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Association of UGT1A1*28 and CYP2B6 c.516G>T Variants with Adverse Effects in HIV Patients Receiving Antiretroviral Therapy in Chile

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ABSTRACT

Efavirenz (EFV) and atazanavir (ATV) are key components of antiretroviral therapy (ART) for individuals living with HIV, acting as a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor, respectively. Clinical responses to these drugs vary greatly among patients, particularly regarding adverse drug reactions (ADRs). Previous studies suggest that the UGT1A1*28 and CYP2B6 c.516G>T genetic variants may increase susceptibility to ATV- and EFV-related toxicities. This study investigated whether UGT1A1*28 and CYP2B6 c.516G>T polymorphisms are associated with ADRs in Chilean HIV patients receiving EFV or ATV. A retrospective, observational, case–control study was conducted in 67 adult patients treated with either EFV or ATV at San Juan de Dios Hospital. Clinical data were extracted from medical records. Genotyping for rs887829 (proxy for UGT1A1*28) and rs3745274 (CYP2B6 c.516G>T) was performed using real-time PCR with TaqMan® probes. Associations between variants and ADRs were assessed using univariate logistic regression under codominant, recessive, and dominant models. Hyperbilirubinemia (total bilirubin >1.2 mg/dL) occurred in 61.11% of patients on ATV, with moderate-to-severe cases (bilirubin >1.9 mg/dL) significantly linked to UGT1A1*28 under recessive and codominant models (OR = 16.33, p = 0.028; OR = 10.82, p = 0.036). In EFV-treated patients, CNS-related ADRs were observed in 34.21%, with nightmares significantly associated with CYP2B6 c.516G>T (codominant OR = 12.00, p = 0.031; recessive OR = 7.14, p = 0.042). Combined CNS ADRs—including insomnia, anxiety, and suicide attempts—also showed strong associations with this variant (codominant OR = 30.00, p = 0.011; recessive OR = 14.99, p = 0.021). These results indicate that UGT1A1*28 and CYP2B6 c.516G>T significantly contribute to ATV- and EFV-related ADRs, respectively. Incorporating pharmacogenetic testing into ART could improve safety and adherence in HIV patients. Further prospective studies are warranted to confirm these findings in the Chilean population and support evidence-based, personalized therapy strategies.

Keywords: HIV, Antiretroviral therapy, Pharmacogenetics, UGT1A1, CYP2B6, Adverse drug reactions

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Introduction

Human immunodeficiency virus (HIV) continues to affect approximately 38 million individuals worldwide, representing a persistent global health challenge. While HIV/AIDS was the eighth leading cause of death in 2010, it fell to the nineteenth position by 2019, reflecting the success of prevention, early detection, and treatment strategies over the past decades. Nevertheless, the World Health Organization (WHO) has recently highlighted a slowdown in progress against major infectious diseases, including HIV, tuberculosis, and malaria. In response, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set the ambitious 95–95–95 targets, aiming that by 2030, 95% of people living with HIV will know their status, 95% of diagnosed individuals will receive sustained antiretroviral therapy (ART), and 95% of those on ART will achieve viral suppression. In Chile, current figures indicate a 90–68–62 achievement along these metrics.

Combination ART, typically involving three antiretroviral drugs, is highly effective at suppressing viral replication, promoting immune recovery, preventing disease progression, and reducing HIV-related mortality, although it does not eradicate the virus. A standard potent regimen usually consists of two nucleoside reverse transcriptase inhibitors (NRTIs) combined with a third agent from another class—either a non-nucleoside reverse transcriptase inhibitor such as efavirenz (EFV), a protease inhibitor such as atazanavir (ATV), or an integrase inhibitor such as raltegravir. In Chile, there has been a recent trend toward prescribing integrase inhibitors, reducing the use of EFV and ATV, primarily due to their improved safety profiles and lower risk of adverse drug reactions (ADRs).

Therapeutic adherence is critical to optimizing HIV treatment outcomes, and ADRs are a major cause of treatment discontinuation. Approximately 5–10% of patients on ATV discontinue therapy due to ADRs, while at least half of those receiving EFV experience ADRs. Interindividual variability in ADRs arises from both drug-related factors and patient-specific characteristics, including genetic differences, which can significantly influence the risk of adverse events.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides evidence-based, peer-reviewed guidelines to facilitate the clinical use of pharmacogenetic testing. These resources offer genotype-informed recommendations to guide drug prescribing and improve patient safety.

EFV and ATV are known for their considerable variability in ADRs. EFV is primarily metabolized by the highly polymorphic enzyme CYP2B6, with certain genetic variants increasing the risk of central nervous system (CNS) toxicity. The single-nucleotide polymorphism CYP2B6 c.516G>T (rs3745274) has been widely studied; alleles carrying this variant, such as CYP2B6*6 in haplotype with c.A785G, are associated with reduced enzymatic activity. Multiple studies have linked CYP2B6 c.516G>T to elevated plasma EFV concentrations. Consequently, CPIC guidelines provide a moderate recommendation to initiate EFV at a reduced dose (200–400 mg/day) in patients with this genotype, although most CYP2B6 poor metabolizers tolerate the standard 600 mg/day regimen without discontinuation.

Atazanavir (ATV) acts as an inhibitor of hepatic uridine diphosphate glucuronosyltransferase (UGT)1A1, the principal enzyme of the UGT1A subfamily predominantly expressed in the liver and gastrointestinal tract. UGT1A1 plays a key role in the conjugation and elimination of bilirubin and certain drugs. Reduced enzymatic activity, whether due to genetic variants or drug-mediated inhibition, can lead to accumulation of unconjugated bilirubin in blood and tissues. Mechanistic studies have demonstrated that the presence of seven TA repeats (TA7, corresponding to the UGT1A128 allele) in the UGT1A1 promoter, compared with the reference six-repeat allele (TA6, UGT1A11), decreases transcription, likely due to lower affinity for transcription factors such as TATA-binding protein. Consequently, ATV treatment may impair bilirubin glucuronidation, resulting in indirect hyperbilirubinemia, jaundice, and potential discontinuation of therapy. Individuals carrying the UGT1A128 allele are particularly susceptible to bilirubin-related treatment interruptions. CPIC guidelines recommend considering UGT1A1 genotyping prior to initiating ATV to inform clinical decisions. Given the technical challenges of direct TA-repeat genotyping, most population studies use a linked single-nucleotide polymorphism (SNP), rs887829 (c.−364C>T; UGT1A180), which is in strong linkage disequilibrium ($r^2 \approx 0.99$) with TA7. While UGT1A1*6 also reduces enzyme activity, its prevalence in non-Asian populations is very low and was not considered in this study. Given that UGT1A1*28 and CYP2B6 c.516G>T have been associated with higher toxicity for ATV and EFV, respectively, the primary objective of this study was to evaluate the relationship between these polymorphisms and the occurrence of adverse drug reactions (ADRs) in Chilean HIV patients.

Materials and Methods

An epidemiologic, retrospective, observational, case–control study was conducted involving 80 adult patients. Inclusion criteria were: 1) age ≥18 years; 2) treatment with either EFV (600 mg/day) or ATV (300 mg/day with 100 mg/day ritonavir booster); 3) classified as A1, A2, B1, or B2 (outpatients without AIDS) according to the Chilean HIV Clinical Guide; 4) adherence to therapy; and 5) availability of clinical records for review. Exclusion criteria included: 1) pre-existing kidney or liver insufficiency; 2) concurrent voriconazole therapy; 3) untreated opportunistic infections predisposing to severe immune reconstitution inflammatory syndrome (IRIS) or tuberculosis; and 4) non-adherence to hospital treatment and monitoring protocols.

Clinical data were collected from medical records and organized in a coded database including patient demographics, clinical record number, sex, age, weight, lymphocyte count, viral load, liver transaminases, total bilirubin, serum creatinine, and lipid profile (total cholesterol, HDL, LDL, triglycerides).
Prior to initiating EFV therapy, patients were assessed by a psychologist to exclude preexisting CNS conditions. Participants were enrolled in the SJDH Adherence Program, which includes baseline evaluation and follow-ups at two weeks, one month, and every three months thereafter. Each visit included a pharmacist and physician assessment, documenting ADRs and clinical laboratory findings. Recorded ADRs included hyperbilirubinemia (total bilirubin >1.2 mg/dL), gastrointestinal disturbances, rash, dizziness, nightmares, insomnia, headache, fever, anxiety, lipodystrophy, dyslipidemia, and suicide attempts. Hyperbilirubinemia was graded as follows: grade 1 (mild, 1.3–1.9 mg/dL), grade 2 (moderate, 1.9–3.1 mg/dL), grade 3 (severe, 3.1–6.1 mg/dL), and grade 4 (serious, >6.1 mg/dL). Adherence was evaluated using a validated questionnaire and cross-checked with pharmacy refill records and viral load measurements. Participation was voluntary, and informed consent was obtained from all patients.

Genotyping analyses
Venous blood samples were collected in EDTA tubes at San Juan de Dios Hospital (SJDH) and transported to the Laboratory of Chemical Carcinogenesis and Pharmacogenetics at the University of Chile's Faculty of Medicine. Samples were kept at 4–6°C until centrifugation, which was performed at 3,000 rpm for 15 minutes at 4°C. The resulting buffy coat (250 µL) was carefully separated and stored in labeled tubes at −80°C until DNA extraction. Genomic DNA was isolated using the E.Z.N.A.® Blood DNA Mini Kit (OMEGA Bio-tek, Norcross, GA, USA) and quantified using a Denovix® DS-11 FX Series spectrophotometer. DNA purity was assessed by the 260/280 nm absorbance ratio, with values above 1.7 considered acceptable.
Genotyping was carried out on a Stratagene® Mx3000P Real-Time PCR platform (Agilent Technologies, Germany). Each 10 µL reaction contained 30 ng of gDNA, 5 µL of TaqMan® Genotyping Master Mix 2X, 0.5 µL of the specific TaqMan® SNP assay, and nuclease-free water. Cycling conditions included an initial denaturation at 95°C for 10 minutes, followed by 50 cycles of 95°C for 15 seconds and 60°C for 90 seconds. CYP2B6 c.516G>T (rs3745274) genotyping was performed using assay ID C_7,817,765_60. For UGT1A1*28, indirect genotyping was achieved via the rs887829 SNP (assay ID C_2,669,357_10), which is in near-complete linkage disequilibrium with the TA7 allele.

Statistical analyses
Associations between genotypes and adverse drug reactions were evaluated using univariate logistic regression in STATA 12.0 under three inheritance models: codominant, dominant, and recessive. For each outcome, the model providing the strongest statistical association was reported. Differences in proportions between groups were tested using χ^2 or Fisher's exact test as appropriate, with p-values <0.05 considered statistically significant.

Ethical considerations
This study was conducted following ethical standards and approved by the Ethics Committee of the Faculty of Medicine, University of Chile (September 5, 2016) and authorized by the SJDH director (Resolution No. 4855, September 23, 2016). All procedures adhered to the Declaration of Helsinki and relevant Chilean laws (20,120; 20,584; 19,628), as well as Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participants.

Results and Discussion

Baseline characteristics of the 67 patients living with HIV are presented in **Table 1**. The mean age was 35.7 ± 10.4 years, and the median age was 34 years. The largest age group was 30–39 years (35.8%). The cohort comprised 54 men (80.6%) and 13 women (19.4%). Regarding ART, 31 patients received EFV, 29 received ATV, and 7 patients switched between EFV and ATV during treatment; these individuals were included in both drug-specific analyses. Co-administered nucleoside reverse transcriptase inhibitors (NRTIs) for EFV regimens included abacavir/lamivudine (n = 21, 55.3%), tenofovir/emtricitabine (n = 13, 34.2%), and zidovudine/lamivudine (n = 4, 10.5%). For ATV-based therapy, patients received abacavir/lamivudine (n = 24, 66.7%), tenofovir/emtricitabine (n = 10, 27.8%), and zidovudine/lamivudine (n = 2, 5.6%).

Table 1. Baseline characteristics of the patients (*n* = 67).

Characteristic	Value
Age (years)	
Mean ± SD	35.7 ± 10.4
Median (range)	34
Age group, n (%)	
20–29 years	23 (34.3%)
30–39 years	24 (35.8%)
40–49 years	15 (22.4%)
≥50 years	5 (7.5%)
Sex, n (%)	
Female	13 (19.4%)
Male	54 (80.6%)
Antiretroviral Therapy (ART) Regimen	
Atazanavir (ATV)-based regimens (n = 36)	
+ Abacavir/lamivudine	24 (66.7%)
+ Tenofovir/emtricitabine	10 (27.8%)
+ Zidovudine/lamivudine	2 (5.6%)
Efavirenz (EFV)-based regimens (n = 38)	
+ Abacavir/lamivudine	21 (55.3%)
+ Tenofovir/emtricitabine	13 (34.2%)
+ Zidovudine/lamivudine	4 (10.5%)

SD, standard deviation; n, number of patients; ART, antiretroviral therapy; EFV, efavirenz; ATV, atazanavir.
[a] Seven patients received EFV and ATV in different treatment regimens.

A total of twelve distinct adverse drug reactions (ADRs) were documented from patients' clinical records, with their frequency stratified according to the administered drug **(Table 2)**. Hyperbilirubinemia was the most frequently observed ADR, accounting for 26.0% of all reported events, and occurred in 61.1% of patients receiving ATV. Gastrointestinal disturbances were reported in 18 patients (18.8%), while central nervous system (CNS)–related ADRs were identified in 15 patients (15.6% of all ADRs).

Table 2. Type of adverse drugs reactions in patients undergoing antiretroviral therapy with EFV or ATV.

Adverse Drug Reaction	Total n (%)	EFV-treated patients (n = 38)	ATV-treated patients (n = 36)
Hyperbilirubinemia*	25 (26.0%)	3	22
Gastrointestinal upset	18 (18.8%)	6	12
Rash	10 (10.4%)	7	3
Dizziness	13 (13.5%)	12	1
Nightmares	12 (12.5%)	11	1
Insomnia	5 (5.2%)	4	1
Headache	6 (6.3%)	3	3
Fever	2 (2.1%)	1	1
Anxiety	1 (1.0%)	1	0
Lipodystrophy	1 (1.0%)	1	0
Dyslipidemia	1 (1.0%)	1	0
Suicide attempt	2 (2.1%)	1	1
Any CNS symptom†	15 (15.6%)	13	2

ADR, adverse drugs reaction; CNS, central nervous system; EFV, efavirenz; ATV, atazanavir.
[a] Total bilirubin level >1.2 mg/dl.
[b] Nightmare, insomnia, anxiety, and suicide attempt were also grouped as CNS ADRs.

Although some adverse drug reactions (ADRs) were observed in both patient groups (EFV- and ATV-treated), CNS-related ADRs occurred significantly more often in individuals receiving EFV (χ^2 = 9.3924; p = 0.002). Conversely, hyperbilirubinemia (total bilirubin >1.2 mg/dL) was predominantly observed in patients treated with ATV (χ^2 = 23.4030; p < 0.0001). Importantly, the distribution of concomitant antiretroviral regimens between the ATV and EFV groups **(Table 1)** did not differ significantly (p = 0.592, Fisher's exact test).

Table 3 summarizes the genotypic and allelic distributions of the polymorphisms examined in this cohort. The minor allele frequencies were relatively high for both variants (CYP2B6 c.516G>T, T allele: 0.38; UGT1A1*28, TA7 allele: 0.36), providing adequate statistical power for subsequent association analyses.

Table 3. Genotype and allele frequencies in patients recruited for this study.

Genetic Variant	Genotype	All patients (n = 67) n (%)	EFV-treated (n = 38) n (%)	ATV-treated (n = 36) n (%)	Allele Frequency (All patients)
CYP2B6 c.516G>T (*6/*9)	G/G (wild-type)	26 (38.8%)	14 (36.8%)	—	f(G) = 0.62
	G/T (heterozygous)	31 (46.3%)	18 (47.4%)	—	f(T) = 0.38
	T/T (homozygous variant)	10 (14.9%)	6 (15.8%)	—	
UGT1A1 (*28 promoter repeat)	TA6/TA6 (wild-type)	31 (46.3%)	—	10 (27.8%)	f(TA6) = 0.64
	TA6/TA7 (heterozygous)	24 (35.8%)	—	18 (50.0%)	f(TA7) = 0.36
	TA7/TA7 (homozygous *28)	12 (17.9%)	—	8 (22.2%)	

n, number of patients; f, frequency; EFV, efavirenz; ATV, atazanavir.
[a] Indirect identification of the UGT1A1*28 allele using rs887829.

Among 36 individuals treated with ATV, seven developed notably high bilirubin levels, exceeding 3.1 mg/dl. Analysis revealed that patients carrying two copies of the UGT1A1*28 allele were at a markedly higher risk of this condition (recessive model: OR = 8.33, p = 0.023, 95% CI: 1.33–52.03). Other genetic models could not be evaluated due to too few cases. No patient reached bilirubin levels above 6.1 mg/dl.

When examining moderate and severe elevations of bilirubin (>1.9 mg/dl), the presence of UGT1A1*28 was significantly associated with increased risk under both codominant and recessive inheritance models (OR = 16.33, p = 0.028 and OR = 10.82, p = 0.036, respectively; **Table 4**). Common side effects, including headache, rash, and gastrointestinal discomfort, were not significantly related to this allele (data not shown).

Table 4. Relationship between UGT1A1*28 (TA7) and total bilirubin >1.9 mg/dl in patients on ATV, based on univariate logistic regression.

Inheritance model	Genotypes [a]	OR	*p*-value	95% CI
Codominant model	TA_6/TA_6	1.00	Ref	-
	TA_6/TA_7	1.87	0.456	0.36–9.63
	TA_7/TA_7	16.33	0.028*	1.35–197.77
Recessive model	$TA_6/TA_6 + TA_6/TA_7$	1.00	Ref	-
	TA_7/TA_7	10.82	0.036*	1.17–100.44
Dominant model	TA_6/TA_6	1.00	Ref	-
	$TA_6/TA_7 + TA_7/TA_7$	3.18	0.146	0.67–15.15

OR: odds ratio; CI: confidence interval; ref: reference; *p-value < 0.05.
[a] Indirect identification of the UGT1A1*28 (TA_7) allele using rs887829.

The same analysis was conducted in 38 patients receiving EFV. No significant associations were found between the genetic variants studied and hyperbilirubinemia, gastrointestinal symptoms, rash, headache, insomnia, or dizziness (data not shown). In contrast, nightmares were significantly associated with the CYP2B6 c.516G>T

polymorphism under both codominant and recessive inheritance models (OR = 12.00, p = 0.031 and OR = 7.14, p = 0.042, respectively). The dominant model, however, showed no significant effect **(Table 5)**.

Table 5. Univariate logistic regression between *CYP2B6* c.516G>T (rs3745274) and nightmares in EFV-treated patients.

Inheritance model	Genotypes	OR	*p*-value	95% CI
Codominant model	G/G	1.00	Ref	-
	G/T	2.31	0.367	0.37–14.21
	T/T	12.00	0.031*	1.25–115.36
Recessive model	G/G + G/T	1.00	Ref	-
	T/T	7.14	0.042*	1.08–47.42
Dominant model	G/G	1.00	Ref	-
	G/T + T/T	3.6	0.142	0.65–19.90

OR, odds ratio; CI, confidence interval; ref, reference; *p-value < 0.05.

Nightmares, insomnia, anxiety, and suicide attempts were collectively categorized as CNS adverse drug reactions (ADRs). Univariate logistic regression analysis revealed that the CYP2B6 c.516G>T variant was significantly associated with these CNS ADRs under both codominant and recessive inheritance models (OR = 30.00, p = 0.011 and OR = 14.99, p = 0.021, respectively). No significant association was observed in the dominant model **(Table 6)**.

Table 6. Univariate logistic regression between *CYP2B6* c.516G>T (rs3745274) and CNS toxicity (nightmares, insomnia, anxiety, and suicide attempt grouped) in EFV-treated patients.

Inheritance model	Genotypes	OR	*p*-value	95% CI
Codominant model	G/G	1.00	Ref	-
	G/T	3.00	0.229	0.50–17.95
	T/T	30.00	0.011*	2.19–410.99
Recessive model	G/G + G/T	1.00	Ref	-
	T/T	14.99	0.021*	1.52–148.31
Dominant model	G/G	1.00	Ref	-
	G/T + T/T	5.08	0.061	0.93–27.75

OR, odds ratio; CI, confidence interval; ref, reference; *p-value < 0.05.

In this study, the most common adverse effects observed in patients on antiretroviral therapy were hyperbilirubinemia (26.0%), gastrointestinal disturbances (18.8%), and central nervous system (CNS) symptoms (15.6%). This pattern aligns with earlier observations at the same hospital, where hyperbilirubinemia, gastrointestinal, and CNS effects were also predominant (19.7%, 21.1%, and 13.2%, respectively) [1].

Some adverse effects, such as gastrointestinal upset and headache, appeared across the patient population, whereas others were closely linked to specific treatments. For instance, CNS effects were primarily associated with EFV, while hyperbilirubinemia was largely seen in patients receiving ATV. Pharmacogenetic analysis confirmed that the CYP2B6 c.516G>T variant is strongly associated with CNS toxicity in EFV-treated patients. Similarly, UGT1A1*28 carriers receiving ATV were more likely to develop moderate to severe hyperbilirubinemia (total bilirubin >1.9 mg/dl).

Despite the high prevalence of gastrointestinal effects, univariate logistic regression did not reveal significant associations with CYP2B6 c.516G>T or UGT1A1*28 under dominant, codominant, or recessive models. Likewise, no significant link was found between genotypes and symptoms such as headache or fever.

CNS adverse reactions, including nightmares, insomnia, anxiety, and suicide attempts, are well documented but show variable prevalence (10–74%) and treatment discontinuation rates (2–11%) [2, 3]. In our cohort, nightmares were significantly associated with the T/T genotype of CYP2B6 c.516G>T under codominant (OR = 12, p = 0.031) and recessive models (OR = 7.14, p = 0.042), but not under the dominant model (OR = 3.6, p = 0.142), likely reflecting the limited sample size.

When CNS symptoms were analyzed collectively—including nightmares, insomnia, anxiety, and suicide attempts—the T/T genotype remained significantly associated with toxicity in both codominant (OR = 30.00, p = 0.011) and recessive models (OR = 14.99, p = 0.021), while the dominant model did not reach statistical significance (OR = 5.08, p = 0.061).

In this study, the UGT1A128 allele was observed at a frequency of 0.36, which is comparable to the 0.33 previously reported in a Chilean study on Gilbert's syndrome. In that study, the presence of UGT1A128 was inferred indirectly by analyzing the rs6742078 (G > T) variant in intron 1 of the UGT1A1 gene, which is in strong linkage disequilibrium with UGT1A1*28 [4]. These results are consistent with frequencies reported in other Latin American populations (Colombia: 0.34; Peru: 0.45; Mexico: 0.37) and European populations (0.30; 1000 Genomes Project), but differ from Asian populations, where frequencies of 0.16 have been documented [5].

For the CYP2B6 c.516G>T variant (rs3745274), genotype frequencies in our cohort were 38.81% for G/G, 46.27% for G/T, and 14.92% for T/T **(Table 3)**, closely matching a prior study in a Chilean EFV-treated population (G/G: 43%, G/T: 42%, T/T: 15%) [6]. The T allele frequency (0.38) also aligns with data from other Latin American populations, including Colombia (0.37), Mexico (0.31), and Puerto Rico (0.35), and is higher than European populations (0.24; 1000 Genomes Project).

Given the observed frequencies of CYP2B6 c.516G>T and UGT1A1*28 in Chile and the broader Latin American region, further studies are warranted to validate the CPIC guidelines for ATV [7] and EFV [8] in these populations. These guidelines recommend alternative therapies to prevent toxicity in patients with poor metabolizer genotypes (e.g., homozygous CYP2B6 c.516G>T) or reduced initial dosing for the same drug (e.g., efavirenz at 400 or 200 mg/day) [8].

Despite the relatively small sample size, we identified statistically significant associations between specific adverse reactions to ATV and EFV and the corresponding genetic variants (UGT1A1*28 and CYP2B6 c.516G>T, respectively), highlighting the importance of pharmacogenetic studies. Previous national research has similarly demonstrated a link between CYP2B6 variants and elevated plasma EFV levels [6].

This study has limitations. The modest number of participants may have limited the detection of other associations. Additionally, potentially relevant variants with lower evidence levels (e.g., CYP3A4/5, CYP2A6, SLCO1B1) were not analyzed. Missing clinical data and possible misclassification bias could also influence the observed associations between genetic factors and adverse reactions.

To our knowledge, this is the first study in Latin America assessing the relationship between these genetic variants and ADRs in antiretroviral therapy, providing an initial characterization of therapeutic outcomes in Chilean patients living with HIV.

Conclusion

Our results indicate that the UGT1A1*28 and CYP2B6 c.516G>T (rs3745274) genetic variants are associated with the development of moderate-to-severe hyperbilirubinemia and CNS toxicity in patients treated with ATV and EFV, respectively. While larger, prospective studies are needed to confirm these findings in our population, this preliminary evidence supports the use of pharmacogenetic-guided prescriptions in line with CPIC recommendations for EFV and ATV.

Ensuring adherence in people living with HIV remains essential for successful therapy. At the same time, optimizing the use of drugs often considered "unsafe" is important, as their effectiveness can be limited by concerns about adverse reactions. Pharmacogenetic research highlights that ADRs are influenced not only by the drug itself but also by individual patient genetics. By applying genotype-guided dosing strategies, highly effective therapies can be safely maintained.

Implementing and validating international pharmacogenetic guidelines in Latin American populations could enhance the precision of antiretroviral therapy, contributing to better treatment outcomes and supporting the achievement of the UNAIDS 90–90–90 targets.

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Conflict of Interest: None

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Ethics Statement: The studies involving human participants were reviewed and approved by the Ethics Committee of the Faculty of Medicine of the University of Chile. The patients/participants provided their written informed consent to participate in this study.

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