

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *UGT1A1* and Atazanavir Prescribing

RS Gammal¹, MH Court², CE Haidar¹, OF Iwuchukwu^{3,4}, AH Gaur⁵, M Alvarellos⁶, C Guillemette⁷, JL Lennox⁸, M Whirl-Carrillo⁶, SS Brummel⁹, MJ Ratain¹⁰, TE Klein⁶, BR Schackman¹¹, KE Caudle¹ and DW Haas¹²

The antiretroviral protease inhibitor atazanavir inhibits hepatic uridine diphosphate glucuronosyltransferase (UGT) 1A1, thereby preventing the glucuronidation and elimination of bilirubin. Resultant indirect hyperbilirubinemia with jaundice can cause premature discontinuation of atazanavir. Risk for bilirubin-related discontinuation is highest among individuals who carry two *UGT1A1* decreased function alleles (*UGT1A1**28 or *37). We summarize published literature that supports this association and provide recommendations for atazanavir prescribing when *UGT1A1* genotype is known (updates at www.pharmgkb.org).

The purpose of this guideline is to provide information to allow the interpretation of clinical *UGT1A1* genotype tests so that the results can be used to inform the prescribing of atazanavir. Detailed guidelines for the use of atazanavir as well as analyses of cost effectiveness are beyond the scope of this article. CPIC guidelines are periodically updated at <http://www.pharmgkb.org>.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *UGT1A1* genotype and atazanavir-related hyperbilirubinemia/jaundice and atazanavir discontinuation (details in **Supplement**) was conducted.

GENE: *UGT1A1*

Background

The uridine diphosphate (UDP) glucuronosyltransferases (UGT) are a large family of enzymes (19 in humans) that mediate conju-

gation of glucuronic acid with lipophilic drugs, xenobiotics, and endogenous substances, thereby increasing their water solubility and enabling efficient elimination in bile and/or urine. Three UGT subfamilies have been identified based on gene sequence similarity: UGT1A, UGT2A, and UGT2B. The UGT1A subfamily of enzymes (nine in humans) are encoded by a single gene locus through differential splicing of unique first exons (exon 1) to shared exons 2 to 5.

The major UGT1A subfamily enzyme, UGT1A1, is expressed primarily in the liver and gastrointestinal tract¹ and is essential for the efficient elimination of bilirubin, the main byproduct of heme catabolism.² Reduced UGT1A1 activity either through developmental delay in neonates,³ genetic variation,^{4,5} or catalytic inhibition by drugs⁶ results in the accumulation of unconjugated (indirect) bilirubin in blood and tissues. When bilirubin elevation is high enough to cause visible yellow discoloration of the skin and eyes it is called jaundice (also known as icterus). In neonates, extreme bilirubin accumulation can lead to severe adverse neurological effects, namely, kernicterus.⁵

Genetic variants that have been identified in *UGT1A1* exon 1, promoter, enhancer, and shared *UGT1A* exons 2 to 5 as well as the accepted allele nomenclature are listed at <http://www.pharmacogenomics.pha.ulaval.ca/files/content/sites/pharmacogenomics/files/Nomenclature/UGT1A/UGT1A1.htm>. The most frequent genetic variant that affects UGT1A1 function is a dinucleotide TA_n repeat polymorphism (rs1875347)

¹Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; ²Individualized Medicine Program, Department of Veterinary Clinical Sciences, Washington State University College of Veterinary Medicine, Pullman, Washington, USA; ³Division of Pharmaceutical Sciences, Fairleigh Dickinson University School of Pharmacy, Florham Park, New Jersey, USA; ⁴Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; ⁵Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; ⁶Department of Genetics, Stanford University, Stanford, California, USA; ⁷Laval University CHU de Québec Research Center, Quebec, Quebec, Canada; ⁸Division of Infectious Disease, Emory University School of Medicine, Atlanta, Georgia, USA; ⁹Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; ¹⁰Center for Personalized Therapeutics, Comprehensive Cancer Center, The University of Chicago, Chicago, Illinois, USA; ¹¹Department of Healthcare Policy and Research, Weill Cornell Medical College, New York, New York, USA; ¹²Departments of Medicine, Pharmacology, Pathology, Microbiology & Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA. Correspondence: DW Haas (david.haas@vanderbilt.edu, cpic@pharmgkb.org)

Table 1 Assignment of likely *UGT1A1* phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Extensive metabolizer	An individual carrying two reference ^b function (*1) ^c and/or increased function alleles (*36). Alternatively identified by homozygosity for rs887829 C/C.	*1/*1; *1/*36; *36/*36; rs887829 C/C
Intermediate metabolizer	An individual carrying one reference ^b function (*1) ^c or increased function allele (*36) plus one decreased function allele (*6, *28, *37). Alternatively identified by heterozygosity for rs887829 C/T.	*1/*28; *1/*37; *36/*28; *36/*37; rs887829 C/T, *1/*6
Poor metabolizer	An individual carrying two decreased function alleles (*6, *28, *37). Alternatively identified by homozygosity for rs887829 T/T (*80/*80)	*28/*28; *28/*37; *37/*37; rs887829 T/T (*80/*80), *6/*6 ^a

^aHomozygosity for *UGT1A1**6, which occurs almost exclusively in individuals of Asian descent, is associated with Gilbert’s syndrome. However, at this time it is unclear if patients with this diplotype are at increased risk of severe atazanavir-associated hyperbilirubinemia. ^b“Reference” function refers to the *UGT1A1* alleles to which other alleles are compared. ^cThe reference function *1 allele is fully functional and refers to the rs8175347 TA₆ allele.

located in a TATAA consensus element in the *UGT1A1* promoter at -53 relative to the translation start site. This varies from five to eight TA repeats. In all populations studied to date, TA₆ (*UGT1A1**1) and TA₇ (*UGT1A1**28) are most frequent, while TA₅ (*UGT1A1**36) and TA₈ (*UGT1A1**37) repeats are infrequent or absent depending on geographic region of ancestry.^{7,8}

The *UGT1A1**28 allele was originally identified as a causative genetic variant of Gilbert syndrome, a form of mild unconjugated hyperbilirubinemia that affects ~3–9% of individuals of European ancestry.⁹ Mechanistic studies using promoter-reporter constructs have shown that the TA₇ (*UGT1A1**28) allele causes a moderate reduction in gene transcription as compared with the reference TA₆ (*UGT1A1**1) allele,⁹ possibly due to reduced binding affinity for transcription factors including TATA-binding protein.¹⁰ The TA₈ repeat (*UGT1A1**37) appears to cause lower transcription levels compared to TA₇, while TA₅ (*UGT1A1**36) appears to cause higher transcription levels than TA₆. In studies of human liver microsomes, the amount of UGT1A1 protein is ~2-fold less in *UGT1A1**28/*28 donors than in *UGT1A1**1/*1 donors.¹¹

Genome-wide association studies (GWAS) that genotyped single nucleotide polymorphisms but not the TA repeat^{12–14} have consistently associated another polymorphism that is within 300 basepairs of the TA repeat, namely, rs887829 (c.-364C>T; *UGT1A1**80), with indirect hyperbilirubinemia in the general population (i.e., Gilbert syndrome). The rs887829 T allele is in very strong linkage disequilibrium (LD) with the TA₇ and TA₈ alleles, while rs887829 C is in very strong LD with the TA₅ and TA₆ alleles ($r^2 \cong 0.99$).⁷ The rs887829 polymorphism explains ~15% of interindividual variability in indirect bilirubin concentrations in African-American and European populations.

Other *UGT1A1* single nucleotide polymorphisms (SNP) that have been associated with increased bilirubin concentrations in GWAS include rs11891311 in a Korean population¹⁵ and rs6742078 in a Chinese population,¹⁶ both of which are in significant LD with rs887829. The SNP rs4148323 (c.211G>A; p.Gly71Arg; *UGT1A1**6) was also identified as an independent

predictor of bilirubin concentrations in Korean and Chinese populations accounting for about 5% of variability (about 10% total when combined with *UGT1A1**28 linked SNPs).^{15,16} *UGT1A1**6 is relatively common with East Asian (Japanese, Chinese, and Korean) ancestry but is absent in European and African populations.¹⁶

A polymorphism affecting a phenobarbital response element in the *UGT1A1* enhancer (rs4124874; -3279T>G; *UGT1A1**60) has also been associated with Gilbert syndrome,¹⁷ likely because this variant is in incomplete LD with *UGT1A1**28.¹⁸ There is no evidence that *UGT1A1**60 alone results in decreased UGT1A1 function. There are also a relatively large number of rare variants that have been discovered through sequencing of the *UGT1A1* gene in individuals with Gilbert syndrome (see <http://www.pharmacogenomics.pha.ulaval.ca/files/content/sites/pharmacogenomics/files/Nomenclature/UGT1A/UGT1A1.htm>).

Genetic test interpretation

Clinical laboratories generally report *UGT1A1* genotype assay results for the more frequent alleles, using either the star (*) allele nomenclature and/or the number of TA repeats in the *UGT1A1* gene promoter region. Each named * allele is defined by one or more specific polymorphisms (see **Supplemental Table S1** online and <http://www.pharmacogenomics.pha.ulaval.ca/files/content/sites/pharmacogenomics/files/Nomenclature/UGT1A/UGT1A1.htm>). The level of UGT1A1 activity associated with the most frequent allelic variants is summarized in **Supplemental Table S2** online. Genotyping rs8175347 for the number of TA repeats allows assignment to *UGT1A1**28 (TA₇), *UGT1A1**36 (TA₅), *UGT1A1**37 (TA₈), or *UGT1A1**1 (TA₆, reference genotype).¹⁹ Because rs887829 is in almost complete linkage with rs8175347 ($r^2 \cong 0.99$), metabolizer status may also be inferred based on rs887829. **Table 1** summarizes the assignment of the likely UGT1A1 phenotype based on * allele and number of TA repeats.

Alleles of *UGT1A1* have been characterized in various geographically, racially, and ethnically diverse populations (**Supplemental Table S3**). The *UGT1A1**6 allele (rs4148323, 211G>A) is associated with reduced UGT1A1 enzyme function and is

found almost exclusively among individuals of Asian descent. In general, genotyping tests do not identify very rare or *de novo* variants.

Available genetic test options

See the **Supplementary Material** for more information on commercially available clinical testing options.

Incidental findings

Gilbert syndrome. Reduced hepatic UGT1A1 activity to ~30% of normal is a hallmark of Gilbert syndrome, a benign condition characterized by mild unconjugated hyperbilirubinemia.⁴ Individuals with Gilbert syndrome may experience transient elevations in unconjugated plasma bilirubin in response to various triggers (e.g., fasting, infection, or medications). Genotypes most commonly implicated in Gilbert syndrome are *UGT1A1**28/*28 and *UGT1A1**6/*6.

Crigler-Najjar syndrome. Crigler-Najjar syndrome is a very rare and severe form of unconjugated hyperbilirubinemia that results from various deleterious *UGT1A1* mutations,^{5,20} most of which are not tested in commercial genotyping platforms. Crigler-Najjar syndrome type 1, the severest form of the disease, is characterized by a complete absence of UGT1A1 activity. Without appropriate treatment that includes phototherapy and liver transplantation, patients usually die in childhood. Crigler-Najjar syndrome type 2 is less severe and is characterized by severely reduced but detectable UGT1A1 activity. Crigler-Najjar syndrome is generally diagnosed early in life, so is therefore very unlikely to be an incidental finding of genetic screening. However, identification of a heterozygous carrier state for a Crigler-Najjar mutation may have implications for prenatal genetic counseling. Many rare *UGT1A1* mutations have been associated with Crigler-Najjar syndrome types 1 and 2 (see <http://www.pharmacogenomics.pha.ulaval.ca/files/content/sites/pharmacogenomics/files/Nomenclature/UGT1A/UGT1A1.htm>).

Implications of *UGT1A1* genotype for other drugs. Decreased function genotypes of *UGT1A1* may affect toxicity and/or tolerability of other drugs. Such drugs include irinotecan, the active SN-38 metabolite of which undergoes detoxification to SN-38-glucuronide by UGT1A1, belinostat, which is also extensively metabolized by UGT1A1, and nilotinib or pazopanib, which inhibits UGT1A1.²¹

Other considerations

None.

DRUG: ATAZANAVIR

Background

Atazanavir efficacy and tolerability. In 2003, atazanavir was US Food and Drug Administration (FDA)-approved as the first once-daily human immunodeficiency virus type 1 (HIV-1) protease inhibitor. To maintain plasma concentrations necessary for optimal antiviral effect, atazanavir is typically prescribed with a pharmacokinetic enhancer, either low-dose ritonavir or cobicistat. For the past decade, atazanavir, together with low-dose ritonavir

(atazanavir/r) and two nucleoside analogs, had constituted a recommended first-line regimen for HIV-1 infection in adults and children 6 years and older and an alternative agent for children 3 months through 5 years of age.^{22–24} In April 2015, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents downgraded regimens containing atazanavir/r from recommended to alternative status based on a large comparative trial showing the rate of toxicity-related discontinuation was greater with the atazanavir/r than with either darunavir/r or raltegravir, each given with tenofovir/emtricitabine.²⁵ In 2015, the FDA approved a coformulated tablet comprising atazanavir with cobicistat,²⁶ which was likewise relegated to alternative status.

Atazanavir/r is generally safe and well tolerated. However, atazanavir inhibits UGT1A1-mediated glucuronidation of bilirubin, thus increasing plasma indirect bilirubin concentrations.⁶ Plasma indirect bilirubin increases from baseline in virtually every patient who takes this drug, while direct bilirubin and hepatic transaminase concentrations are unaffected. This indirect hyperbilirubinemia does not indicate hepatic injury.^{22,27,28} With once-daily atazanavir 300 mg plus ritonavir 100 mg, the frequency of grade 3 or higher bilirubin elevations (at least 2.5 times the upper limit of normal) is ~40%,^{22,28} and of grade 4 (at least 5 times the upper limit of normal) bilirubin elevation is ~4–8%.^{22,24,28} Among children and adolescents in a trial that involved atazanavir, 9% had a bilirubin value ≥ 5.1 times the upper limit of normal and 1.4% experienced jaundice.²⁹

Premature discontinuation of atazanavir and *UGT1A1* polymorphisms.

Three studies have examined associations between *UGT1A1* genotype and premature discontinuation of atazanavir/r.^{30–32} Two studies only evaluated all-cause discontinuation,^{30,31} whereas one also evaluated bilirubin-related discontinuation.³² The latter approach minimizes the impact of factors unrelated to *UGT1A1* genotype (e.g., nonadherence) and therefore better reveals genetic associations. Among 121 Swiss HIV Cohort Study participants (80% Caucasian) who had received atazanavir/r, carriage of *UGT1A1* decreased function alleles (*28/*28 or *28/*37) was associated with increased risk of all-cause atazanavir/r discontinuation. Eighteen participants had two decreased function alleles, 48 had one decreased function allele, and 55 participants had none, with estimated first-year cumulative discontinuation rates of 63%, 24%, and 15%, respectively.³⁰ In contrast, among 646 participants randomized to receive atazanavir/r in the AIDS Clinical Trials Group (ACTG) protocol A5202 there was no significant association between decreased function *UGT1A1* genotype (primarily *UGT1A1**28) and increased likelihood of all-cause atazanavir/r discontinuation among either White or Black participants, but there was an association among Hispanic participants.³¹

Among 481 patients who initiated randomized atazanavir/r with tenofovir disoproxil fumarate (TDF)/emtricitabine in ACTG protocol A5257, bilirubin-related discontinuation of atazanavir was strongly associated with rs887829 T/T (**Figure 1**). As discussed earlier, the rs887829 variant is in very high LD with the promoter TA repeat ($r^2 \cong 0.99$), the C allele being in linkage

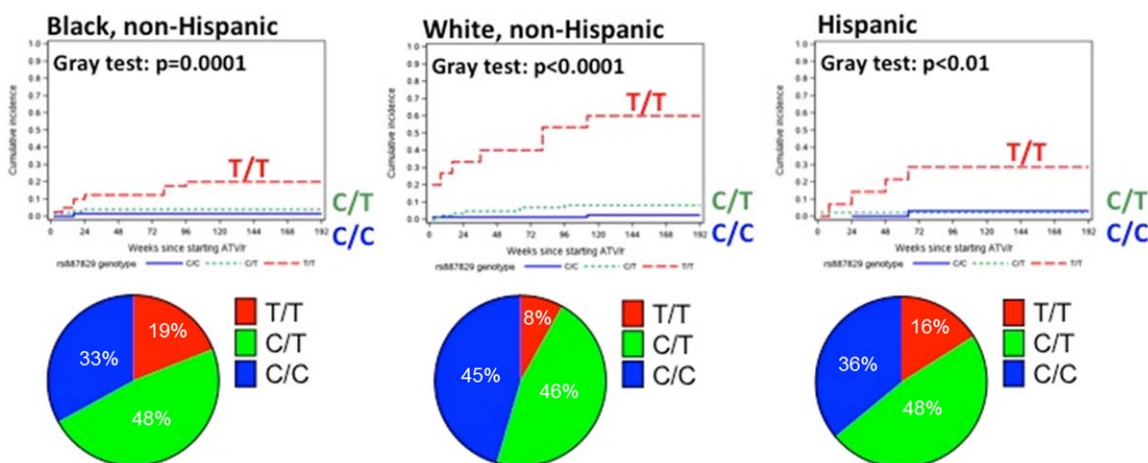


Figure 1 Cumulative incidence of time to bilirubin-associated discontinuation of atazanavir stratified by *UGT1A1* genotype in AIDS Clinical Trials Group protocol A5257 (adapted from ref. 32). Top panels: Lines estimate the cumulative incidence of time to bilirubin-associated discontinuation of atazanavir, stratified by *UGT1A1* rs887829 genotype and self-reported race/ethnicity. *P* values are given by Gray’s test for testing equality of cumulative incidence functions. Dashed red lines represent rs887829 T/T, dotted green lines rs887829 C/T, and solid blue lines rs887829 C/C. Bottom panels: Proportions of individuals in this analysis with rs887829 T/T, C/T, and C/C genotypes.

with (TA)₅ and (TA)₆, and the T allele with (TA)₇ and (TA)₈.^{7,32} Without T/T homozygosity, bilirubin-related discontinuation was infrequent regardless of race/ethnicity.³² Positive predictive values of rs887829 T/T for bilirubin-related discontinuation through 96 weeks of atazanavir (with 95% confidence intervals) were 60% (32–84%) in White, 29% (8–58%) in His-

panic, 20% (9–36%) in Black participants; negative predictive values were 95% (90–98%), 97% (90–100%), and 97% (93–99%), respectively. The authors speculated that the higher discontinuation rate among White participants with rs887829 T/T may have reflected differences in physical manifestations of icterus.

Table 2 Recommended use of atazanavir (boosted with either ritonavir or cobicistat*) by *UGT1A1* phenotype

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations ^a
Extensive metabolizer	Reference ^b <i>UGT1A1</i> activity; very low likelihood of bilirubin-related discontinuation of atazanavir.	There is no need to avoid prescribing of atazanavir based on <i>UGT1A1</i> genetic test result. Inform the patient that some patients stop atazanavir because of jaundice (yellow eyes and skin), but that this patient’s genotype makes this unlikely (less than about a 1 in 20 chance of stopping atazanavir because of jaundice).	Strong
Intermediate metabolizer	Somewhat decreased <i>UGT1A1</i> activity; low likelihood of bilirubin-related discontinuation of atazanavir.	There is no need to avoid prescribing of atazanavir based on <i>UGT1A1</i> genetic test result. Inform the patient that some patients stop atazanavir because of jaundice (yellow eyes and skin), but that this patient’s genotype makes this unlikely (less than about a 1 in 20 chance of stopping atazanavir because of jaundice).	Strong
Poor metabolizer	Markedly decreased <i>UGT1A1</i> activity; high likelihood of bilirubin-related discontinuation of atazanavir.	Consider an alternative agent particularly where jaundice would be of concern to the patient. If atazanavir is to be prescribed, there is a high likelihood of developing jaundice that will result in atazanavir discontinuation (at least 20% and as high as 60%).	Strong

*All studies correlating *UGT1A1* genotypes with atazanavir adverse events have involved ritonavir boosting. However, concentration-time profiles are equivalent when boosted with either cobicistat or ritonavir,²⁶ and bilirubin-related adverse events including discontinuation of atazanavir occur in a similar percentage of patients prescribed atazanavir with cobicistat or ritonavir.²⁶ Associations between *UGT1A1* genotype, bilirubin elevations, and atazanavir/r discontinuation therefore almost certainly translate to atazanavir/cobicistat.

^aRating scheme is described in **Supplementary Data** online. ^b“Reference” function refers to the *UGT1A1* allele to which other alleles are compared.

Associating genetic variability with variability in drug-related phenotypes

Substantial evidence associates *UGT1A1* genotype with phenotypic variability (see **Supplemental Table S4**). Most evidence is of high quality based on a standard grading scale (**Supplemental Table S4**). The evidence in the **Supplemental Material** and in **Supplemental Table S4** provides the basis for the dosing recommendations in **Table 2**.

Therapeutic recommendations

Atazanavir-associated indirect hyperbilirubinemia does not indicate hepatic injury,^{22,27,28} but some patients are not prescribed atazanavir to avoid the possibility of jaundice. Implications of *UGT1A1* genotype data for prescribing of atazanavir, boosted with either ritonavir or cobicistat, may be influenced by several factors. These include consequences of jaundice for the particular patient (e.g., workers who frequently interact with the public), access to alternative protease inhibitor antiretrovirals (e.g., darunavir), and whether the provider finds it useful to monitor atazanavir-induced changes in bilirubin concentrations to assess adherence. Recommendations are provided in **Table 2**.

A *UGT1A1* genotype is most helpful if available before atazanavir is prescribed. If noticeable jaundice does not develop while taking atazanavir chronically (or develops but is not bothersome), then the risk for bilirubin-related atazanavir discontinuation is probably low regardless of *UGT1A1* genotype.

For individuals carrying two *UGT1A1* decreased function alleles (i.e., *UGT1A1**28/*28, *UGT1A1**28/*37, *UGT1A1**37/*37, or rs887829 T/T), the likelihood of bilirubin-related atazanavir discontinuation is substantial.^{30,31} Before such individuals are prescribed atazanavir (boosted with either ritonavir or cobicistat), all such patients should be advised about the substantial likelihood of developing jaundice. Prescribing atazanavir to such individuals should generally be avoided unless the patient does not consider jaundice to be a concern, or there are other compelling reasons to prescribe atazanavir.

For individuals carrying fewer than two *UGT1A1* decreased function alleles (i.e., *1/*28, *1/*37, *36/*28, *36/*37, rs887829 C/C or rs887829 C/T), the likelihood of bilirubin-related atazanavir discontinuation is low.^{31,33} This risk is extremely low for individuals carrying no *UGT1A1* decreased function alleles (i.e., *UGT1A1**1/*1, *UGT1A1**1/*36, *UGT1A1**36/*36, or rs887829 C/C). Among patients with extensive metabolizer *UGT1A1* phenotypes it may not be necessary to discuss the possibility of jaundice with atazanavir. This decision about whether to discuss possible jaundice should be based on the clinical situation and provider judgment. If advice is offered, such discussion may note that the likelihood of developing jaundice that would require discontinuation of atazanavir is very low.

Recommendations for pediatrics. At the time of this writing there are no pediatric data regarding associations between *UGT1A1* genotypes and likelihood of bilirubin-related discontinuation of atazanavir. However, *UGT1A1* genotypes are expected to affect atazanavir-related hyperbilirubinemia similarly in adults and chil-

dren. Therefore, recommendations for adults may be directly adapted to pediatric patients.

Recommendations for incidental findings

Individuals who are homozygous for *UGT1A1**28 or *UGT1A1**6 are very likely to have Gilbert syndrome. Knowing an individual's *UGT1A1* genotype prior to prescribing may have implications for selection and dosing for drugs known to be *UGT1A1* substrates or inhibitors, such as irinotecan and nilotinib.

Other considerations

Other *UGT1A1* variants. Homozygosity for *UGT1A1**6 or *27, which occurs almost exclusively in individuals of Asian descent, is associated with Gilbert syndrome. However, there is a lack of evidence regarding whether patients with these diplotypes are at increased risk of severe atazanavir-associated hyperbilirubinemia. One study found no association between *UGT1A1**6/*6 and the incidence of severe hyperbilirubinemia with atazanavir,³⁴ although the lack of a statistically significant association may reflect the small number of patients with this genotype, with only seven patients homozygous for *UGT1A1**6. Therefore, at this time, it is unclear whether *UGT1A1**6/*6 or *27/*27 genotypes confer increased risk of severe atazanavir-associated hyperbilirubinemia.

Higher plasma atazanavir concentrations correlate directly with greater increases in plasma bilirubin concentrations. In a GWAS involving 475 HIV-infected patients prescribed atazanavir/r, no genetic variant (including candidate pharmacogenetic polymorphisms) was strongly associated with plasma atazanavir clearance.³⁵

Bilirubin as a biomarker of adherence. All HIV-1 protease inhibitors have relatively high genetic barriers to viral drug resistance and are therefore somewhat forgiving of nonadherence. For this reason, protease inhibitor-based regimens are sometimes prescribed to patients considered at high risk for nonadherence. With atazanavir/r, failure of plasma bilirubin to increase from baseline (regardless of *UGT1A1* genotype) is strong evidence that atazanavir/r was not taken during the prior ~24 hours.^{36–38} This biomarker of adherence, often available from chemistry panels obtained at routine clinic visits, may still be used among *UGT1A1* extensive metabolizers who are prescribed atazanavir/r.

Implications of *UGT1A1* polymorphisms for atazanavir with cobicistat. All studies correlating *UGT1A1* genotypes with atazanavir adverse events have involved ritonavir boosting. Such data are lacking for atazanavir boosted with cobicistat. However, atazanavir plasma concentration–time profiles are equivalent when boosted with either cobicistat or ritonavir.²⁶ In addition, 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 (e.g., 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).²⁶ Associations between *UGT1A1* genotype, bilirubin elevations, and atazanavir/r

discontinuation therefore almost certainly translate to atazanavir/cobicistat. These guidelines regarding *UGT1A1* genotype do not apply to rare situations where atazanavir is prescribed without either ritonavir or cobicistat.

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The benefit of prospective *UGT1A1* genotyping would be to determine the individual’s likelihood of bilirubin-related discontinuation of atazanavir prior to beginning therapy.³² This may allow atazanavir to be prescribed to patients at low risk for bilirubin-related discontinuation and avoided in patients at high risk. Some patients may still develop bilirubin-related discontinuation of atazanavir despite low-risk genotypes. There is little apparent risk of *UGT1A1* genotyping that results in a recommendation to avoid atazanavir, as alternative protease inhibitor-containing regimens are comparable in terms of efficacy and pill burden, although costs may vary depending on the payer.

Other possible limitations include laboratory error and an incomplete *UGT1A1* genetic profile, as many tests only report results for *UGT1A1**28. As individuals’ genotypes do not change over time, genotyping errors could remain in the medical record for the lifetime of the patient.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

A systematic review of the literature concluded that homozygosity of *UGT1A1**28 is a risk factor for occurrence of severe atazanavir-associated unconjugated hyperbilirubinemia, with a pooled positive predictive value of 40.3% and a pooled negative predictive value of 88.1%. Bilirubin-related discontinuation of atazanavir through 96 weeks is strongly associated with rs887829 T/T (in significant LD with *UGT1A1**28), with reported positive predictive value ranging from 20% to 60% depending on race/ethnicity.³² Thus, race/ethnicity may modify the genetic effect (Figure 1). Nongenetic factors such as fasting and diet can also affect bilirubin concentrations.^{39,40}

This CPIC guideline assumes that the *UGT1A1* genotype results are already available to the prescriber. It is beyond the scope of this guideline to make recommendations regarding whether or not *UGT1A1* genotyping should be performed.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely

made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC’s guidelines, or for any errors or omissions.

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CONFLICT OF INTEREST

D.W.H. has been a consultant to Merck. All other authors declare no conflicts.

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1. Court, M.H. *et al.* Quantitative distribution of mRNAs encoding the 19 human UDP-glucuronosyltransferase enzymes in 26 adult and 3 fetal tissues. *Xenobiotica* **42**, 266–277 (2012).
2. Bosma, P.J. *et al.* Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. *J. Biol. Chem.* **269**, 17960–17964 (1994).
3. Strassburg, C.P. *et al.* Developmental aspects of human hepatic drug glucuronidation in young children and adults. *Gut* **50**, 259–265 (2002).
4. Strassburg, C.P. Pharmacogenetics of Gilbert’s syndrome. *Pharmacogenomics* **9**, 703–715 (2008).
5. Kadakol, A. *et al.* Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. *Hum. Mutat.* **16**, 297–306 (2000).
6. Zhang, D. *et al.* In vitro inhibition of UDP glucuronosyltransferases by atazanavir and other HIV protease inhibitors and the relationship of this property to in vivo bilirubin glucuronidation. *Drug Metab. Dispos.* **33**, 1729–1739 (2005).
7. Horsfall, L.J. *et al.* Prevalence of clinically relevant UGT1A alleles and haplotypes in African populations. *Ann. Hum. Genet.* **75**, 236–246 (2011).
8. Hall, D., Ybazeta, G., Destro-Biso, I.G., Petzl-Erler, M.L. & Di Rienzo, A. Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. *Pharmacogenetics* **9**, 591–599 (1999).
9. Bosma, P.J. *et al.* The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert’s syndrome. *N. Engl. J. Med.* **333**, 1171–1175 (1995).
10. Hsieh, T.Y. *et al.* Molecular pathogenesis of Gilbert’s syndrome: decreased TATA-binding protein binding affinity of UGT1A1 gene promoter. *Pharmacogenet. Genomics* **17**, 229–236 (2007).
11. Girard, H. *et al.* UGT1A1 polymorphisms are important determinants of dietary carcinogen detoxification in the liver. *Hepatology* **42**, 448–457 (2005).
12. Johnson, A.D. *et al.* Genome-wide association meta-analysis for total serum bilirubin levels. *Hum. Mol. Genet.* **18**, 2700–2710 (2009).
13. Chen, G. *et al.* UGT1A1 is a major locus influencing bilirubin levels in African Americans. *Eur. J. Hum. Genet.* **20**, 463–468 (2012).
14. Sanna, S. *et al.* Common variants in the SLC01B3 locus are associated with bilirubin levels and unconjugated hyperbilirubinemia. *Hum. Mol. Genet.* **18**, 2711–2718 (2009).
15. Kang, T.W. *et al.* Genome-wide association of serum bilirubin levels in Korean population. *Hum. Mol. Genet.* **19**, 3672–3678 (2010).
16. Dai, X. *et al.* A genome-wide association study for serum bilirubin levels and gene-environment interaction in a Chinese population. *Genet. Epidemiol.* **37**, 293–300 (2013).
17. Sugatani, J. *et al.* Identification of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. *Biochem. Biophys. Res. Commun.* **292**, 492–497 (2002).

18. Chen, Z. *et al.* UGT1A1 sequence variants associated with risk of adult hyperbilirubinemia: a quantitative analysis. *Gene* **552**, 32–38 (2014).
19. Barbarino, J.M., Haidar, C.E., Klein, T.E. & Altman, R.B. PharmGKB summary: very important pharmacogene information for UGT1A1. *Pharmacogenet. Genomics* **24**, 177–183 (2014).
20. Bartlett, M.G. & Gourley, G.R. Assessment of UGT polymorphisms and neonatal jaundice. *Semin. Perinatol.* **35**, 127–133 (2011).
21. Singer, J.B. *et al.* UGT1A1 promoter polymorphism increases risk of nilotinib-induced hyperbilirubinemia. *Leukemia* **21**, 2311–2315 (2007).
22. Molina, J.M. *et al.* Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* **372**, 646–655 (2008).
23. Daar, E.S. *et al.* Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann. Intern. Med.* **154**, 445–456 (2011).
24. Lennox, J.L. *et al.* Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann. Intern. Med.* **161**, 461–471 (2014).
25. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. <<http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>>. Accessed on April 14, 2015.
26. Gallant, J.E. *et al.* Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV type 1-infected patients: week 48 results. *J. Infect. Dis.* **208**, 32–39 (2013).
27. Malan, D.R. *et al.* Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naïve patients. *J. Acquir. Immune Defic. Syndr.* **47**, 161–167 (2008).
28. Torti, C. *et al.* Hyperbilirubinemia during atazanavir treatment in 2,404 patients in the Italian atazanavir expanded access program and MASTER Cohorts. *Infection* **37**, 244–249 (2009).
29. Rutstein, R.M. *et al.* Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the Pediatric AIDS Clinical Trials Group Protocol 1020A. *Pediatr. Infect. Dis. J.* **34**, 162–167 (2015).
30. Lubomirov, R. *et al.* Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. *J. Infect. Dis.* **203**, 246–257 (2011).
31. Ribaud, H.J. *et al.* Impact of UGT1A1 Gilbert variant on discontinuation of ritonavir-boosted atazanavir in AIDS Clinical Trials Group Study A5202. *J. Infect. Dis.* **207**, 420–425 (2013).
32. Vardhanabhuti, S. *et al.* Screening for UGT1A1 Genotype in Study A5257 would have markedly reduced premature discontinuation of atazanavir for hyperbilirubinemia. *Open Forum Infect. Dis.* **2**, ofv085 (2015).
33. Eley, T. *et al.* Clinical and pharmacogenetic factors affecting neonatal bilirubinemia following atazanavir treatment of mothers during pregnancy. *AIDS Res. Hum. Retroviruses* **29**, 1287–1292 (2013).
34. Park, W.B. *et al.* Genetic factors influencing severe atazanavir-associated hyperbilirubinemia in a population with low UDP-glucuronosyltransferase 1A1*28 allele frequency. *Clin. Infect. Dis.* **51**, 101–106 (2010).
35. Johnson, D.H. *et al.* Genomewide association study of atazanavir pharmacokinetics and hyperbilirubinemia in AIDS Clinical Trials Group protocol A5202. *Pharmacogenet. Genomics* **24**, 195–203 (2014).
36. Petersen, K. *et al.* Use of bilirubin as a marker of adherence to atazanavir-based antiretroviral therapy. *AIDS* **19**, 1700–1702 (2005).
37. Rekić, D. *et al.* Bilirubin—a potential marker of drug exposure in atazanavir-based antiretroviral therapy. *AAPS J.* **13**, 598–605 (2011).
38. Morello, J. *et al.* Short communication: use of serum bilirubin levels as surrogate marker of early virological response to atazanavir-based antiretroviral therapy. *AIDS Res. Hum. Retroviruses* **27**, 1043–1045 (2011).
39. Rodrigues, C. *et al.* Bilirubin dependence on UGT1A1 polymorphisms, hemoglobin, fasting time and body mass index. *Am. J. Med. Sci.* **343**, 114–118 (2012).
40. Navarro, S.L. *et al.* Cruciferous vegetable feeding alters UGT1A1 activity: diet- and genotype-dependent changes in serum bilirubin in a controlled feeding trial. *Cancer Prev. Res. (Phila.)* **2**, 345–352 (2009).