UGT1A1: atazanavir 7736 to 7739

*1/*28 = genotype leading to a reduced UGT1A1 activity, *28/*28 = genotype leading to a strongly reduced UGT1A1 activity, BMI = body mass index, CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, HR = hazard ratio, HR_{adj} = adjusted hazard ratio, IM = IM OTHER = intermediate metaboliser, genotype otherwise = *1 in combination with an allele with reduced activity other than *28 (e.g. *1/*6), NS = non-significant, OR = odds ratio, OR_{adj} = adjusted odds ratio, PM = PM, OTHER = poor metaboliser, genotype otherwise = two alleles with reduced activity of which at least one other than *28 (e.g. *6/*28 or *6/*6), S = significant, SmPC = Summary of Product Characteristics, UGT = uridine diphosphate glucuronosyltransferase, ULN = upper limit of normal.
UGT1A1*1 = TA_6 = [A(TA)$_6$TAA] = wild-type, UGT1A1*28 = TA_7 = [A(TA)$_7$TAA] (reduced UGT1A1 activity), UGT1A1*36 = TA_5 = [A(TA)$_5$TAA] (increased UGT1A1 activity), UGT1A1*37 = TA_8 = [A(TA)$_8$TAA] (UGT1A1 activity more strongly reduced than for *28), UGT1A1*6 = gene variant in Asians, reduced activity, comparable to *28.
rs887829C = allele almost completely linked to UGT1A1 *1, rs887829T = allele almost completely linked to UGT1A1 *28 and *37.

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

Brief summary and justification of choices:
Atazanavir increases hyperbilirubinemia and jaundice risk by inhibiting UGT1A1, which is involved in glucuronidation of bilirubin. This risk is especially enhanced in patients having a genetically decreased UGT1A1 activity caused by the *28 allele. While the effect of the *28 and *6 alleles on UGT1A1 activity is comparable, the *28 allele is associated with a higher risk of hyperbilirubinemia, probably due to the presence of three additional gene variations associated with hyperbilirubinemia (one in UGT1A3 and two in UGT1A7).
Atazanavir is not metabolised by UGT1A1.
For *28/*28 (or the almost completely linked rs887829TT), a meta-analysis and all 7 studies with more than 120 patients showed an increase in discontinuation of atazanavir, in atazanavir-induced severe hyperbilirubinemia (total bilirubin > 3.1 mg/dl) or in bilirubin levels (Du 2019 (meta-analyses of 4 studies with 71 *28/*28 (compared to *1/*1) and of 5 studies with 89 *28/*28 (compared to *1/*1+*1/*28)), Leger 2018 (59 rs887829TT), Falvella 2017 (28 *28/*28), Vardhanabhuti 2015 (69 rs887829TT), Johnson 2014 (genome-wide association study, 475 patients, number of rs887829TT not mentioned), Ribaudo 2013 (100 *28/*28), Lubomirov 2011 (18 *28/*28+*28/*37), and Park 2010 (26 *1/*28+*28/*28, among whom 1 *28/*28)). The only inconsistencies were that Leger 2018 did not find an increase in discontinuation within 12 months due to jaundice for Black and Hispanic patients (43 and 3 rs887829TT, respectively) and Ribaudo 2013 did not find a decrease in time to discontinuation of atazanavir for White and Black patients (24 and 48 *28/*28, respectively). However, Vardhanabhuti 2015 found an increased discontinuation due to bilirubin increase or jaundice in the first 96 weeks in Black, White and Hispanic patients (40, 15, and 14 rs887829TT, respectively). Hyperbilirubinemia and jaundice are benign (not reflecting hepatic injury) and reversible upon atazanavir discontinuation. In addition, whereas failure (i.e. discontinuation) of a therapy that is life-saving in the short or long term, can be a serious event (hence code E for the discontinuation of atazanavir), the actual clinical impact will be small in this case. The reasons are that the failure is due to benign adverse events and not to a diminished effectiveness and that in a high-resource country as the Netherlands failure of atazanavir is likely to only slightly impact the number of available treatment options. So, discontinuation of atazanavir will only results in patients being switched to another antiretroviral regimen, not in patients being left without therapy. However, in the two studies mentioning rates of discontinuing for all causes, these were high for (predominantly) White *28/*28 (60% and 63% of patients compared to 5% and 19% for *1/*1+*1/*28) (Vardhanabhuti 2015 (69 rs887829TT) and Lubomirov 2011 (18 *28/*28+*28/*37)). Therefore, the KNMP Pharmacogenetics Working Group decided to recommend using an alternative if an equally suited alternative is available (yes/yes-interaction). Ferraris 2012 (including 24 *28/*28) showed a lower percentage of patients with hyperbilirubinemia grade ≥ 3 on unboosted atazanavir 400 mg/day than on atazanavir/ritonavir 300/100 mg/day, which is confirmed by the SmPC Reyataz (atazanavir) 17-10-2022, while effectiveness remained the same. However, in the Netherlands, unboosted atazanavir is not registered for treatment naive patients and only registered for selected non-treatment naïve patients. Therefore, the DPWG does not consider unboosted atazanavir as an equivalent alternative to boosted atazanavir and decided not to suggest this as an alternative.

For *1/*28 (or the almost completely linked rs887829CT), results are more inconsistent, with a meta-analysis and 4 studies with more than 120 patients showing an increase in discontinuation of atazanavir, in atazanavir-induced severe hyperbilirubinemia (total bilirubin > 3.1 mg/dl) or in bilirubin levels (Du 2019 (meta-analysis of 4 studies with 159 *1/*28), Falvella 2017 (52 *1/*28), Johnson 2014 (genome-wide association study, 475 patients, number of rs887829CT not mentioned), Ribaudo 2013 (285 *1/*28, comparing *28/*28 versus *1/*28 versus *1/*1), and Park 2010 (26 *1/*28+*28/*28, among whom 25 *1/*28)), but with *2* studies with more than 120 patients showing no increase in discontinuation of atazanavir (Leger 2018 (142 rs887829CT), and Lubomirov 2011 (48 *1/*28+*1/*37)). In addition, Vardhanabhuti 2015 (228 rs887829CT and 69 rs887829TT) found an increased discontinuation due to bilirubin increase or jaundice in the first 96 weeks for rs887829CT+ rs887829TT but not for rs887829CT. Lin 2015 did not find a different incidence of gall or renal stones on atazanavir therapy for 34 *1/*28: Apart from the evidence being less convincing, *1/*28 is the major group among White populations including the Dutch population. This indicates that *1/*28 strongly represents the standard patient and that health care provider experience with atazanavir is mainly derived from patients with this genotype. This in turn implicates that atazanavir treatment will be optimised based mainly on patients with the *1/*28 genotype. For this reason, the KNMP Pharmacogenetics Working Group concludes that a gene-drug interaction is present, but that therapy adjustment is neither required nor advisable (yes/no-interaction).
*1/*1: Based on the above, evidence points to a decreased risk of atazanavir discontinuation and hyperbilirubinemia for *1/*1. However, because this is a positive effect, no action is needed for *1/*1. Therefore, the KNMP Pharmacogenetics Working Group decided to refrain from a recommendation for *1/*1.
For IM and PM, the only study with more than 120 patients did not find an increase in hyperbilirubinemia grade 3 or 4 (total bilirubin level > 3.1 mg/dl) for IM+PM (Park 2010 (41 *1/*6+*6/*6, among whom 7 *6/*6)), whereas an effect was found for *28 in this patient group despite a lower allele frequency. This agrees with the observation that *28 is associated with a higher risk of hyperbilirubinemia. The KNMP Pharmacogenetics Working Group concludes that evidence for a clinical effect of IM and PM is lacking, so no adjustment of therapy is required for these gene-drug interactions (yes/no-interactions).
You can find a detailed overview of the observed clinical effects (and the expected lack of kinetic effects) in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting atazanavir to be potentially beneficial for avoiding therapy discontinuation due to adverse events. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 6 out of the maximum of 10 points. Pre-emptive genotyping is considered to be essential for scores ranging from 6 to 10 points (see below and the clinical implication score tables at the end of this risk analysis). However, the KNMP Pharmacogenetics Working Group decided to downgrade this score to potentially beneficial, because the actual clinical impact of discontinuation of therapy will be small in the Netherlands (so severity code ≤ C, corresponding to CTCAE grade ≤ 2). Discontinuation of therapy is not due to diminished efficacy, but to benign adverse events. In addition, although it concerns discontinuation of a life-saving therapy, in resource-rich settings the patient will generally be switched to another combined antiretroviral therapy and not left without therapy, strongly diminishing the clinical impact of discontinuation of atazanavir therapy. Even though atazanavir is not a first-choice drug, alternatives will generally still be available.
The rationale for the (sub)scores of the clinical implication score is indicated below:
*28 homozygotes been shown to have an increased risk for discontinuation of the life-saving atazanavir combination therapy (severity code E, corresponding to CTCAE grade 4). This results in 1 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for CTCAE grade 3-4).
4 studies have severity code E (corresponding to CTCAE grade 4) due to an observed increased risk for therapy discontinuation in *28 homozygotes and/or carriers (Leger 2018, Vardhanabhuti 2015, Ribaudo 2013, and Lubomirov 2011). This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).
The number needed to genotype was deduced from the largest study with a mainly White population having a severity code corresponding to CTCAE grade ≥ 3 (Lubomirov 2011). This study found atazanavir discontinuation in 62.5% of *28/*28 and 18.9% of *1/*1+ *1/*28+*1/*37. This indicates that an additional 43.6% of *28/*28 discontinued therapy. Because the prevalence of *28/*28 is 9% in the Netherlands, this would amount to an additional 3.9% of patients on atazanavir discontinuing therapy due to the *28/*28 genotype. This corresponds with a number to genotype of 25 to avoid one discontinuation of antiretroviral therapy by choosing treatment without atazanavir in *28/*28. The calculated number to genotype of 25 results in 2 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (2 points for 10 ≤ NNG ≤ 100).
The Summary of Product Characteristics of atazanavir (SmPC Reyataz (atazanavir) 17-10-2022) does not mention

any UGT1A1 variant genotype or allele. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).
In addition to the KNMP Pharmacogenetics Working Group recommending considering genotyping only on an individual patient basis, a cost-effectiveness analysis suggested that genotyping UGT1A1 before starting atazanavir was not cost-effective (additional costs per quality-adjusted life-year gained > $100,000) (Schackman 2013).

The table below follows KNMP nomenclature for UGT1A1 polymorphisms. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Du P et al. Association between the UGT1A1*28 allele and hyperbilirubinemia in HIV-positive patients receiving atazanavir: a meta-analysis. Biosci Rep 2019;39:BSR20182105.
PMID: 30962262.</td>
<td>4

*1/*28: B
*28/*28: B</td>
<td>Meta-analysis of 5 studies investigating the effect of *28 on atazanavir-induced hyperbilirubinemia (grade 3 and/or 4, i.e. severe and/or serious)).
4 of the included studies scored 7 of the maximum of 9 points on the Newcastle-Ottawa scale for study quality, and the 5th study 6 points.
4 studies were included in the meta-analyses comparing *1/*28 with *1/*1 (total of 392 patients (233x *1/*1 and 159x *1/*28)), comparing *28/*28 with *1/*1 (total of 304 patients (233x *1/*1 and 71x *28/*28)), and comparing *28/*28 with *1/*28 (total of 230 patients (159x *1/*28 and 71x *28/*28)).
All 5 studies were included in the meta-analysis comparing *28/*28 with *1/*1+*1/*28 (total of 584 patients (495x *1/*1+*1/*28 and 89x *28/*28)).
Of the 5 studies included in the meta-analysis, 4 were also included separately in this risk analysis (Ribaudo 2013, Ferraris 2012, Lubomirov 2011, and Park 2010).
A random-effects model was used for the meta-analyses in case of considerable heterogeneity. Otherwise, a fixed-effects model was used. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias was analysed by the fail-safe number, with significance set at 0.05 for each meta-analysis. As a rule of thumb, if the fail-safe number was higher, the authors of the meta-analysis could be more comfortable assuming that the sample of studies was not likely to be overwhelmed by a future influx of studies with no significant relationship.

Results:
<table>
<tr><td colspan="2">Hyperbilirubinemia risk compared to *1/*1 (incidence for *1/*1 = 13.3% of patients):</td></tr>
<tr><td>*1/*28</td><td>OR = 3.50 (95% CI: 1.35-9.08) (S)</td></tr>
<tr><td>*28/*28</td><td>OR = 10.07 (95% CI: 4.39-23.10) (S)</td></tr>
<tr><td colspan="2">OR was 5.91 (95% CI: 3.30-10.58) (S) for *28/*28 compared to *1/*1+*1/*28.
OR was 3.69 (95% CI: 1.82-7.49) (S) for *28/*28 compared to *1/*28.</td></tr>
<tr><td colspan="2">For all four comparisons, pooled ORs were not significantly affected by removal of each study, one at a time, from the meta-analysis, indicating robust results.</td></tr>
<tr><td colspan="2">Heterogeneity between the studies was high for the following comparison:
- *1/*28 compared to *1/*1

Heterogeneity between the studies was not statistically significant for the following comparison:
- *28/*28 compared to *1/*28

Heterogeneity between the studies was absent for the following comparisons:
- *28/*28 compared to *1/*1</td></tr>
</table>
</td>
<td>Authors' conclusion: 'This meta-analysis suggests that the UGT1A1*28 allele represents a biomarker for an increased risk of hyperbilirubinemia in HIV-positive patients receiving atazanavir.'</td>
</tr>
</table>

<table>
<tr><td>ref. 1, continuation</td><td></td><td>
<table>
<tr><td>- *28/*28 compared to *1/*1+*1/*28</td></tr>
<tr><td>No obvious publication bias was present in any of the four comparisons, with fail-safe numbers being 2.50 for *28/*28 compared to *1/*28, 11.97 for *1/*28 compared to *1/*1, 23.94 for *28/*28 compared to *1/*1, and 31.09 for *28/*28 compared to *1/*1+*1/*28.</td></tr>
<tr><td>Note:
The incidence of hyperbilirubinemia for *28/*28 was 45.1% in the four studies included in all four meta-analyses and 42.7% in all five studies.
The incidence of hyperbilirubinemia for *1/*1+*!/*28 was 19.4% in the four studies included in all four meta-analyses and 16.8% in all five studies.
The incidence of hyperbilirubinemia for *1/*28 was 28.3% in the four studies included in all four meta-analyses.</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 2
Leger P et al. Race/ethnicity difference in the pharmacogenetics of bilirubin-related atazanavir discontinuation. Pharmacogenet Genomics 2018;28:1-6. PMID: 29117017.</td><td>3

rs887829 TT (*28/*28+ *28/*37+ *37/*37): E

rs887829 CT (*1/*28+ *1/*37): AA</td><td>
321 patients were treated with atazanavir for at least 12 months. 48% of patients (n = 153) were Black, 47% (n = 152) White, 4% (n = 14) Hispanic and 1% (n = 2) Asian.
4.6% of patients (n = 15) discontinued atazanavir within 12 months due to jaundice. For Black, White, Hispanic and Asian patients these numbers were 3.3% (n = 5), 5.3% (n = 8), 14% (n = 2), and 0% (n = 0), respectively.
To account for possible population stratification, whole genome data (over 500,000 polymorphisms) were used to generate multidimensional scaling coordinates. For all patients, results were adjusted for the first two multidimensional scaling coordinates.
At baseline, 6 patients had bilirubin concentrations above the normal range, including 5 with bilirubin between 1.1 and 1.3 mg/dl, and 1 with a bilirubin of 2.3 mg/dl. However, for rs887829TT, results were determined without and with additional adjustment for baseline bilirubin concentration (upper and lower value in the table below, respectively).
Comedication was not mentioned, so comedication affecting either UGT1A1 or atazanavir exposure was probably not excluded. In addition, of the original group of 349 patients, 7 discontinued atazanavir for no clear reason.

Genotyping:
rs887829C>T
<table>
<tr><td>all patients</td><td>Black patients</td><td>White patients</td><td>Hispanic patients</td><td>Asian patients</td></tr>
<tr><td>- 120x CC
- 142x CT
- 59x TT</td><td>- 35x CC
- 75x CT
- 43x TT</td><td>- 80x CC
- 59x CT
- 13x TT</td><td>- 4x CC
- 7x CT
- 3x TT</td><td>- 1x CC
- 1x CT</td></tr>
</table>
Results:
<table>
<tr><td colspan="3">Atazanavir discontinuation due to jaundice compared to rs887829CC:</td></tr>
<tr><td>ethnicity</td><td>rs887829TT</td><td>rs887829CT</td></tr>
<tr><td rowspan="2">all</td><td>HR_{adj} = 7.4 (95% CI: 1.7-31.5) (S)</td><td>NS</td></tr>
<tr><td>$HR_{adj\ (also\ for\ baseline\ bilirubin)}$ = 5.2 (95% CI: 1.1-24.5) (S)</td><td></td></tr>
<tr><td rowspan="2">Black</td><td>NS</td><td>NS</td></tr>
<tr><td>Also NS after adjustment for baseline bilirubin.</td><td></td></tr>
<tr><td rowspan="2">White</td><td>HR = 14.4 (95% CI: 2.6-78.7) (S)</td><td>NS</td></tr>
<tr><td>HR_{adj} = 9.4 (95% CI:</td><td></td></tr>
</table>
</td><td>Authors' conclusion: 'Among patients who initiated atazanavir/ritonavir-containing regimens, UGT1A1 slow metabolizer genotype rs887829 T/T was associated with increased bilirubin-related discontinuation of atazanavir in White but not in Black patients, this despite T/T genotype being more frequent in Black patients.'</td></tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td></td>
<td>
<table>
<tr><td></td><td>1.3-66.9) (S)</td><td></td></tr>
<tr><td>Hispanic</td><td>NS (significance not determined)</td><td>NS (significance not determined)</td></tr>
<tr><td colspan="3">Note: Adjusted for rs887829C>T genotype, and in the case of all ethnicities, for the first two multidimensional scaling coordinates, baseline bilirubin concentration did not increase the risk of atazanavir discontinuation due to jaundice for all ethnicities and White patients, but did so with an extremely wide confidence interval for Black patients (HR_{adj} = 140.6 (95% CI: 3.6-5481) (S)).</td></tr>
</table>

Note: The rs887829C>T polymorphism is in almost complete linkage disequilibrium with *28 (Johnson 2014). In addition, *37, which was present in 19 individuals in Johnson 2014, was perfectly tagged by the rs887829T allele (Haas DW, personal communication, 10 June 2017).
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Falvella FS et al. Pharmacogenetics-based optimisation of atazanavir treatment: potential role of new genetic predictors. Drug Metab Pers Ther 2017;32:115-7. PMID: 28599374.</td>
<td>3

*28/*28: B
*1/*28: B</td>
<td>Blood trough samples of 128 patients on maintenance therapy with atazanavir/ritonavir 300/100 mg/day were analysed. Multivariate analyses were performed, using a general linear model, adjusting for age, sex, BMI, hepatitis C-virus co-infection and alcohol intake. This model was performed including UGT1A1 and peroxisome proliferator-activated receptor alpha (PPARA) genotypes with or without (bilirubin only) CYP3A4/5 genotypes as variables.
Comedication was not mentioned, so comedication affecting either UGT1A1 or atazanavir exposure was probably not excluded.

Genotyping:
- 48x *1/*1
- 52x *1/*28
- 28x *28/*28

Results:
<table>
<tr><td colspan="6">Results compared to *1/*1:</td></tr>
<tr><td></td><td>multivariate model</td><td>*28/*28</td><td>*1/*28</td><td>value for *1/*1</td></tr>
<tr><td rowspan="3">total bilirubin</td><td rowspan="2">with CYP-3A4/5</td><td>x 1.32</td><td>x 1.09</td><td rowspan="2">2.2 mg/dl</td></tr>
<tr><td colspan="2">S for *28/*28 versus *1/*28 versus *1/*1</td></tr>
<tr><td rowspan="2">without CYP-3A4/5</td><td>x 1.97</td><td>x 1.22</td><td rowspan="2">1.6 mg/dl</td></tr>
<tr><td colspan="2">S for *28/*28 versus *1/*28 versus *1/*1</td></tr>
<tr><td rowspan="2">median atazanavir trough plasma concentration</td><td rowspan="2">with CYP-3A4/5</td><td>x 0.78</td><td>x 0.76</td><td rowspan="2">833 ng/ml</td></tr>
<tr><td colspan="2">NS for *28/*28 versus *1/*28 versus *1/*1</td></tr>
</table>
</td>
<td>Authors' conclusion: 'Our data confirm the association between UGT1A1 *28 allele and the risk of hyperbilirubinemia, suggesting that the PPARA rs4253728 variant allele may be an additional genetic predictor of higher serum bilirubin.'</td>
</tr>
<tr>
<td>ref. 4
Lin KY et al. Cholelithiasis and nephrolithiasis in HIV-posi-</td>
<td>3</td>
<td>177 patients, treated with atazanavir (unboosted in the majority of patients) for more than 3 months, underwent routine abdominal sonography for chronic viral hepatitis, fatty liver, or elevated aminotransferases. A gall or renal stone was detec-</td>
<td>Authors' conclusion: 'With the limitation of insufficient sample size, we failed to demonstrate statis-</td>
</tr>
</table>

<table>
<tr>
<td>tive patients in the era of combination antiretroviral therapy.
PLoS One 2015;10: e0137660.
PMID: 26360703.

ref. 4, continuation</td>
<td>*1/*28: AA</td>
<td>ted in 16 patients (9.0%). None of the 177 patients had a gall or renal stone before start of atazanavir.
Non-antiretroviral comedication was not known so comedication affecting either UGT1A1, atazanavir exposure or cholelithiasis and/or nephrolithiasis was probably not excluded.

Genotyping:
- 143x *1/*1
- 34x *1/*28

Results:
<table><tr><td colspan="2">Incidence of gall or renal stones on atazanavir therapy compared to *1/*1 (value for *1/*1 = 9.8% of patients):</td></tr><tr><td>*1/*28</td><td>NS</td></tr></table>
Note: In all patients on atazanavir (genotyped and not-genotyped) (n = 363 of whom 50 on atazanavir/ritonavir), this study showed exposure to atazanavir/ritonavir for over 2 years to be associated with a 6.29-fold increase in the risk for incident cholelithiasis. In addition, incident cholelithiasis risk increased with serum total bilirubin concentration.</td>
<td>tically significant associations between plasma atazanavir concentrations, genetic polymorphisms altering atazanavir metabolism and incident cholelithiasis and nephrolithiasis.’</td>
</tr>
<tr>
<td>ref. 5
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 2015;2:ofv085.
PMID: 26180834.</td>
<td>3

rs887829 TT (*28/*28+ *28/*37+ *37/*37): E</td>
<td>481 patients were treated with atazanavir/ritonavir/tenofovir disoproxil fumarate/emtricitabine 300/100/300/200 mg/day for 96 weeks. 44% of patients (n = 211) were Black, 38% (n = 183) White, and 18% (n = 87) Hispanic.
30% of patients (n = 146) discontinued atazanavir within 96 weeks. For Black, White, and Hispanic patients these numbers were 29% (n = 62), 30% (n = 54), and 34% (n = 30), respectively.
Most premature discontinuations were not bilirubin related. 8% of patients (n = 37) prematurely discontinued atazanavir due to bilirubin increase or jaundice. For Black, White, and Hispanic patients these numbers were 6% (n = 13), 10% (n = 18), and 7% (n = 6), respectively.
Ethnicities were self-identified.
Hazard ratios were adjusted for baseline bilirubin and baseline hemoglobin.
Comedication was not mentioned, so comedication affecting either UGT1A1 or atazanavir exposure was probably not excluded.

Genotyping:
rs887829C>T
all patients - 184x CC - 228x CT - 69x TT
Black patients - 70x CC - 101x CT - 40x TT
White patients - 83x CC - 85x CT - 15x TT
Hispanic patients - 31x CC - 42x CT - 14x TT

Results:
<table><tr><td colspan="3">Atazanavir discontinuation due to bilirubin-related causes compared to rs887829CC:</td></tr><tr><td>ethnicity</td><td>rs887829TT</td><td>rs887829CT</td></tr><tr><td rowspan="3">Black</td><td>HR_{adj} = 10 (95% CI: 1.2-85) (S)</td><td>NS</td></tr><tr><td colspan="2">Time to bilirubin-related discontinuation decreased with increasing number of rs887829T alleles (S).</td></tr><tr><td colspan="2">20% of rs887829TT and 3% of rs887829CC+ rs887829CT discontinued due to bilirubin-related</td></tr></table></td>
<td>Authors’ conclusion: ‘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.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>rs887829 CT (*1/*28+ *1/*37): E</td>
<td>
<table>
<tr><td></td><td colspan="2">causes, indicating a positive and negative predictive value of rs887829TT of 20% and 97%, respectively.
19% of Black patients was rs887829TT.</td></tr>
<tr><td rowspan="3">White</td><td>HR_{adj} = 24 (95% CI: 4.7-119) (S))</td><td>NS</td></tr>
<tr><td colspan="2">Time to bilirubin-related discontinuation decreased with increasing number of rs887829T alleles (S).</td></tr>
<tr><td colspan="2">60% of rs887829TT and 5% of rs887829CC+ rs887829CT discontinued due to bilirubin-related causes, indicating a positive and negative predictive value of rs887829TT of 60% and 95%, respectively.
8% of White patients was rs887829TT.</td></tr>
<tr><td rowspan="3">Hispanic</td><td>HR_{adj} = 12 (95% CI: 1.3-113) (S)</td><td>NS</td></tr>
<tr><td colspan="2">Time to bilirubin-related discontinuation decreased with increasing number of rs887829T alleles (S).</td></tr>
<tr><td colspan="2">29% of rs887829TT and 3% of rs887829CC+ rs887829CT discontinued due to bilirubin-related causes, indicating a positive and negative predictive value of rs887829TT of 29% and 97%, respectively.
16% of Hispanic patients was rs887829TT.</td></tr>
<tr><td>all</td><td colspan="2">Time to bilirubin-related discontinuation decreased with increasing number of rs887829T alleles (S).</td></tr>
<tr><td colspan="3">Results were unchanged after removal of outliers if analyses were repeated with patient ethnicities based on multidimensional scaling coordinates generated with whole genome data (over 500,000 polymorphisms) instead of on self-identification.</td></tr>
</table>

Note 1: The rs887829C>T polymorphism is in almost complete linkage disequilibrium with *28 (Johnson 2014).

Note 2: Compared to the trial arms with either darunavir/ritonavir or raltegravir, discontinuation due to all causes was approximately 10% higher for atazanavir/ritonavir for all patients. For rs887829TT, this difference was more than 30%.
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Johnson DH et al.
Genome-wide association study of atazanavir pharmacokinetics and hyperbilirubinemia in AIDS Clinical Trials Group protocol A5202.
Pharmacogenet Genomics 2014;24:195-203.
PMID: 24557078.</td>
<td>4</td>
<td>A genome-wide association study was performed on 475 patients from Ribaudo 2013 (treated with atazanavir/ritonavir 300/100 mg/day for 24 weeks). Peak unconjugated bilirubin concentration was available for 443 patients. 45% of patients (n = 212) were White, 31% (n = 145) Black, and 25% (n = 118) Hispanic.
Atazanavir clearance was determined from a population pharmacokinetic model based on measured atazanavir plasma concentrations at different time intervals after dosing.
Genetic associations were assessed by univariate analysis, as well as by a linear regression model that adjusted for covariates that showed significance in univariate analysis. For peak unconjugated bilirubin, adjustment was for age, baseline bilirubin concentration, baseline haemoglobin concentration, and atazanavir clearance. There was no adjustment for sex; because significance for sex in univariate analysis disappeared after correcting for haemoglobin. For atazanavir clearance, adjustment was for body mass index, abacavir/lamivudine versus tenofovir disoproxil fumarate/emtricitabine assignment at randomisation, sex, and occurrence of an atazanavir</td>
<td>Authors' conclusion: 'Atazanavir-associated hyperbilirubinemia is best predicted by considering UGT1A1 genotype, baseline bilirubin, and baseline hemoglobin values in combination.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 6, continuation</td>
<td>rs887829 TT (*28/*28+ *28/*37+ *37/*37): B

rs887829 CT (*1/*28+ *1/*37): B</td>
<td>concentration below limit of quantification.
To correct for population stratification, principal components were determined separately for each population. Adjustment was for the first four principal components generated with the whole group for associations investigated in the whole group. Adjustment was for the first two principal components for associations investigated in the separate ethnicities.
P values were adjusted for genomic inflation factor based on median chi-squared value.

Results:
<table>
<tr><td colspan="2">Results of the genome-wide association study:</td></tr>
<tr><td>peak unconjugated bilirubin concentration</td><td>In multivariate analysis of the whole group, 10 polymorphisms in or near UGT1A1 were genome-wide significant, the smallest P value being for rs887829. Greater peak bilirubin was associated with rs887829 T allele (β=0.30 mg/dl per T allele) (S). After adjusting for rs887829, no additional polymorphisms were genome-wide significant.
Of 27 candidate gene polymorphisms selected a priori, only those in or near UGT1A1 were significant after Bonferroni correction.
Because the UGT1A1 tandem TA repeat (rs8175347 which defines UGT1A1 *28, *36 and *37 alleles) was in almost complete linkage disequilibrium with rs887829 (R^2=0.99), investigating rs8175347 directly was not informative beyond rs887829.</td></tr>
<tr><td>atazanavir clearance</td><td>No polymorphism was associated at genome-wide significance, whether in the whole group or in each ethnicity separately.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 7
Ribaudo HJ et al. Impact of UGT-1A1 Gilbert variant on discontinuation of ritonavir-boosted atazanavir in AIDS Clinical Trials Group Study A5202. J Infect Dis 2013;207:420-5. PMID: 23148286.</td>
<td>4</td>
<td>646 patients were treated with atazanavir/ritonavir 300/100 mg/day for at least 96 weeks. 45% of patients (n = 291) were White, 31% (n = 202) Black, and 24% (n = 153) Hispanic. Ethnicity was self-identified.
27% of all patients prematurely discontinued atazanavir/ritonavir (24% of Whites, 32% of Blacks and 27% of Hispanics). In Whites, 4% of discontinuations (n = 3) were caused by bilirubin-associated issues. In Blacks and Hispanics this was 11% (n = 7) and 21% (n = 9), respectively. The difference between the ethnicities was significant. Discontinuation was in most cases (79%) not due to bilirubin-associated issues. For 11% of discontinuations the reason for discontinuation was not clear.
Maximum total bilirubin levels and incidence of jaundice were determined in the first 24 weeks of treatment. Grade 4 elevations in bilirubin level were defined as total bilirubin ≥ 5x the upper limit of normal (ULN).
Cox proportional hazard models were stratified by race and adjusted for randomised nucleoside reverse-transcriptase inhibitor (abacavir/lamivudine versus tenofovir/emtricitabine), sex, age, BMI (<18, 18–25, >25–30, and >30), and plasma HIV-1 RNA concentration at study entry.
Comedication affecting atazanavir was excluded.

Genotyping:
all White Black Hispanic</td>
<td>Authors' conclusion: 'There was an association between *28/*28 and increased atazanavir/ritonavir discontinuation among Hispanic participants but not among white or black participants. The positive predictive value of 28*/28* for atazanavir/ritonavir discontinuation among Hispanic participants was only 32%.'</td>
</tr>
</table>

ref. 7, continuation

28/*28: E

*1/*28: E

patients	patients	patients	patients
- 261x *1/*1	- 136x *1/*1	- 64x *1/*1	- 61x *1/*1
- 285x *1/*28	- 131x *1/*28	- 90x *1/*28	- 64x *1/*28
- 100x*28/*28	- 24x *28/*28	- 48x *28/*28	- 28x *28/*28

Results:

Results compared to *1/*1:

	ethnicity	*28/*28	*1/*28	value for *1/*1
time to discontinuation of atazanavir	all	decrease with increasing number of *28 alleles (S)		
		Over >3 years of follow-up, the estimated cumulative incidence of atazanavir discontinuation attributed to bilirubin-associated issues was <3% for *1/*1+ *1/*28 and 8% for *28/*28.		
	White	NS for *28/*28 versus *1/*28 versus *1/*1		
	Black	NS for *28/*28 versus *1/*28 versus *1/*1		
	Hispanic	decrease with increasing number of *28 alleles (S)		
		Significance was confirmed in the Cox proportional hazard model (S).		
		The positive predictive value of *28/*28 for atazanavir/ritonavir discontinuation was low (32%; 95% CI: 16%-52%).		
	Results were unchanged if ethnicity was based on EIGENSTRAT values generated from whole genome data instead of self-identification.			
% of patients with bilirubin ≥ 5x ULN	all	x 6.7	x 1.7	3%
		S for *28/*28 versus *1/*28 versus *1/*1		
	White	x 12.5	x 3.0	2%
		S for *28/*28 versus *1/*28 versus *1/*1		
	Black	x 4.3	x 1.3	3%
		S for *28/*28 versus *1/*28 versus *1/*1		
	Hispanic	x 5.8	x 1.0	5%
		S for *28/*28 versus *1/*28 versus *1/*1		
% of patients with incident jaundice	all	x 6.3	x 1.7	3%
		S for *28/*28 versus *1/*28 versus *1/*1		
	White	x 12.5	x 2.5	2%
		S for *28/*28 versus *1/*28 versus *1/*1		
	Black	NS for *28/*28 versus *1/*28 versus *1/*1		5%
	Hispanic	x 9.7	x 2.0	3%
		S for *28/*28 versus *1/*28 versus *1/*1		

Note: The frequency of *36 and *37 was low. *36 was included

<table>
<tr><td></td><td></td><td>in the *1 group and *37 in the *28 group.</td><td></td></tr>
<tr><td>ref. 8
Ferraris L et al. Switching to unboosted atazanavir reduces bilirubin and triglycerides without compromising treatment efficacy in UGT1A1*28 polymorphism carriers. J Antimicrob Chemother 2012;67:2236-42.
PMID: 22661571.</td><td>4

Unboosted versus ritonavir-boosted atazanavir in *28-carriers: AA#</td><td>51 patients, treated with atazanavir/ritonavir 300/100 mg/day, had viral suppression (defined as HIV RNA level <37 copies/ml) for ≥6 months, no virological failure under atazanavir therapy, CD4 cell counts stable at 200 cells/mm^3, and no evidence of liver decompensation and grade 3 or 4 alanine aminotransferase (ALT) elevations. 22% of patients received lipid-lowering therapy compatible with ritonavir exposure.
26 *28-carriers were switched to unboosted atazanavir 400 mg/day for 12 months. One *1/*28 was not switched, so only provided data on atazanavir/ritonavir. No clinical data were available for two *1/*28 switched to unboosted atazanavir. One of them had undetectable atazanavir level on unboosted atazanavir, suggesting a complete lack of adherence, subsequently confirmed by the patient. The other was lost to follow-up due to moving. The 24 *1/*1 patients were maintained on atazanavir/ritonavir 300/100 mg/day.
Severe bilirubinemia was defined as total bilirubin level > 3.1 mg/dl (bilirubinemia grade 3 and 4). Jaundice becomes evident with total bilirubin levels > 2.5 mg/dl.
Comedication affecting atazanavir exposure was excluded.

Genotyping:
- 24x *1/*1
- 21x *1/*28
- 6x *28/*28

Results:
<table>
<tr><td colspan="3">Results for *1/*28+*28/*28 on unboosted atazanavir compared to on atazanavir/ritonavir:</td></tr>
<tr><td></td><td></td><td>value for atazanavir/ritonavir</td></tr>
<tr><td>atazanavir plasma concentration</td><td>trend for a lower plasma concentration (p = 0.08) (NS)
The atazanavir trough concentration on unboosted atazanavir was found to be below the minimum effective concentration of 150 ng/ml only in the patient, who had undetectable atazanavir levels due to a complete lack of adherence.</td><td>1231 ng/ml</td></tr>
<tr><td>total bilirubin</td><td>x 0.44 (S)</td><td>4.09 mg/dl</td></tr>
<tr><td>% of patients with hyperbilirubinemia grade ≥ 3</td><td>lower (S)</td><td></td></tr>
<tr><td>total cholesterol</td><td>trend for a decrease (p = 0.05) (NS)</td><td>187 mg/dl</td></tr>
<tr><td>triglycerides</td><td>x 0.78 (S)</td><td>165 mg/dl</td></tr>
<tr><td>γ-glutamyl transpeptidase</td><td>x 0.97 (S)</td><td>32 U/L</td></tr>
<tr><td>% of patients with undetectable HIV-RNA</td><td>NS, was also 100% after 48 weeks of unboosted atazanavir</td><td>100 %</td></tr>
<tr><td>CD4 T cell</td><td>NS, was not changed after 48</td><td></td></tr>
</table></td><td>Authors' conclusion: 'UGT1A1*28 is significantly related to hyperbilirubinaemia in HIV-1 patients receiving atazanavir. Genotyping before the initiation of antiretroviral therapy can reduce the emergence of severe hyperbilirubinaemia. Unboosted atazanavir-containing therapy is safe and efficacious in patients with an undetectable viral load with a UGT1A1 *28 polymorphism, allowing the use of atazanavir in patients otherwise likely unable to receive it.'</td></tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td>*28/*28: B
*1/*28: B</td>
<td>
<table>
<tr><td>count</td><td>weeks of unboosted atazanavir</td><td></td></tr>
<tr><td colspan="3">Note: No change in bilirubin, total cholesterol, triglycerides, and γ-glutamyl transpeptidase was observed in the *1/*1 patients, who remained on atazanavir/ritonavir (all NS).</td></tr>
</table>
<table>
<tr><td colspan="4">Results on atazanavir/ritonavir compared to *1/*1:</td></tr>
<tr><td></td><td>*28/*28</td><td>*1/*28</td><td>value for *1/*1</td></tr>
<tr><td rowspan="2">% of patients with hyperbilirubinemia grade ≥ 3</td><td>x 6.4 (S)</td><td>x 5.5 (S)</td><td rowspan="2">13%</td></tr>
<tr><td colspan="2">S for *28/*28 versus *1/*28 versus *1/*1</td></tr>
<tr><td rowspan="2">total bilirubin</td><td>x 3.1</td><td>x 2.4</td><td rowspan="2">1.43 mg/dl</td></tr>
<tr><td colspan="2">S for *28/*28 versus *1/*28 versus *1/*1</td></tr>
<tr><td>total cholesterol</td><td colspan="2">NS for *28/*28 versus *1/*28 versus *1/*1</td><td>184 mg/dl</td></tr>
<tr><td>triglycerides</td><td colspan="2">NS for *28/*28 versus *1/*28 versus *1/*1</td><td>148 mg/dl</td></tr>
<tr><td>γ-glutamyl transpeptidase</td><td colspan="2">NS for *28/*28 versus *1/*28 versus *1/*1</td><td>48 U/L</td></tr>
<tr><td>atazanavir plasma concentration</td><td colspan="2">NS for *28/*28 versus *1/*28 versus *1/*1</td><td></td></tr>
<tr><td colspan="4">Note: No relationship between atazanavir plasma concentrations and bilirubin levels among the three genetic groups was found.</td></tr>
</table>
Note: The administration of unboosted atazanavir at a dose of 400 mg once daily was validated in a simplification trial in ritonavir-intolerant patients (Ghosn J et al. Unboosted atazanavir-based therapy maintains control of HIV type-1 replication as effectively as a ritonavir-boosted regimen. Antivir Ther 2010; 15:993-1002). The atazanavir dose of 400 mg once daily is licensed for the treatment of naive patients who cannot tolerate ritonavir in the USA, but not in Europe.
</td>
<td></td>
</tr>
<tr>
<td>ref. 9
Lubomirov R et al.
Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study.
J Infect Dis 2011;203:246-57.
PMID: 21288825.</td>
<td>3</td>
<td>
121 patients were treated with atazanavir/ritonavir for 1 year. 25% of patients (n = 30) discontinued atazanavir/ritonavir (varying from 0% to 47% for the different participating centres). None of the patients had virological treatment failure. Hazard ratios and P values were adjusted for parameters with a significant association in univariate analysis (evaluated parameters: body weight, sex, ethnicity, CD4 T cell count and viral RNA concentration, transmission category, year of starting antiretroviral therapy, treatment regimen, clinical centre, and pregnancy status).
Non-antiretroviral comedication was not known so comedication affecting UGT1A1 or atazanavir exposure was probably not excluded.

Genotyping:
- 55x *1/*1
- 48x *1/*28+*1/*37
- 18x *28/*28+*28/*37

Results:
<table>
<tr><td colspan="4">Percentage of patients discontinuing atazanavir compared to *1/*1 (all reasons) or to *1/*1+*1/*28+*1/*37 (specified reasons):</td></tr>
<tr><td>reason for discontinuation</td><td>*28/*28+*28/*37</td><td>*1/*28+*1/*37</td><td>value for *1/*1 or</td></tr>
</table>
</td>
<td>Authors' conclusion: 'Several pharmacogenetic markers identify individuals at risk for early treatment discontinuation. These markers should be considered for validation in the clinical setting.'</td>
</tr>
</table>

<table>
<tr><td>ref. 9, continuation</td><td>*28/*28+*28/*37: E

*1/*28+*1/*37: AA</td><td></td><td></td><td></td><td>*1/*1+ *1/*28 + *1/*37</td><td></td></tr>
<tr><td></td><td></td><td>all</td><td>x 4.3 (S)</td><td>NS</td><td>14.6%</td><td></td></tr>
<tr><td></td><td></td><td></td><td>HR_{adj} = 9.13 (95% CI: 3.38-24.69) (S)</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>For the 4 centres prescribing atazanavir to more than 10 patients, there was a statistically significant correlation between discontinuation rate and frequency of *28/*28+*28/*37 (r^2 = 0.858) (S).</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>The 2 patients discontinuing atazanavir within the first week were both *28/*28 or *28/*37.</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td colspan="2">The percentage of patients was 62.5% for *28/*28 and 18.9% for *1/*1+ *1/*28+*1/*37.</td><td></td><td></td></tr>
<tr><td></td><td></td><td>virological treatment failure</td><td>NS</td><td></td><td>0%</td><td></td></tr>
<tr><td></td><td></td><td>drug associated toxicity</td><td>x 4.9 (S)</td><td></td><td>6.80%</td><td></td></tr>
<tr><td></td><td></td><td>patient decision</td><td>NS</td><td></td><td>5.83%</td><td></td></tr>
<tr><td></td><td></td><td>physician decision</td><td>NS</td><td></td><td>4.85%</td><td></td></tr>
<tr><td></td><td></td><td>other</td><td>NS</td><td></td><td>0.97%</td><td></td></tr>
<tr><td>ref. 10
Park WB et al. Genetic factors influencing severe atazanavir-associated hyperbilirubinemia in a population with low UDP-glucuronosyltransferase 1A1*28 allele frequency. Clin Infect Dis 2010;51:101-6. PMID: 20504240.</td><td>3</td><td colspan="5">129 patients were treated with unboosted atazanavir 400 mg/day for 3 months. Only patients showing viral suppression after treatment were included. In one of the patients, *6 was not determined.
Atazanavir-associated hyperbilirubinemia was defined as hyperbilirubinemia (total bilirubin level > 1.3 mg/dl) that developed after initiation of atazanavir therapy in the absence of other causes of hyperbilirubinemia. 78% of patients developed hyperbilirubinemia. Severe hyperbilirubinemia was defined as grade 3 and 4 hyperbilirubinemia (total bilirubin level > 3.1 mg/dl).
Logistic regression analysis adjusted for age, baseline CD4 cell count, and presence of MDR1 2677G>T/A. Other parameters investigated, but not showing a significant effect or trend ($p < 0.01$) in univariate analysis and so, not included in the logistic regression analysis, were sex, hepatitis B or C virus infection, *6 and MDR1 3435C>T.
The only comedication mentioned was atorvastatin or rosuvastatin in 3 patients. No patient used a H_2 antagonist, proton pump inhibitor or tenofovir. The authors indicate that medication affecting bilirubin levels was not excluded.
Apart from patients showing no viral suppression, 12 patients</td><td>Authors' conclusion: 'The MDR1 G2677 T/A variation and UGT1A1*28 are independent risk factors for severe atazanavir-associated hyperbilirubinemia in Korean human immunodeficiency virus-infected patients.'</td></tr>
</table>

<table>
<tr>
<td>ref. 10, continuation</td>
<td>IM+PM:
AA

*1/*28+*28/*28: B</td>
<td>discontinuing atazanavir within 3 months (6 because of jaundice) were also excluded.

Genotyping:
*6
- 87x *1/*1
- 34x *1/*6
- 7x *6/*6

*28
- 103x *1/*1
- 25x *1/*28
- 1x *28/*28

Results:
<table>
<tr><td colspan="4">Percentage of patients developing hyperbilirubinemia grade 3 or 4 (total bilirubin level > 3.1 mg/dl) compared to *1/*1:</td></tr>
<tr><td>gene variant</td><td>homozygotes for variant</td><td>heterozygotes for the variant</td><td>value for *1/*1</td></tr>
<tr><td>*6</td><td colspan="2">NS for *1/*6+*6/*6 compared to *1/*1</td><td>20.7%</td></tr>
<tr><td rowspan="3">*28</td><td>x 6.45</td><td>x 2.58</td><td rowspan="3">15.5%</td></tr>
<tr><td colspan="2">S for *1/*28+*28/*28 compared to *1/*1 in both univariate and logistic regression analysis:
OR_{adj} = 4.15 (95% CI: 1.46-11.84) (S)</td></tr>
<tr><td colspan="2">The severity of hyperbilirubinemia was associated with *28 (S).</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Risk group	*28/*28 with UGT1A1 inhibitors (e.g. ketoconazole and gemfibrozil)

Comments:

- Only articles investigating a possible alternative or with more than 120 patients were included. Other articles did not add enough to the evidence.
- Existing guideline:
  - Gammal RS et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for UGT1A1 and Atazanavir Prescribing. Clin Pharmacol Ther 2016;99:363-9. PMID: 26417955.
    CPIC distinguishes the following UGT1A1 variant phenotypes: intermediate metaboliser (including both *1/*28 and IM OTHER) and poor metaboliser (including both *28/*28 and PM OTHER).
    CPIC indicates that Lubomirov 2011, Ribaudo 2013, and Vardhanabhuti 2015 have examined associations between UGT1A1 genotype and premature discontinuation of atazanavir/ritonavir. In addition, CPIC indicates that Lubomirov 2011 and Ribaudo 2013 only evaluated all-cause discontinuation, whereas Vardhanabhuti 2015 also evaluated bilirubin-related discontinuation, with the latter approach minimizing the impact of factors unrelated to UGT1A1 genotype (e.g., nonadherence) and therefore better revealing genetic associations. CPIC mentions that among the 121 participants in Lubomirov 2011 who had received atazanavir/ritonavir, carriage of UGT-1A1 decreased function alleles (*28/*28 or *28/*37) was associated with increased risk of all-cause atazanavir/ritonavir discontinuation, with estimated first-year cumulative discontinuation rates of 63%, 24%, and 15% in participants with two decreased function alleles, with one decreased function allele, and without decreased function allele, respectively. CPIC indicates that, in contrast, among the 646 participants in Ribaudo 2013 randomised to receive atazanavir/ritonavir, there was no significant association between decreased function UGT1A1 genotype (primarily UGT1A1*28) and increased likelihood of all-cause atazanavir/ritonavir discontinuation among either White or Black participants, but there was an association among Hispanic participants. CPIC mentions that among the 481 patients who initiated randomised atazanavir/ritonavir with tenofovir disoproxil fumarate/emtricitabine in Vardhanabhuti 2015, bilirubin-related discontinuation of atazanavir was strongly associated with homozygosity for the rs887829 T allele, which is in very high linkage disequilibrium with the promoter TA repeat characterizing *28, *37 and *36 (r^2 = 0.99), the T allele being in linkage with *28 and *37, and the C allele with *1 and *36. In addition, CPIC indicates that, without T allele homozygosity, bilirubin-related discontinuation was infrequent regardless of race/ethnicity: positive predictive values of rs887829 TT for bilirubin-related discontinuation through 96 weeks of atazanavir (with 95% confidence intervals) were 60% (32-84%) in White, 29% (8-58%) in Hispanic, 20% (9-36%) in Black participants; negative predictive values were 95% (90-98%), 97% (90-100%), and 97% (93-99%), respectively. CPIC mentions that the authors speculated that the higher discontinuation rate among White participants with rs887829 TT may have reflected differences in physical manifestations of icterus. Based on Lubomirov 2011 and Ribaudo 2013, CPIC indicates that for individuals carrying two UGT1A1 decreased function alleles (i.e., UGT1A1*28/*28, UGT1A1*28/*37, UGT1A1*37/*37, or rs887829 TT), the likelihood of bilirubin-related atazanavir discontinuation is substantial. Based on Ribaudo 2013 and Eley T et al. Clinical and

pharmacogenetic factors affecting neonatal bilirubinemia following atazanavir treatment of mothers during pregnancy. AIDS Res Hum Retroviruses 2013;29:1287-92, CPIC indicates that for individuals carrying fewer than two UGT1A1 decreased function alleles (i.e., *1/*28, *1/*37, *36/*28, *36/*37, rs887829 CC or rs887829 CT), the likelihood of bilirubin-related atazanavir discontinuation is low.
CPIC mentions that homozygosity for UGT1A1*6 or *27, which occurs almost exclusively in individuals of Asian descent, is associated with Gilbert syndrome, but that there is a lack of evidence regarding whether patients with these diplotypes are at increased risk of severe atazanavir-associated hyperbilirubinemia. CPIC mentions that Park 2010 found no association between UGT1A1*6/*6 and the incidence of severe hyperbilirubinemia with atazanavir, 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. CPIC does not mention that Park 2015 found a significant association for *28, despite the number of patients homozygous for UGT1A1 *28/*28 in this study being only one. CPIC concludes, that at this time, it is unclear whether UGT1A1*6/*6 or *27/*27 genotypes confer increased risk of severe atazanavir-associated hyperbilirubinemia.
CPIC indicates that substantial evidence associates UGT1A1 genotype with phenotypic variability and that most evidence is of high quality based on a standard grading scale.
Recommendation per variant genotype group:

Genotype groups	Implications	Recommendation[a]	Classification of recommendation[b]
*1/*28 + IM OTHER	Somewhat decreased UGT1A1 activity; low likelihood of bilirubin-related discontinuation of atazanavir.	Same recommendation as for *1/*1: There is no need to avoid prescribing of atazanavir based on UGT1A1 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
*28/*28 + PM OTHER	Markedly decreased UGT-1A1 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

[a]: Recommendations are for atazanavir boosted with either ritonavir or cobicistat.
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, and bilirubin-related adverse events including discontinuation of atazanavir occur in a similar percentage of patients prescribed atazanavir with cobicistat or ritonavir (Gallant JE et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. J Infect Dis 2013;208:32-9). Associations between UGT1A1 genotype, bilirubin elevations, and atazanavir/ritonavir discontinuation therefore almost certainly translate to atazanavir/cobicistat.
[b]: Strong = the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

On 21-4-2023, there was not a more recent version of the recommendations present on the CPIC-site.

- Cost-effectiveness
  - Schackman BR et al. Cost-effectiveness analysis of UGT1A1 genetic testing to inform antiretroviral prescribing in HIV disease. Antivir Ther 2013;18:399-408. PMID: 23264445.
  In patients with CD4 < 500 cells/µl, UGT1A1 genotype guided atazanavir treatment (darunavir for *28/*28 and atazanavir for *1/*1 and *1/*28 and patients in whom genotyping failed (0.3%)), was not cost-effective (additional costs were higher than US$ 100,000 per quality-adjusted life-year (QALY) gained) compared to atazanavir for all. UGT1A1 genotype guided treatment was cost-effective (additional costs below US$ 100,000/QALY gained) if genotyping cost decreased to US$10 (as may occur if UGT1A1 testing were to be included in a multiplex testing panel), or if avoiding hyperbilirubinemia by UGT1A1 testing reduced loss to follow-up by 5%. If atazanavir and darunavir differed in cost or efficacy, testing for UGT1A1 was not cost-effective under any scenario.
  Costs were evaluated from a health system perspective. Lifelong medical costs were calculated. For atazanavir for all patients, the calculated cost per patient were US$ 475,500 and the calculated QALYs 16.02. For genotype guided therapy, the additional costs per patient were US$ 100 and the QALYs gained 0.000049. This corresponds to additional cost of US$ 2,058,200 per QALY gained. Patients developing hyperbilirubinemia on atazanavir were assumed to be switched to darunavir. Opportunistic infection prophylaxis and antiretroviral therapy were initiated according to current US guidelines. Patients who experienced virologic rebound were switched to the next available antiretroviral regimen, up to a maximum of five additional regimens. The calculation was

based on a price of antiretroviral therapy with atazanavir or darunavir of US$ 1,841/month, a price of second-line antiretroviral therapy of US$ 1,276/month, a price of third-line antiretroviral therapy of US$ 1,822/month, a price of fourth-line antiretroviral therapy of US$ 2,385/month, a price of fifth-line antiretroviral therapy of US$ 4,306/ month, a price of sixth-line antiretroviral therapy of US$ 1,593/month, cost of evaluating a case of drug-induced hyperbilirubinemia of $114 (cost of a single clinic visit, including associated laboratory tests), and genotyping cost of US$ 107. Atazanavir discontinuation rates were derived from Lubomirov 2011: 33.3% of *28/*28, and 6.8% of *1/*1+*1/*28. A *28/*28 frequency of 14.9% was assumed, as were equal efficacy and costs of atazanavir and darunavir. Atazanavir and darunavir were both assumed to be combined with ritonavir, tenofovir and emtricitabine.

At a hypothetical cost of US$ 10 per genotyping assay, UGT1A1 genotype guided treatment would be cost-effective (additional cost of US$ 88,500/QALY), and the cost-effectiveness of testing became sensitive to the frequency of *28/*28, varying from US$ 220,600/QALY at a frequency of 9% (the lowest reported prevalence among Whites) to cost-saving at a frequency of 33% (the highest reported prevalence among Blacks). When the discontinuation rates associated with the presence and absence of *28/*28 were both reduced by one half, the additional cost increased to US$ 290,700/QALY, and varied from US$ 560,100/QALY at 9% prevalence to US$ 69,100/QALY at 33% prevalence of *28/*28. At US$ 10 per assay, the cost-effectiveness of testing was also sensitive to the duration and magnitude of the impact of hyperbilirubinemia on quality of life and the cost of evaluating a case of atazanavir-induced hyperbilirubinemia. The additional cost exceeded US$ 100,000/QALY when the duration of hyperbilirubinemia was reduced from 14 to 7 days, when the quality-of-life multiplier for patients experiencing hyperbilirubinemia was increased from 0.97 to 0.99, and when the cost of case evaluation was reduced from $114 to $45. In contrast, the cost-effectiveness ratio for testing was US$ 44,300/QALY when the duration of hyperbilirubinemia was increased to 28 days, US$ 33,200/QALY when the quality-of-life multiplier was reduced to 0.92, and US$ 49,300/QALY when the cost of case evaluation was increased to US$ 153. In probabilistic sensitivity analyses, 76% of simulations that simultaneously varied the quality of life and cost parameters across these ranges had a cost-effectiveness ratio below US$ 100,000/QALY.

Assuming that 5% of patients experiencing hyperbilirubinemia were lost to follow-up and returned after their disease had progressed further decreased the cost per QALY gained. For example, assuming patients who are lost to follow up to return either when they experience an opportunistic infection or when their CD4 count decreases to 200/µl, the additional cost were US$ 70,000/QALY at the US$ 107 genotyping cost, and US$ 56,600/QALY at the hypothetical US$ 10 genotyping cost. Results were similar for a hypothetical cohort with an initial CD4 count of 350/µl. Results were sensitive, however, to the CD4 count at which patients return to care. Assuming patients lost to follow up to return either when they experience an opportunistic infection or reach a CD4 count of 350/µl, the additional cost was higher than US$ 100,000/QALY at the current genotyping cost for a hypothetical cohort with initial CD4 count of 500/µl. Results were not substantially affected by varying age, baseline quality of life, or the proportion with failed genotyping.

Date of literature search: 2 January 2023.

	Genotype	Code	Gene- drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	*1/*28	4 E	Yes	No	16 May 2023
	*28/*28	4 E	Yes	Yes	
	IM	3 AA	Yes	No	
	PM	3 AA	Yes	No	

Mechanism:

Atazanavir increases hyperbilirubinemia and jaundice risk by inhibiting UGT1A1, which is involved in glucuronidation of bilirubin. This risk is especially enhanced in patients having a genetically decreased UGT1A1 activity caused by the *28 allele. While the effect of the *28 and *6 alleles on UGT1A1 activity is comparable, the *28 allele is associated with a higher risk of hyperbilirubinemia, probably due to the presence of three additional gene variations associated with hyperbilirubinemia (one in UGT1A3 and two in UGT1A7).

Atazanavir is not metabolised by UGT1A1.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +

Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	+
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	++
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	6+
Corresponding Clinical Implication Score:		Essential
Score after taking additional considerations into account:		Potentially beneficial