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PharmGKB Summary: Atazanavir Pathway, Pharmacokinetics/ Pharmacodynamics

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Introduction

Atazanavir (ATV) is an azapeptide of the protease inhibitor (PI) drug class because it selectively inhibits HIV genotype I (HIV-I) protease, an enzyme critical for HIV-1 virion maturation. ATV is typically administered in combination with a pharmacokinetic enhancer (also known as a “booster”) to improve its pharmacokinetic (PK) profile and two different nucleoside reverse transcriptase inhibitors (NRTIs) as part of combination anti-retroviral therapy (cART) [1, 2]. Once-daily-dosing, fewer metabolic side effects as compared to other PIs, and a high-barrier to drug resistance make ATV, particularly when boosted, a good option for HIV-1 positive individuals with poor adherence, cardiovascular diseases or diabetes mellitus [3–6]. Genetic variants in the genes encoding the principal enzymes involved in the metabolism of ATV, which are also central to the metabolism of many commonly prescribed drugs, have been found to be associated with adverse events and changes in the pharmacokinetics of ATV. Common adverse effects associated with ATV include hyperbilirubinemia, cosmetic jaundice, nephrolithiasis and cholelithiasis [7]. The updated Health and Human Services 2017 “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents” now favors integrase strand transfer inhibitor (INSTI) regimens over PIs, including ATV, as the preferred initial regimen for treatment naïve patients and now considers ATV/ritonavir (ATV/r) with two NRTIs as a “Recommended, Alternative, and Other Antiretroviral Regimen Options for Treatment-

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Conflict of Interest

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Naïve Patients” but recognizes that it may still be “the preferred regimen for some patients” [6].

Pharmacokinetics

ATV is rapidly absorbed and peak ATV concentration (C_{max}) is reached between 2 – 2.5 hours post-dose. ATV absorption is improved when it is taken with food. The primary route of ATV elimination is through bile (79% of administered dose) and the secondary route is through urine (13% of administered dose excreted as metabolites). There are well-established pharmacokinetic differences when comparing between races, men and women, and HIV-1 positive subjects compared to HIV-1 negative subjects that have yet to be explained [3, 8]. In addition, there are also documented differences between men and women with respect to time to virologic failure, although study results are contradictory [9–11].

ATV is primarily and extensively metabolized by the cytochrome P450, family 3, subfamily A (CYP3A) polypeptide isoenzymes 4 and 5 (CYP3A4/5) [8]. What is unknown is whether it enters cells through diffusion, or whether influx is mediated by specific transporters. The organic anion transporter protein 1B1 (OATP1B1), which is encoded by the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene, is known to facilitate the uptake of conjugated-bilirubin from blood and possibly unconjugated bilirubin and ritonavir. According to the results of at least one *in vitro* study ATV may be an inhibitor of OATP1B1 [12]. However, the effect of any polymorphisms of *SLCO1B1* in patients administered ATV may actually be due to the fact that ritonavir may be an inhibitor of OATP1B1, rather than ATV, although this is not yet established [12–15]. ATV may be a substrate of P-glycoprotein (P-gp) which is encoded by the ATP-binding cassette sub-family B member 1 (*ABCB1*) gene as well as an inhibitor although more evidence may be needed to clarify this relationship [16–20]. None of the studies discussed here have demonstrated a genetic association between ATV and the nuclear receptor subfamily 1 group I member 2 (*NR1I2*) gene that encodes the pregnane X receptor, variants in this gene have been investigated with respect to ATV PK, possibly because it regulates the expression of *CYP3A4*, *SLCO1B1*, and *ABCB1* [19, 21, 22]. Figure 1 shows the pharmacodynamic and pharmacokinetic pathways of ATV and a fully interactive version of these pathways can be accessed at PharmGKB (<https://www.pharmgkb.org/pathway/PA166170503>).

The US Food and Drug Administration (FDA)-approved drug label for ATV indicates that the major biotransformation pathways of ATV are mono- and di-oxygenation while minor biotransformation pathways include glucuronidation, *N*-dealkylation, hydrolysis, oxygenation and dehydrogenation [23]. Four studies investigating biotransformation pathways of ATV confirm that mono-oxidation is a major pathway of ATV biotransformation with two explicitly identifying the structures of one or two mono-oxidation products (M1, M2), such as “a hydroxylated phenylbutane moiety”, while two others solely identified multiple “mono-oxidated” metabolites of ATV without specifying their structures. All four studies detected the presence of metabolites that were the product of carbamate hydrolysis on the prime and non-prime sides of ATV (M3, M4), and three studies detected one *N*-dealkylation metabolite (M5) (Figure 1) [24–27]. None of the

studies, which assessed metabolites in human plasma, human liver microsomes, hepatocytes, or in mouse feces and urine, reported identifying glucuronidated ATV metabolites. In addition, no ATV glucuronide structures are deposited in Pubchem, which contradicts information on the FDA-approved drug label. When unboosted, mono-oxidation and oral clearance (CL/F) of ATV may occur more rapidly in those individuals who carry of at least one functional version of *CYP3A5* as compared to individuals who carry no functional copies due to homozygosity of *CYP3A5**3 (c.219-237 C>T at rs776746), *CYP3A5**6 (c.624 C>T at rs10264272), or *CYP3A5**7 (c.1035_1036 insT at rs41303343) [26, 28, 29].

Ritonavir as a pharmacokinetic enhancer of Atazanavir

Ritonavir is also a protease inhibitor, but its ability to block CYP3A-mediated metabolism of ATV makes it an effective pharmacokinetic enhancer (or “booster”). When boosted with ritonavir (300 mg ATV and 100 mg ritonavir; ATV/r) ATV’s pharmacokinetic profile is improved and individual differences in ATV pharmacokinetics are diminished [8]. Treatment with unboosted ATV is approved by the FDA for specific cases although the European Medicines Agency (EMA) does not formally approve it [30]. ATV administered without a pharmacokinetic enhancer is not a recommended course of therapy for treatment naïve individuals, individuals with a very high viral load (e.g. 100,000 copies HIV-1 RNA/mL) [6, 23], patients with previous virologic failure (> 50 copies HIV-1 RNA/mL), or pregnant women. ATV without a pharmacokinetic enhancer may be recommended in special cases such as to reduce pill burden, improve treatment adherence, or to prevent long-term toxicities associated with ritonavir in individuals with hepatic impairment [30].

The ATV drug labels advises against co-administration of unboosted ATV with tenofovir since tenofovir had been shown to decrease ATV exposure, mostly through increased clearance. However, current consensus regarding the effect of tenofovir on ATV exposure in subjects administered ATV/r is less clear: some studies continue to find that tenofovir is associated with a decrease in ATV exposure [30–34] while others report no significant negative effects on ATV exposure in patients administered ATV/r [35–39]. In a randomized, controlled pilot study in which patients were switched to ATV without ritonavir, a pharmacogenetically-informed dosing algorithm helped patients maintain ATV at therapeutic levels, despite co-administration with tenofovir [40]. Interestingly, another study in Taiwanese patients undergoing therapeutic drug monitoring (TDM) that had been switched to ATV without ritonavir from a ATV/r regimen actually found that 16.5% of the tenofovir group (N = 103) but 35.1% patients without tenofovir (N = 94) had ATV concentrations below the recommended therapeutic values (P < 0.01). Time to virologic failure was not different between groups [41]. It is important to note that in both studies, patients were only included if they had no history of virologic failure or resistance associated mutations (RAMs). A recent meta-analysis of five randomized controlled trials compared ART regimens including ATV versus ATV/r in treatment-experienced subjects for whom ritonavir was no longer advised. This study reported improved safety outcomes in the groups without ritonavir without sacrificing efficacy but the authors cautioned that longer-term studies of efficacy and safety were needed [42].

Pharmacodynamics

HIV-1 protease

The target of ATV is HIV-1 protease. ATV interferes with maturation of the HIV virion by blocking the active site of the HIV-1 protease so that it cannot cleave the viral gag and gag-pol polyproteins (Figure 1) [43]. There is a high barrier to resistance with PIs, but certain resistance associated mutations (RAMs) in HIV-1 protease do confer resistance to ATV and increase susceptibility to the remaining PIs, notably isoleucine to leucine at amino acid residue 50 (I50L), the isoleucine to valine mutation at residue 84 (I84V), and the arginine to serine mutation at residue 88 (N88S). Knowing whether a patient carries one of these mutations is very helpful for clinicians to decide the best treatment course for a patient [3, 44, 45].

UGT1A1

Glucuronidation of substrates increases their water solubility and facilitates their excretion in bile and urine. The UDP glucuronosyltransferase (UGT) family of enzymes is responsible for the glucuronidation of a wide variety of endogenous and xenobiotic substrates. Among the 19 functional enzymes of the human UGT super family, only UGT family 1 member A1 (UGT1A1) is known to be capable of glucuronidating bilirubin, a product of heme catabolism. Since ATV is a competitive inhibitor of UGT1A1, a common adverse effect in patients administered ATV is elevation of non-glucuronidated (unconjugated) bilirubin, a condition known as hyperbilirubinemia. Since UGT1A1 does not metabolize ATV this relationship appears to be an off-target PD interaction. Hyperbilirubinemia due to ATV is not necessarily indicative of hepatic injury but may result in cosmetic jaundice and there is concern that it may compromise drug adherence in certain patients [46, 47].

Drug-Drug Interactions

Many commonly prescribed drugs are metabolized, inhibited, or induced by the main ATV metabolizing enzymes CYP3A4/5 so there is a high potential for drug-drug interactions, especially in older patients where polypharmacy is common, and in patients co-infected with hepatitis C, tuberculosis, or other opportunistic bacterial or fungal infections, a common complication in individuals with HIV [48]. A case series in four HIV positive patients reported that ATV and ritonavir C_{min} and AUC were only moderately reduced in patients administered voriconazole, a triazole antifungal agent [49]. A recent study in healthy volunteers reported that co-administration of ATV/r with voriconazole also lead to reductions of ATV C_{min} of between 20–30% regardless of the metabolizer phenotype of the primary metabolizing enzyme of voriconazole, *CYP2C19*. Although *CYP2C19* is the primary metabolizing enzyme, voriconazole is also metabolized by *CYP3A4* [50]. The study also found that co-administration of voriconazole and ATV/r led to decreased voriconazole exposure in subjects with the *CYP2C19* extensive metabolizer phenotype, and increased voriconazole exposure in the *CYP2C19* poor metabolizer phenotype, which the authors attribute to *CYP2C19* induction by ritonavir [51]. The FDA-approved drug label for ATV also gives specific dose scheduling and dosing recommendations for patients who are concomitantly taking H_2 receptor antagonists, proton-pump inhibitors (PPIs), antacids, or

buffered didanosine because ATV absorption depends on low gastric pH [3, 8, 52]. Other drugs that are extensively metabolized by UGT1A1, such as the cancer drug irinotecan, are contraindicated due to the high potential for toxicity [3, 23].

Pharmacogenomics of ATV/r

UGT1A1

Gilbert's Syndrome is characterized by mild and intermittent elevations of bilirubin caused by homozygosity of the c.-53_-52 [TA]₆ > [TA]₇ allele in *UGT1A1* at rs8175347 (*28). The UGT1A1*28 allele consists of seven thymidine-adenine (TA) tandem repeats in the promoter region of *UGT1A1* where normally there are six (*UGT1A1**1 allele). The *28 allele causes a ~50% decrease in UGT1A1 protein expression. Similarly, the *37 ([TA]₈) allele also decreases *UGT1A1* transcriptional activity relative to *28, whereas the *36 ([TA]₅) allele in *UGT1A1* leads to increased transcriptional activity relative to *28 [47]. The *36 and *37 alleles are rare in White and Asian populations, but are more common in West and sub-Saharan African populations [53]. The *UGT1A1**6 allele (c.211 G>A at rs4148323), which causes a missense mutation (G71R), is more prevalent in individuals of East Asian descent but has not been found to be associated with ATV-associated hyperbilirubinemia [54].

The *UGT1A1* *28/*28 genotype has been repeatedly shown to be associated with hyperbilirubinemia in patients administered ATV and there is some evidence that the homozygous genotype may also be associated with drug discontinuation [29, 54–60]. Most recently, a study in 321 patients reported an association between the T allele at rs887829 in the promoter region of *UGT1A1* (c.-364 C>T) and bilirubin-associated discontinuation. The hazard ratio (HR) for bilirubin-related discontinuation for all subjects with the TT genotype (vs. CC genotype) was 7.3 [95% CI: 1.7–31.5; P = 0.007]. However, when stratified by race, hazard ratio [HR] for discontinuation in White subjects (N = 152) was 14.4 (95% CI: 2.6–78.7; P = 0.002), but 0.8 (95% CI: 0.05–12.7; P = 0.87) for Black subjects (N = 153). The authors speculate that if jaundice as a result of hyperbilirubinemia is less obvious in individuals with darker skin, it may explain the decrease in bilirubin-associated discontinuation in Black subjects as compared to White subjects [61]. An earlier genomewide association study (GWAS) of 475 patients administered ATV/r as part of the AIDS Clinical Trial Protocol Group A2502 previously found that the T allele at rs887829 in the promoter region of *UGT1A1* (c.-364 C>T) was associated with increased peak bilirubin concentrations ($P=6.4\times10^{-12}$) [62]. The T allele is in almost complete linkage disequilibrium with *UGT1A1* *28, which would allow for genotyping only at rs887829, thereby facilitating the detection of the *UGT1A1* *28 allele. An earlier study reported that the TT genotype at rs887829 was associated with cumulative incidence of bilirubin-related ATV/r drug-discontinuation ($P=9.3\times10^{-14}$) when it was assessed in 481 Black, White, and Hispanic patients [63].

Cholelithiasis is infrequent among HIV positive individuals treated with ATV/r, but long-term (>2 years) treatment may increase the incidence of cholelithiasis. A study of 890 Japanese patients showed a positive association between treatment duration greater than 2 years with increased likelihood of cholelithiasis, although it did not reach statistical

significance in multivariate analysis [64]. In line with these findings, a retrospective observational study of fourteen patients treated with ATV who had developed complicated cholelithiasis reported that in four patients, 100% of the biliary calculi was made up of ATV [65]. Incidence of cholelithiasis has not been found to differ between patients treated with ATV/r and those treated with other protease inhibitors boosted with ritonavir [66]. One retrospective pharmacogenetic study of 910 HIV-positive individuals who had undergone therapeutic drug monitoring and abdominal sonography reported no association between either *UGT1A1**28 or rs2032582 (c. c.2677 A>C/T) in *ABCB1* (also known as MDR1 2677A>C/T) with risk of cholelithiasis [7].

Nephrolithiasis is also infrequent in patients treated with ATV/r but incidence may also increase in patients treated over a year [67, 68]. Two studies reported that nephrolithiasis incidence was higher in patients treated with ATV/r as compared to other PIs (darunavir, fosamprenavir, and lopinavir) with or without ritonavir [69, 70]. A pharmacogenetic study of seventy-one Japanese patients treated with ATV/r reported that three single nucleotide polymorphisms (SNPs) in high LD within the 3' untranslated region (UTR) of *UGT1A1* were associated with nephrolithiasis: the CT genotype versus the CC genotype at rs10929303 (c.*211T>C) (adj. OR 3.7 (95% CI 1.13–11.9; $P=0.030$), the CG genotype versus the CC genotype at rs1042640 (c.*339G>C) (adj. OR of 5.8 (95% 1.56–21.3; $P=0.009$)) and the GG or CG genotypes versus the CC genotype at rs8330 (c.*440G>C) (adj. OR of 5.8 (95% CI 1.56–21.3; $P=0.009$)). Additional factors associated with increased risk of nephrolithiasis included elevated serum bilirubin concentrations and hepatitis C co-infection [71].

Additional UGT1A Variants

The structure of the *UGT1A* locus is complex and involves a shared set of coding exons and alternative first exons for each gene [46]. Since the span of the whole *UGT1A* locus is less than 200,000 bases, variants within the boundaries upstream of the *UGT1A* gene may be linked to variants in *UGT1A1*. In a study of HIV-1 positive patients taking ATV/r (N=106) additional *UGT1A* variants were found to be associated with severity of hyperbilirubinemia. Patients were genotyped at rs3806596 (c.861+35196 T>C) in *UGT1A3* and rs7586110 (c.855+44504 T>G) in *UGT1A7*, both in the respective promoter regions of those first exons. They were also genotyped at a haplotype that results in two amino acid changes in *UGT1A7* (*UGT1A7*^{129K/131K}) and this haplotype is the result of several possible single nucleotide changes, which the authors do not differentiate^a [46]. rs3806596 CC, rs7586110 GG, and homozygosity of *UGT1A7*^{129K/131K} and *UGT1A1**28 was designated as the “homozygous haplotype”. Patients were sorted by the severity of hyperbilirubinemia from grade 0 (<19 μmol bilirubin/L) to grade 3–4 (≥43 μmol/L bilirubin) and the frequency of the homozygous haplotype was compared between groups as well as to a group of healthy controls. The incidence of the homozygous haplotype in healthy controls was 9.6% but in individuals with severe (grade 3–4) hyperbilirubinemia it was 41.2% ($P<0.0001$). All six patients with grade 4 hyperbilirubinemia (severe ≥85 μmol bilirubin/L) had the homozygous haplotype [55]. When rs3806596, rs7586110 and rs17863778 were analyzed in a large genomewide association study (GWAS) of 475 patients administered ATV/r (AIDS Clinical Trial Protocol

Group A2502) they were not found to be associated with increased likelihood of developing hyperbilirubinemia after correcting for presence of the rs887829 T allele in *UGT1A1* [62].

ABCB1, SLCO1B1, NR1I2

The P-gp transporter mediates the efflux of many xenobiotic substances and its function is therefore an important determinant of drug pharmacokinetics. Three polymorphisms in *ABCB1*, rs1045642 (c.3435A>G), rs2032582 (c.2677A>C/T) and rs1128503 (c.1236 A>G) have been thoroughly investigated because of their effects on many drugs [72]. Two small studies (N= 88 and N= 37) reported no association between ATV C_{trough} concentrations in HIV-1 positive subjects and rs1045612 [73, 74] or rs2032582 [74]. In 188 HIV-1 positive subjects treated with ATV/r the GG genotype at rs1045642 was associated with increased plasma concentration of ATV as compared to the AA or AG genotypes ($P < 0.01$) and the A allele was independently associated with lower ATV concentrations [59]. When the three *ABCB1* SNPs were assessed simultaneously (rs1128503 G, rs2032582 C, and rs1045642 G) in healthy volunteers administered ATV/r, clearance (CL/F in L/h/kg) was fastest in subjects with zero GCG copies (0.1) as compared to those with one (0.073) or two (0.070) copies of the haplotype ($P < 0.03$). After controlling for the number of CGC copies, race and sex were no longer associated with ATV CL/F ($P = 0.86$ and $P = 0.21$, respectively)[29].

In a study that evaluated ATV and ritonavir concentrations in plasma and peripheral blood mononuclear cells (PBMCs) thirty-five HIV-1 positive subjects the AC and CC genotypes in rs2032582 in *ABCB1* were associated with a higher ratio of ATV intracellular: plasma concentrations ($P = 0.007$), and significantly lower plasma ATV concentration ($P = 0.043$). No other SNPs were associated with ATV intracellular or plasma concentrations, although CC and CT at rs4149056 (c.521T>C) in *SLCO1B1* and AG and GG at rs1523130 (c.-1663T>C) in *NR1I2* were associated with increased intracellular concentrations of ritonavir [19]. This is supported by the findings of the AIDS Clinical Trial Group A5202 GWAS which found no association between rs1045642 or rs1128503 in *ABCB1*, nor in rs4149056 in *SLCO1B1* with ATV clearance [62]. Altogether, little evidence suggests a potential association between the G allele at rs1045642 with increased exposure to ATV and more studies would need to confirm this. Two additional studies reported finding no significant association between polymorphisms in *ABCB1* with risk of cholelithiasis or nephrolithiasis [7, 71] and a third found no association with rs2472677 (c.-22-7659C>T) in *NR1I2* or rs1045642 in *ABCB1* and likelihood of drug discontinuation in patients administered ATV/r [58].

Pharmacogenomics of atazanavir without ritonavir

UGT1A1

In a single-arm, open-labelled, two-phase study of thirty-one HIV-negative volunteers, grouped by genetically determined *CYP3A5* expressor status, ATV was administered alone for seven days, followed by ATV/r for another seven days and ATV pharmacokinetics and bilirubin concentrations were evaluated on days seven and fourteen. During the unboosted phase, median increases in indirect bilirubin concentrations were significantly lower in

subjects with the *UGT1A1* *1/*1 and *UGT1A1* *1/*28 genotypes as compared to subjects with the *UGT1A1* *28/*28 genotype ($P < 0.003$) [29].

In a pilot study of HIV-1 positive subjects who had been taking ATV/r as part of ART, bilirubin concentrations, immunologic, virologic and metabolic outcomes were assessed to determine whether a switch to ATV without ritonavir would be beneficial for those patients harboring *UGT1A1* *28 alleles. Subjects that had one or two copies of *UGT1A1* *28 were switched to the unboosted ATV regimen and had significantly lower total bilirubin when they were evaluated at twelve months (1.82 mg/dL) as compared to baseline (4.09mg/dL) ($P < 0.001$). In addition, these differences were accompanied by improvements in lipid profile and hepatic enzymes (λ -GT and transaminases) without alterations in efficacy: HIV-1 RNA was undetectable in the 24 patients that switched and there were no changes CD4 T-cell counts in any patient at 48 weeks [75].

CYP3A5

Variability in ATV pharmacokinetics when it is administered without ritonavir has been attributed to the presence of variants in *CYP3A5* that confer functionality when lack of function is more common. Individuals who carry any combination of two non-functional alleles are often designated as “non-expressors” relative to individuals with one or two functional alleles who are designated “expressors”. In the aforementioned two-phase study of thirty-one HIV-negative volunteers administered 400 mg of ATV without ritonavir for the first seven days of the study, ATV CL/F on day seven was 1.39 times faster in the “expressor” group as compared to “non-expressor” group ($P=0.045$). Minimum concentration (C_{min}) was lower and half-life was shorter in expressors versus non-expressors but it was not significant. Significant differences were not seen in C_{max} or AUC and differences according to expressor status were only observed in the non-African-American (NAA) men and women. However, within the African-American (AA) group CL/F differences according to *CYP3A5* expressor status were not observed in men ($N=6$) or women ($N=7$) although low numbers make this difficult to interpret with confidence. When controlling for presence of the GCG haplotype in *ABCB1*, *CYP3A5* expressors still had faster CL/L versus non-expressors ($P=0.01$) [29].

In a follow up to that study, fourteen of the original plasma samples were reanalyzed to determine how ATV pharmacokinetics related to the ratio of ATV-metabolites to ATV and significant differences were found when comparing between *CYP3A5* expressor groups within the AA and NAA subjects. Within the NAA group, ATV AUC was 1.8 times higher in *CYP3A5* non-expressors as compared to *CYP3A5* expressors. ATV AUC was 2.4-fold higher in AA *CYP3A5* expressors as compared to NAA *CYP3A5* non-expressors. There were no significant differences between *CYP3A5* expressors and non-expressors within the AA group, although there was a consistently higher M1: ATV ratio within the AA and NAA in the *CYP3A5* expressor group as compared to *CYP3A5* non-expressor group [26].

In a third follow-up study, ATV pharmacokinetic parameters were re-evaluated and assessed using a population pharmacokinetic model that incorporated additional clinical and genetic variants (*CYP3A4/5*, *ABCG2*, *NR1I2*, and *SLCO1B1*). In this study, ATV CL/F was 26% slower in *CYP3A5* non-expressors, 33% slower in subjects that carried one or two copies of

the *ABCB1* GCG haplotype, and 31% lower in subjects who carried one or more *CYP3A4**1B alleles ($P=0.0074$). The authors also found an interaction between *CYP3A5* expressor status and genotype at rs2472677 in *NR1I2*. When compared to the CT and TT genotypes, the CC genotype was associated with a 37% lower CL/F in *CYP3A5* non-expressors, and a 63% faster CL/F in *CYP3A5* expressors. Additional demographic factors that were associated with lower CL/F were African-American ethnicity (33% decrease), female sex (25% decreased), and age (1.7% decrease/year over age 30)[18].

A subset of the retrospective Prospective Evaluation of Antivirals in a Resource Limited Settings study (PEARLS) included sixty-nine treatment-naïve HIV-positive subjects treated with ATV without ritonavir from the United States, Peru and South Africa. A single plasma sample was collected at four and eight weeks and population pharmacokinetic modeling was used to predict CL/F and C_{24} , metabolite to parent compound ratios (M1: ATV and M2: ATV) as well as likelihood of virologic failure by *CYP3A5* expressor status, or genotype. *CYP3A5* expressors had a statistically significant decrease in likelihood of virologic failure (OR 0.95 (95% CI 0.89–1) as compared to *CYP3A5* non-expressors (OR 0.73 (95% CI 0.57–0.94) $P=0.026$) at 72 weeks. No statistically significant associations were found between ATV CL/F, C_{24} , M1:ATV or M2:ATV with *CYP3A5* expressor status after adjusting for race and gender, or in ranked analysis. When subjects were grouped by genotype rather than by *CYP3A5* status, ATV CL/F was found to be significantly faster for subjects with the *CYP3A5**1/*1 as compared to *CYP3A5**1/*3 and *CYP3A5**3/*3 ($P=0.0006$) genotypes and the difference with *1/*3 when adjusting for race and gender ($P=0.001$). Surprisingly, the *CYP3A5**1/*6 genotype was associated with **faster** CL/F (15.7 [14.6–16.8]) as compared to *CYP3A5**1/*1 genotype (12.4 ng/ml) [11.6–13.4]) ($P=0.004$) even after adjusting for race and gender. *CYP3A5* genotypes were not associated with C_{24} , nor M1: ATV or M2: ATV after adjusting for race and gender or in ranked analysis [28].

ABCB1, SLCO1B1, NR1I2

In a two-part study, in which healthy volunteers were administered ATV followed by ATV/r, several pharmacokinetic parameters such as CL/F and C_{min} of ATV were determined. During the phase in which ATV was administered without ritonavir, ATV CL/F was reported to be faster, and C_{min} was reported to be lower, respectively, in subjects with zero versus one or two copies of the GCG haplotype in *ABCB1* ($P<0.007$ for CL/F and $P<0.02$ for C_{min}). Homozygosity for the GCG haplotype in *ABCB1* was also associated with higher bilirubin concentration as compared to zero copies ($P=0.036$). [29]. In a separate study of seventy-four White patients administered ATV only, only the G allele at rs1045642 in *ABCB1* was found to be associated with higher median plasma concentrations of ATV and median ATV C_{min} was also higher in patients with the GG genotype as compared to the AA and AG genotypes ($P<0.01$). A greater proportion of subjects with the GG genotype (92%) also had bilirubin concentrations above the upper limit of normal (ULM > 1.3 mg/dl), as compared to patients with the AG (67%) ($P<0.05$) or AA genotypes (41 %) ($P<0.05$) [17].

Polymorphisms in *NR1I2*, *SLCO1B1* and *ABCB1* were also evaluated in PEARLS study. That study included people from Peru, South Africa and the U.S.A (N = 69) of various ethnicities who were co administered unboosted ATV with didanosine-EC + emtricitabine.

In that study, the CT genotype at rs2472677 in *NR1I2* was associated with a significant decrease in ATV C₂₄ (48.4 ng/ml) as compared to either the CC (126.8 ng/ml) or TT genotypes (172.6 ng/ml) ($P=0.01$ and $P=0.007$, respectively) even after adjustment for race and sex. Subjects with two copies of *ABCB1* GCG haplotype had decreased ATV C₂₄ as compared to subjects with one, although the association did not remain significant after adjusting for race and gender or in ranked analysis. Neither rs2306283, nor rs4149056 in *SLCO1B1* were associated with CL/F, C₂₄, M1: ATV or M2: ATV [28]. This is contradicted by two other studies in which HIV-1 positive patients were administered ATV without ritonavir. In the first study (N = 109; 26% female, ethnicities unknown) the TT genotype at rs2472677 in *NR1I2* was associated with lower median trough concentrations of ATV (C_{trough}) (34 ng/mL versus 152 ng/mL; $P=.001$), and an increased likelihood that ATV concentrations were below the minimum effective concentration of 150 ng/mL in two cohorts (OR 18 95% CI [2.1–153.9] $P=0.008$). In addition, tenofovir was not associated with C_{trough} in either group [21]. In the second study, which used many subjects from the same cohort as well as a new cohort (N = 182; 64% male), population pharmacokinetic modeling was used to show that the CT and CC genotypes at rs2472677 in *NR1I2* were associated with a 17.2% increase in CL/F as compared to the TT genotype [22].

Finally, a randomized controlled pilot study investigated whether pharmacogenetic-based dosing could improve ATVs pharmacokinetic profile in patients switched to 400 mg ATV without ritonavir due to issues of toxicity, tolerability or dose simplification. The pharmacogenetic-guided dosing arm (N = 40) was assigned to a dosing schedule guided by genotypes at three different SNPs: rs2472677 in *NR1I2*, rs1045642 in *ABCB1*, and rs4149056 in *SLCO1B1*. The TT genotype at rs2472677, AA or AG genotypes at rs1045642, and the TT genotype at rs4149056 were considered “unfavorable genotypes” because they had previously been associated with decreased exposure to ATV. Each unfavorable genotype was given one point and patients with two to three points received twice daily 200 mg doses of ATV to improve ATV exposure whereas those with zero or one point received 400 mg ATV once daily. Patients in the non-pharmacogenomic-guided dosing arm (N=40) received a once daily dose of 400 mg of ATV without regard to genotype. The geometric mean of ATV C_{trough} in the pharmacogenetic arm was values was 253 ng/mL (150–542) versus 111 ng/mL (64–190) in the standard-dose arm. In addition, 75.7% of the subjects in the pharmacogenetic arm had ATV C_{trough} concentrations within the therapeutic range (>150 ng/ml) while only 38.9% of subjects in the standard dose arm did ($P=0.001$; RR 4.89, 95% CI 1.79–13.38)[40]. Current evidence, along with the pharmacogenetic-guided dosing study, may support the association between the TT genotype at rs2472677 in *NR1I2* and the G allele at rs1045642 in *ABCB1* with increased ATV exposure when it is administered without a pharmacokinetic enhancer.

Conclusions

The findings summarized here are limited by the small cohort sizes and the overrepresentation of White, male subjects in most studies thereby minimizing the extent to which they may be extrapolated to more diverse populations. Future studies in larger and more diverse cohorts could help to explain why *CYP3A5* appears to affect unboosted ATV differently in Black versus White subjects. In addition, the incorporation of genetic variants

known to affect ritonavir pharmacokinetics into a dosing algorithm that includes genetic variants known to affect ATV pharmacokinetic may help to more precisely estimate dosing strategies for individual patients, although dose reductions in ATV and/or ritonavir have also shown promise in some patients [76]. There is also good and consistent evidence of an association is between *UGT1A1* rs8175347 (*28, *37) and the TT genotype at rs8175347 with increased likelihood of hyperbilirubinemia in patients administered ATV/r, as well as an increased likelihood of drug-discontinuation. The Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines for pharmacogenomic prescribing of ATV, recommends discussing the high likelihood of developing jaundice in patients homozygous for these alleles as well as considering alternative ART regimens unless jaundice is not of concern to the patient [60]. Other variants in other genes may influence severity of hyperbilirubinemia or nephrolithiasis but have not been replicated and are not yet clinically actionable. An effective pharmacogenetic-guided dosing strategy will likely require larger studies, in more diverse cohorts in order to uncover additional genetic and non-genetic factors, such as race, sex, concomitant drug use or co-infection to improve drug adherence and minimize adverse events in patients receiving ATV.

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Figure 1.

A stylized diagram showing atazanavir metabolism and transport in the liver. A fully interactive version of this figure can be found at <https://www.pharmgkb.org/pathway/PA166170503>.

Table 1

PGx associations of and ATV/r and *UGT1A* genes

Gene	Variant (rsID)	Main Findings	Type/Size
<i>UGT1A1</i>	c.-53_-52 [TA] ₆ >[TA] ₇ rs8175347 <i>UGT1A1</i> *28	The [TA] ₇ /[TA] ₇ genotype is associated with hyperbilirubinemia vs. [TA] ₆ /[TA] ₆ + [TA] ₆ /[TA] ₇ genotypes. ^[29, 54–60] The [TA] ₇ allele not associated with cholelithiasis vs. [TA] ₆ allele. ^[7]	N = 31, single-arm, open-label 2-phase; N = 129, observational; N = 106; observational; N = 646 subset of phase IIIb randomized; N = 96 subset of longitudinal & observational; N = 121 observational; N = 118 observational; N = n.a, guideline N = 910, retrospective
	c.211 G>A at rs4148323 <i>UGT1A1</i> *6	The A allele is not associated with hyperbilirubinemia vs G allele. ^[54]	N = 129, observational
	c.-364 C>T rs887829 <i>UGT1A1</i> *80	The TT genotype is associated with increased risk of bilirubin-associated drug discontinuation vs. CT + CC genotypes. ^[61] The T allele is associated with hyperbilirubinemia vs. the C allele. ^[62] The TT genotype is associated with increased cumulative incidence of drug discontinuation vs. CT + CC genotypes. ^[63]	N = 321, observational N = 443, subset of phase IIIb equivalence study N = 481, subset of phase III prospective randomized open-label trial
	c.*211T>C rs10929303	The CT genotype is associated with risk of nephrolithiasis vs. CC genotype. ^[71]	N=31 cases & N = 47 controls
	c.*339G>C rs1042640	The CG genotype is associated with risk of nephrolithiasis vs. CC genotype. ^[71]	N=31 cases & N = 47 controls
	c.*440G>C rs8330	The GG + CG genotypes are associated with risk of nephrolithiasis vs. CC genotype. ^[71]	N=31 cases & N = 47 controls
<i>UGT1A3</i>	c.861+35196T>C -66 T>C rs3806596	The CC genotype is associated with hyperbilirubinemia vs. CT + TT <i>when a part of a "haplotype" that includes rs7586110 GG, rs8175347 [TA]₇/[TA]₇, and UGT1A^{Δ29K/131K}/UGT1A^{Δ29K/131K}.^[55]a The C allele is not associated with hyperbilirubinemia vs. the T allele.^[62]</i>	N = 106, observational N = 443, GWAS
<i>UGT1A7</i>	c.855+44504 T>G -57 T>G rs7586110	The GG genotype is associated with hyperbilirubinemia vs. GT + TT <i>when a part of a "haplotype" that includes rs3806596 CC, rs8175347 [TA]₇/[TA]₇, and UGT1A^{Δ29K/131K}/UGT1A^{Δ29K/131K}.^[55]a The G allele is not associated with hyperbilirubinemia vs. the T allele.^[62]</i>	N = 106, observational N = 443, subset of phase IIIb equivalence study
	c.855+44947T>G N129K rs17868323	The G allele is not associated with hyperbilirubinemia vs. the T allele. ^[62]	N = 443, subset of phase IIIb equivalence study
	<i>UGT1A</i> ^{Δ29K/131K}	The <i>UGT1A</i> ^{Δ29K/131K} / <i>UGT1A</i> ^{Δ29K/131K} is associated with hyperbilirubinemia vs. <i>UGT1A</i> ^{Δ29N/131R} / <i>UGT1A</i> ^{Δ29N/131R} <i>when part of a "haplotype" that</i>	N = 106, observational

Gene	Variant (rsID)	Main Findings	Type/Size
		includes rs8175347 [TA] ₇ /[TA] ₇ , rs3806596 CC and rs7586110 GG; ^[55] ^a	

^aUGT1A7^{L29K/131K} may consist of the following variants:

rs17868323 (NM_019075.2:c.855+44947T>G; NP_061950.2:p.A129K)

rs17863778 (NM_019075.2:c.855+44951C>A; NP_061950.2:p.R131R)*

rs17868324 (NM_019075.2:c.855+44952G>A; NP_061950.2:p.R131Q)*

* The reference genome has a CGA at position 131, which encodes an arginine (R) but the combination of the rs17863778 C>A and rs17868324 G>A single nucleotide polymorphisms (SNPs) would result in a AAA codon at position 131 which encodes a lysine (K). AAG also encodes a lysine, but this change would require three changes, rather than two.

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Table 2PGx associations of ATV/r and *Other* Genes

Gene	Variant (rsID)	Main Findings	Type/Size
<i>ABCB1</i>	c.1236 A>G rs1128503 c.2677A>C/T rs2032582 c.3435A>G rs1045642	Slower CL/F of ATV is associated with more copies of the “GCG” haplotype (0>1>2). ^[29]	N = 31 single-arm, open-label, 2-phase
	c.3435A>G rs1045642	The G allele is not associated with ATV C _{trough} vs. the A allele. ^[73, 74] The A allele is associated with lower plasma ATV concentrations vs. the G allele. ^[59] The G allele is not associated with ATV clearance vs. the A allele. ^[62] The G allele is not associated with drug discontinuation vs. the A allele. ^[58]	N = 88, observational; N = 103, observational N = 118, observational N = 443, subset of phase IIIb equivalence N = 121 observational
	c.2677A>C/T rs2032582	The C+ T alleles are not associated with risk of cholelithiasis vs. the A allele. ^[7] The C+ T alleles are not associated with ATV C _{trough} vs. the A allele. ^[74] The AC + CC genotypes are associated with higher ATV intracellular: plasma concentrations as well as lower plasma ATV concentrations. ^[19] The C/T alleles are not associated with risk of nephrolithiasis vs. the A allele. ^[71]	N = 910, retrospective N = 103, observational N = 35, observational N=31 cases & N = 47 controls
	c.1236 A>G rs1128503	The G allele is not associated with ATV clearance vs. the A allele. ^[62]	N = 443, subset of phase IIIb equivalence
<i>SLCO1B1</i>	c.521T>C rs4149056	The C allele is not associated with ATV clearance vs. the T allele. ^[62]	N = 443, subset of phase IIIb equivalence
<i>NR1I2</i>	c.-22-7659C>T rs2472677	The T allele is not associated with drug discontinuation versus the C allele. ^[58]	N = 121, observational

Table 3PGx associations with *UGT1A* Variants without Ritonavir

Gene	Variant (rsID)	Main Findings	Type/Size
<i>UGT1A1</i>	c.-53_-52 [TA] ₆ >[TA] ₇ rs8175347 *28	The [TA] ₇ /[TA] ₇ genotype is associated with hyperbilirubinemia vs. [TA] ₆ /[TA] ₆ + [TA] ₆ /[TA] ₇ genotypes. ^[29, 75]	N = 31, single-arm, open-label 2-phase; N = 51, open-label, non-randomized, controlled pilot

Table 4PGx associations of *CYP3A5* Gene Variants without Ritonavir

Gene	Variant	Main Findings	Type/Size
<i>CYP3A5</i>	non-expressor	<p>ATV CL/F was faster in <i>CYP3A5</i> expressors vs. <i>CYP3A5</i> non-expressors <u>only</u> when comparing within <i>NAA subjects</i> ATV C_{min}, C_{max}, AUC, and half-life were not significantly different between groups. <u>No significant differences</u> in PK parameters were reported between expressor groups <i>within AA subjects</i>.^[29]^{a,b}</p> <p>ATV AUC was higher in <i>CYP3A5</i> non-expressors as compared to <i>CYP3A5</i> expressors but <u>only</u> in <i>NAA</i>. ATV AUC was also higher in <i>AA CYP3A5</i> expressors as compared to <i>NAA CYP3A5</i> non-expressors.^[26]^{a,b}</p> <p>ATV CL/F was slower in <i>CYP3A5</i> non-expressors vs. <i>CYP3A5</i> expressors. The CC genotype at rs2472677 (<i>NR1I2</i>) was associated with slower CL/F in <i>CYP3A5</i> non-expressors and faster CL/F in <i>CYP3A5</i> expressors.^[18]^{a,b}</p> <p><i>CYP3A5</i> expressors had a statistically significant decrease in likelihood of virologic failure vs. <i>CYP3A5</i> non-expressors at 72 weeks. <i>CYP3A5</i> expressor status was not associated with ATV CL/F, C_{24}, M1:ATV or M2:ATV except when grouped by genotype: the <i>CYP3A5</i>*1/*1 genotype was reported to be associated with faster ATV CL/F vs. <i>CYP3A5</i>*1/*3.^[28]^b</p>	<p>N = 31, single-arm, open-label 2-phase</p> <p>N = 14, observational, in vitro</p> <p>N = 30, open-label, parallel group observational</p> <p>N = 69, subset retrospective observational</p>

^aPlease note: references 18, 26, and 29 all re-analyzed data from the same volunteer subjects^bAA: African-American, NAA: non-African-American, CL/F: clearance, C_{min} : minimum concentration, C_{max} : maximum concentration

Table 5

Other PGx Gene Variants without Ritonavir

Gene	Variant (rsID)	Main Findings	Type/Size
<i>ABCB1</i>	c.1236 A>G rs1128503 c.2677A>C/T rs2032582 c.3435A>G	Slower CL/F and higher C_{min} of ATV is associated with more copies of the “GCG” haplotype in <i>ABCB1</i> ($0 > 1 > 2$). Homozygosity of the “GCG” haplotype is associated with increased bilirubin concentrations vs. one or zero copies of the “GCG” haplotype. ^[29] Homozygosity of the “GCG” haplotype was not associated with ATV C_{24} after adjusting for race and sex in ranked analysis. ^[28]	N = 31, single-arm, open-label 2-phase N = 69, subset retrospective observational
	c.3435A>G rs1045642	The G allele is associated with higher median plasma concentrations of ATV vs. the A allele. The GG genotype is also associated with higher median C_{min} and bilirubin concentrations above the upper limit of normal (ULM > 1.3 mg/dl) vs. the AA and AG genotypes. ^[17] Incorporation of the genotypes into a PGx dosing algorithm is associated with improved ATV C_{trough} concentrations. The AA + AG genotypes were associated with lower ATV exposure vs. the GG genotype and were given 2×200 mg daily doses instead of 1×400 mg daily dose. ^[40]	N = 74, observational N = 80, randomized controlled pilot
<i>SLCO1B1</i>	rs2306283 c.521T>C	rs2306283 in <i>SLCO1B1</i> was not associated with CL/F, C_{24} , M1: ATV or M2:ATV. ^[28]	N = 69, retrospective observational
	rs4149056 c.521T>C	rs4149056 in <i>SLCO1B1</i> was not associated with CL/F, C_{24} , M1: ATV or M2:ATV. ^[28] Incorporation of the genotypes into a PGx dosing algorithm is associated with improved ATV C_{trough} concentrations. The TT genotype was associated with lower ATV exposure vs. the CC genotype and were given 2×200 mg daily doses instead of 1×400 mg daily dose. ^[40]	N = 69, retrospective observational N = 80, randomized controlled pilot
<i>NR1I2</i>	c.-22-7659C>T rs2472677	The CC genotype is associated with slower ATV CL/F in <i>CYP3A5</i> non-expressors and more rapid ATV CL/F in <i>CYP3A5</i> expressors vs. the CT and TT genotypes. ^[18] The CT genotype was associated with a significant decrease in ATV C_{24} as compared to either the CC or TT genotypes even after adjustment for race and sex. ^[28] The TT genotype is associated with decreased ATV C_{trough} and increased likelihood that concentrations were below minimum effective concentration vs. CT + CC genotypes. ^[21] The CT + CC genotypes are associated with faster ATV CL/F vs. the TT genotype. ^[22] Incorporation of the genotypes into a PGx dosing algorithm is associated with improved ATV C_{trough} concentrations. The TT genotype was associated with lower ATV exposure vs. the CT + CC genotypes and were given 2×200 mg daily doses instead of 1×400 mg daily dose. ^[40]	N = 30, open-label, parallel group observational N = 69, subset retrospective observational N = 109, observational N = 182, observational N = 80, randomized, control, pilot
<i>CYP3A4</i>	*1B rs2740574 C>T	The T allele is associated with decreased ATV CL/F vs. the C allele. ^[18]	N = 30, open-label, parallel group, observational