37) was associated with increased risk of atazanavir/r discontinuation, with cumulative rates of 63% among 18 participants carrying 2 alleles, 24% among 48 participants carrying one allele, and 15% among 55 participants carrying no allele [19]. (The *28 and *37 low-expressor alleles and the *36 high-expressor allele of UGT1A1 are all collectively identified an rs8175347.) In contrast, an analysis involving 646 participants randomized to receive atazanavir/r in ACTG protocol A5202 found no significant association between low-expressor UGT1A1 genotype (primarily UGT1A1*28) and increased likelihood of atazanavir/r discontinuation among either White participants or Black participants, although there was an association among Hispanic participants [17]. Our use of bilirubin-related atazanavir/r discontinuation as the outcome minimized confounding by other factors unrelated to UGT1A1 genotype (eg, nonadherence) and allowed genotype-phenotype associations to be more precisely described. The somewhat different results of these 3 studies are not due to genotyping differences (rs8175347 in prior studies, rs887829 in the present study). These polymorphisms are in almost complete linkage disequilibrium (rs887829 C with both *1 and *36; rs887829 T with both *28 and *37), and the *36 and
were homozygous for vir/r in A5257 was most pronounced among participants who UGT1A1 C/T genotype was almost within the equivalence boundary, and tolerability failure among participants with rs887829). The threshold to discontinue atazanavir/r for jaundice might have been lower in that observational study than in A5257, a prospective clinical trial. Likewise, in ACTG study A5202, atazanavir/r discontinuations unrelated to bilirubin might have obscured associations with UGT1A1 genotype. Consistent with this finding, most atazanavir/r discontinuations in the present study were attributed to causes other than bilirubin. In the A5202 study, the alternative antiretroviral provided for participants who developed jaundice (ie, lopinavir/r) may have been considered less attractive than the alternatives provided by protocol A5257 (ie, darunavir/r and raltegravir), creating a greater barrier to atazanavir/r discontinuation in A5202.

The HIV-1 protease inhibitors have relatively high genetic barriers to viral drug resistance. For this reason, protease inhibitor-based regimens are sometimes prescribed to patients who are at risk for nonadherence. With atazanavir/r, absence of an increase in plasma bilirubin from baseline (regardless of UGT1A1 genotype) strongly indicates that atazanavir/r was not taken within the prior 24 hours. This biomarker of adherence, often available from chemistry panels obtained at routine clinic visits, could still be used among individuals with UGT1A1 non-TT genotypes who are prescribed atazanavir/r. Prior cost-effectiveness modeling indicated that UGT1A1 genotyping to avoid atazanavir-related hyperbilirubinemia is cost effective if comparator antiretroviral therapy regimens (eg, atazanavir/r versus darunavir/r, each with TDF/emtricitabine) have identical drug costs [23]. With UGT1A1 genotyping for atazanavir, drug cost largely drives overall cost effectiveness. In settings where differential drug costs encourage prescribing of atazanavir/r-based regimens, patient care may benefit from UGT1A1 genotyping, with avoidance of atazanavir in the select subset of patients at greatest risk for bilirubin-related discontinuation. Many commercial laboratories in the United States offer genotype testing for UGT1A1 (especially UGT1A1*28, which is in almost complete linkage disequilibrium with rs887829).

Among A5257 participants with UGT1A1 C/C genotype, the cumulative incidence of all-cause tolerability failure by 96 weeks with atazanavir/r versus darunavir/r was within the equivalence boundary, and tolerability failure among participants with UGT1A1 C/T genotype was almost within the equivalence boundary. The tolerability benefit of darunavir/r over atazanavir/r in A5257 was most pronounced among participants who were homozygous for UGT1A1 T/T genotype. For atazanavir/r versus raltegravir comparisons, the cumulative incidence of all-cause tolerability failure by 96 weeks was inferior in atazanavir/r even when considering the UGT1A1 genotype.

The present study had limitations. We focused on genotype and clinical laboratory factors that were predetermined based on previous studies [17, 19]. It is possible that additional genetic or clinical factors could improve prediction of bilirubin-associated discontinuation of atazanavir/r. The smaller sample size for Hispanic participants may limit generalizability of findings in this subgroup. We did not study atazanavir with pharmacokinetic enhancement by cobicistat rather than ritonavir. However, atazanavir plasma concentration-time profiles when prescribed with cobicistat are bioequivalent to those with ritonavir [24]. Furthermore, in a double-blind clinical trial that randomly assigned 692 patients to receive atazanavir with either cobicistat or ritonavir, adverse events related to bilirubin elevations (eg, hyperbilirubinemia, jaundice, and scleral icterus) occurred in a similar percentage of patients in the cobicistat and ritonavir arms (40.7% and 36.2%, respectively), as did bilirubin-associated discontinuation of atazanavir (3.5% and 3.2%, respectively) [25]. We therefore expect the associations between UGT1A1 genotype and bilirubin-associated discontinuation of atazanavir/r reported in the present study to also occur with atazanavir/cobicistat.

CONCLUSIONS

In summary, among participants randomized to receive atazanavir/r with concomitant TDF/emtricitabine in A5257, UGT1A1 T/T genotype predicted an increased likelihood of bilirubin-associated discontinuation of atazanavir/r, regardless of race or ethnicity. Selective avoidance of atazanavir initiation among individuals with UGT1A1 T/T genotype would markedly reduce the likelihood of bilirubin-related discontinuation of atazanavir/r for hyperbilirubinemia. On April 8, 2015, the Department of Health and Human Services’ Antiretroviral Guidelines for Adults and Adolescents were updated to move atazanavir from preferred to alternative status, explicitly based on results of A5257 [4]. The present analyses suggest that, among individuals known to have either rs887829 C/C or C/T genotypes, atazanavir might still be considered for inclusion in preferred regimens.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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