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Pharmacogenetic Implications in the Clinical Approach to Antiretroviral Therapy. a Systematic Review

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Abstract

Introduction: Medicine Based on the PharmacoGenomics (MBPG) of antiretroviral agents against HIV is undergoing key advances in recent years, which can optimize the efficacy and safety of these treatments and improve the quality of life of each patient in practice clinic.

Objective: To carry out a review based on the pharmacogenetic implications in the clinical response of antiretrovirals, to support decision-making, and contribute to the definition of new strategies in precision medicine.

Results: Of a total of 259 articles identified in the information search, 31 met the inclusion criteria. An association was found between abacavir, HLA-B*5701 and hypersensitivity; efavirenz and CYP2B6 QT prolongation; increased plasma levels of dolutegravir and raltegravir associated with UGT1A1; tenofovir, renal failure and ABCC.

Conclusion: Pharmacogomics in HIV is advancing rapidly. There are several antiretroviral treatments (ART) that should be monitored to improve clinical results and personalize drug treatment; It is necessary to implement more studies that include other variants (SNPs), adherence rates, pharmacoeconomics, and other biomarkers that confirm new genetic polymorphisms and their response associated with the efficacy and safety of ART.

Key words: Pharmacogenetics, Pharmacogenomics, HIV, antiretroviral therapy, precision medicin

Introduction

Antiretroviral therapy (ART) is the standard treatment for people infected with the human immunodeficiency virus (HIV), and has undergone significant advances in recent years [1]. It consists of a combination of several antiretroviral drugs that act at different stages of the HIV replication cycle, reducing the viral load in the body and preserving immune

function [2]. These drugs, which include reverse transcriptase inhibitors, protease inhibitors and integrase inhibitors, have been shown to be highly effective in suppressing HIV and preventing progression to advanced disease or the development of acquired immunodeficiency syndrome (AIDS) [3]. In addition, significant improvements have been made in the formulation of antiretroviral drugs, with the emergence of long-acting therapies, such as slow-release injections, which make it possible to reduce the frequency of administration to once every two months or even less [4]. These advances in ART have contributed to improving the quality of life of people living with HIV, as well as reducing the transmission of the virus through viral suppression [5].

Antiretroviral Drug Therapy

The antiretroviral agents used in the treatment of the HIV virus have undergone significant advances in recent years [1]. Currently, different classes of antiretroviral drugs are used, including nucleoside reverse transcriptase inhibitors (NRTIs - zidovudine, didanosine, stavudine, lamivudine, abacavir), non-nucleoside reverse transcriptase inhibitors (NNRTIs - nevirapine, efavirenz, etravirine, rilpivirine), protease inhibitors (PIs - ritonavir, lopinavir/ritonavir, atazanavir), and protease inhibitors (PIs - ritonavir, lopinavir/ritonavir, atazanavir), efavirenz, etravirine, rilpivirine), protease inhibitors (PIs - ritonavir, lopinavir/ritonavir, atazanavir, darunavir, saquinavir) and integrase inhibitors (II - raltegravir, elvitegravir, dolutegravir, bictegravir) [2]. These drugs act on various stages of the HIV replication cycle, preventing its multiplication and reducing the viral load in the body[3]. In addition, long-acting therapies have been developed, such as slow-release injections, which allow for less frequent administration of antiretroviral drugs, improving adherence to treatment [4]. Research advances continue to expand the therapeutic arsenal and improve the efficacy and safety of antiretroviral agents used in the management of HIV [6].

Pharmacogenomics

Pharmacogenomics studies the relationship between variations in DNA and RNA characteristics and drug response, not only to identify new therapeutic targets, but also to perform precision medicine, reducing the uncertainty of the variability and pharmacodynamic and kinetic behaviors of individual patients Other pharmacogenomic studies can be Used to identify patients who require different dosing schedules, either a higher dose to achieve efficacy or a lower dose, or suspension, to avoid greater toxicity In this context, therapeutic ineffectiveness and drug toxicity occur inadvertently in clinical practice, and even in patients with standardized drug treatment [7-13]. This is well known, due to genetic variations that generate changes in the enzyme system, and thus produce different phenotypic effects when treating a patient with HIV [14]. This dynamic can vary in each patient, which leads us to pause and formulate a new conceptualization of medicine, "geno-personalized medicine", guided by a new concept, "genomic-based medicine" (GBM) [15].

The identification of both environmental and genetic factors that influence pharmacokinetics and pharmacodynamics allows for more precise medicine, optimizing the efficacy of all drugs, especially antiretrovirals, and their implications in terms of toxicity, efficacy and even the relationship of phenotypic changes such as molecular and metabolic alterations, clinical risks or response to therapy, and depends on the variability in each patient with HIV (human immunodeficiency virus) and its interaction with ART. In addition, in HIV clinical practice, many other variables are involved, such as the cost-benefit of the therapy, biomarkers involved, the type of HAART therapy (Highly Active Antiretroviral Therapy), the latter can generate confounding variables that, when combining two or more drugs in a patient, can alter the behaviors and measurements of each implication, for example, interactions and metabolomics [16-21].

Currently, not all patients have access to a pharmacogenomic sequencing test, or genotyping with validated SNPs; but, expanding this use can be really useful from the initial approach of a patient with HIV by implementing precision medicine, which is becoming increasingly important in the personalization of care One of the main antiretrovirals studied in pharmacogenetics is abacavir, a nucleoside reverse transcriptase inhibitor, which causes hypersensitivity reactions in 5 to 13% of HIV patients [22-25]. The association between HLA-B*57:01 and abacavir hypersensitivity was reported in 2002 and replicated in subsequent studies It is therefore currently recommended to determine the presence of this biomarker before initiating a therapy that includes this drug [25-27].

The HLA-B57:01 polymorphism is an allele of the human leukocyte antigen (HLA) system that has received attention in medicine because of its association with severe adverse reactions to certain drugs. Individuals carrying HLA-B57:01 have been shown to have an increased risk of developing hypersensitivity reactions to drugs, particularly abacavir, an antiretroviral drug used in the treatment of human immunodeficiency virus (HIV) [28].

Studies have shown that approximately 5-8% of people of European descent carry HLA-B57:01, while this frequency is significantly lower in other ethnic populations [29]. It is important to note that the presence of HLA-B57:01 does not necessarily imply the development of adverse reactions, but its detection prior to initiating abacavir treatment allows precautionary measures to be taken. Screening for HLA-B57:01 polymorphism has become standard practice before initiating abacavir treatment. Genetic tests, such as polymerase chain reaction (PCR), are used to identify the presence of this allele [30]. In cases in which the presence of HLA-B57:01 is confirmed, it is recommended to avoid the use of abacavir and to consider therapeutic alternatives.

The identification and evaluation of genetic polymorphisms, such as HLA-B*57:01, are fundamental for personalized medicine and the prevention of adverse drug reactions. These advances make it possible to select the most appropriate treatments and improve safety and therapeutic efficacy in patients with HIV and other diseases [11].

In accordance with the aforementioned background, this review aims to update the evidence collected on the most relevant pharmacogenetic variables of antiretroviral therapy (ART), especially the drugs commonly used in first and second line according to different guidelines in order to support healthcare professionals and providers in decision making and contribute to the design of new precision medicine strategies, optimizing clinical outcomes and reducing the variability of pharmacological response [31].

Methods

Eligibility Criteria of Studies Selected in This Review

We included randomized controlled trials, cohort, case-control or cross-sectional studies, in full text, that reported on pharmacogenetic implications, molecular implications, metabolic, clinical risks or response to therapy, also according to FDA recommendations [17]. We excluded studies that had confounding variables or interactions with other non-ARTV drugs that could affect patient metabolism, studies in which the full text was not accessible, or studies on genetic variations unrelated to HIV. Studies published in English or Spanish were included. Although there is a conceptual difference between pharmacogenomics and pharmacogenetics, in this review we use the two terms interchangeably [32,33,26].

Search Strategy

Relevant articles were identified from Pubmed, Scielo, Lilacs and EBSCO Host, and EMBASE databases, published in a decade, from January 2009 to December 2019. Manual searches were also performed to access other study reports that were published in journals, proceedings, bibliographies of review articles, monographs, and sources other than those mentioned above such as Google Scholar.

Using MeSH-EMTREE terms, and search equations in both English and Spanish, we used the following abbreviated search strategy: ("pharmacogenetic" OR "pharmacogenomics") AND ("hiv" OR biomarker) AND ("abacavir" OR "ritonavir" OR "dolutegravir" OR "efavirenz" OR "raltegravir" OR "tenofovir" OR "nevirapine" OR "ataznavir" OR "lopinavir"). The literature search and selection of titles and abstracts were performed with one reviewer, duplicate records were eliminated, and the full texts of potentially relevant articles were retrieved.

Data Collection and Análisis

11Data were collected from the selected studies in a web-based questionnaire, using Surveymonkey, with methodology of controlled clinical trials, cohorts, case-control and cross-sectional studies, shown in Table 1, measuring the potential implications of pharmacogenetics and antiretroviral treatment. Scales such as JADAD for ECAS and some CASPe for the other studies were used for the analysis plan of the articles.

Drug	Number of studies	Number of accumulated patients
Abacavir[18,19]	2	334
Efavirenz[45,46,47,48,49,50,]	6	2786
Nevirapina[54,55,56]	3	2150
Tenofovir[58,59,60]	3	358
Atazanavir[63,64,62,65, 66]	5	2129
Lopinavir/r[67, 68,69,70,71]	5	1241
Darunavir/r[72]	1	75
Dolutegravir[76,, 78]	3	172
Raltegravir[77, 79 83]	2	64
Elvitegravir[77]	1	23
Total	**31**	**9332**

Table 1

Results

Of 259 articles identified in the information search, 31 met the above criteria (Figure 1). The summary of data and information collected on antiretroviral treatments (ART) is shown in Table 2. It includes pharmacogenetic testing of ARTs and valuable information for the future implementation of pharmacogenetics as a tool to optimize pharmacotherapy according to variations and polymorphic effects according to their clinical implication.

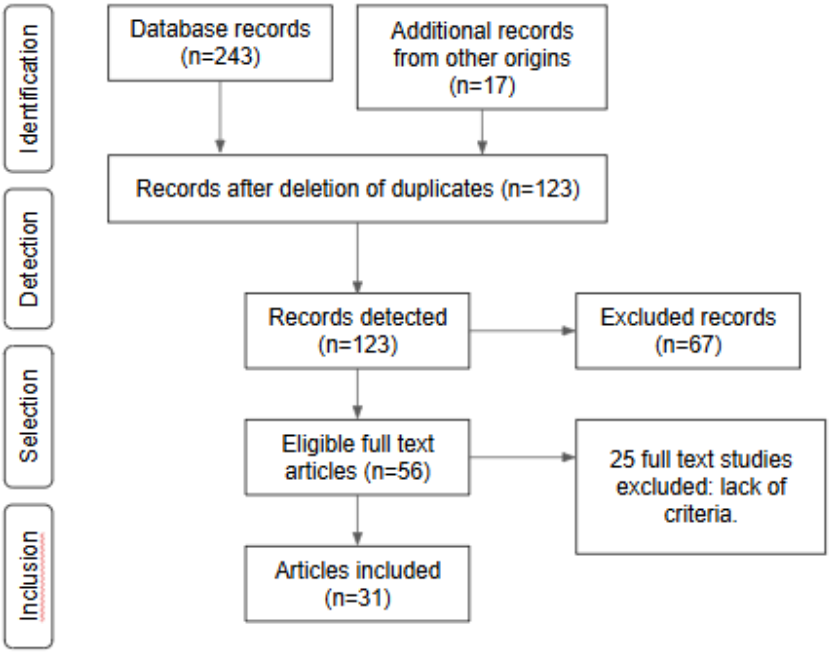

Figure 1

Drug	GEN	Main genetic variant (SNP) or allele involved	Associated effect
Abacavir[18,19]	HLA-B	HLA-B 5701 HLA-B 5703	Hypersensitivity reaction
Efavirenz[44,45,46,47,48,49,50]	CYP2B6	CYP2B6 516TT, CYP2B6 516GT	Neurotoxicity Increased plasma levels Neuropathies QT interval prolongation
	CYP2A9	*9B T>G (rs28399433)	Low EFV metabolism
	ABCB1	3435 C>T 2677 G>T/A	Associated with increased EFV plasma levels. Significant association with lower likelihood of virologic failure

	CYP3A5	6986 >G	Possible increase in plasma levels
Nevirapina[54,55,56,]	CYP2B6	516 G>T (rs3745274) 983 T>C (rs28399499)	Presence of polymorphism associated with varying degrees of neuropsychological toxicity. Associated with decreased NPV clearance
	HLA-DR	HLADRB1*0101	HSS and hepatotoxicity risk
	HLA-C	HLA-Cw*8	
	HLA-B	HLA-B*14	
	ABCB1 (MDR1/P-gp)	3435 C>Ta (rs1045642)	Low risk of hepatotoxicity
Tenofovir[58,59,60]	ABCC4 (MRP4)	3463A>G 4131 T>G o G>G	Associated with increased plasma TDF levels.
	ABCC2 (MRP2)	"CATC" haplotipo 24C>T (rs717620) 1249G>Aa (rs2273697) 3463T>A (rs8187694) 3972C>T (rs3740066) 24CT (rs717620)	Proximal tubule nephrotoxicity Increased TDF levels Possible association with Peripheral Neuropathy
	ABCC10 (MRP7)	526G > A 2759 C	Possible association with Pancreatitis Nephrotoxicity
Atazanavir[63,64,62,65,66]	UGT1A1	UGT1A1 *28 (Síndrome de Gilbert) rs6742078	Hyperbilirubinemia

	ABCB1 (P-gp)	3435 C>Ta (rs1045642)	C/C carriers have higher plasma ATV levels than patients with C/T or T/T genotypes.
Lopinavir[67, 68,69,70,71]	SLCO1B1 (OATP1B1)	521 T>C (rs4149056)	Increased plasma levels of LPV
Darunavir[72]	SLCO	SLCO3A1	Alterations in plasma levels
Ritonavir[65,69]	APOE	APOE, APOC3, APOA5, CETP, y ABCA1	Increased risk of severe hypertriglyceridemia
	APOC3	482 C>T, 455 T>C	Toxicity - hyperlipidemia
Dolutegravir[76,77, 78]	ABCG2	421 C>A (rs2231142)	Variations in plasma levels, (Increases plasma levels/Decrease in dolutegravir clearance).
	UGT1A1	UGT1A1. *28 Síndrome Gilbert	Variation in plasma levels, (Possible neurotoxicity) Possible CNS toxicity
	CYP2D6	rs1065852/rs3892097	
Raltegravir [77,79, 83]	UGT1A1 ABCG2 ABCB1	UGT1A1 *28/*28 ABCG2 421 CA/AA ABCB1 4036 AG/GG	Hyperbilirubinemia Increased raltegravir concentrations
Elvitegravir[77]	CYP3A4 CYP2C8 ABCC2 VKORC1	rs1058930 rs1058930 rs2273697 rs9934438	Neurotoxicity (sleep disturbances, fatigue)

APOC3: Apolipoprotein C-III ABCG: ATP-dependent transporters subfamily G ABCC: ATP-dependent transporters subfamily C APOE: Apolipoprotein C-E CYP: Cytochrome HLA-B: Human Leukocyte Antigen HSS: Hypersensitivity IFNL: Interferon lambda MDR: Resistance-associated protein OATP1: Organic anion transporter oligopeptide SLCO1: Solute carrier organic anion transporter. CNS: Central Nervous System UGT: Uridinadiphosphate glucuronyltransferase-hepatic enzyme VKOR: Vitamin K epoxide reductase. LPV: Lopinavir. TDF: Tenofovir . SNP: Single Nucleotide Polymorphism. UGT1A1: uridine diphosphate glucurunosyltransferase 1. EFV: Efavirenz. NPV: Nevirapine

Table 2

Hla-B 5701-Associated Hypersensitivity Reaction to Abacavir

The results of the association and mechanism studies on the interaction between HLA-B*57:01 antigen and abacavir-associated hypersensitivity imply that detection of HLA-B*57:01 has predictive value of clinical interest for patients prior to initiation of abacavir treatment. The study by Dr. Guo et al and Dr. Munderi et showed that the average incidence of abacavir-induced hypersensitivity is 2%, indicating a benefit of pre-treatment HLA-B*57:01 screening to reduce the incidence of this adverse event [18]. These results were confirmed in the United Kingdom and France, where the incidence of abacavir-induced hypersensitivity decreased from 12% to less than 0.5% after the introduction of HLA-B*57:01 screening [34]. In fact, the results of these studies suggest that HLA-B*57:01 screening is cost-effective, especially for populations with higher prevalence of HLA-B*57:01 (Example: Low prevalence: < 1% Africa; intermediate prevalence: Colombia 2,7%, Chile 2,7% a 3,7, Peru 2%, Argentina 4,8%; High prevalence: USA 5,6%, Mexico 2 to 6%, Spain 6,2% to 7%, Brazil 3,1-5,6%) [35-43]. Thus, depending on each population, it is suggested to perform a test prior to treatment with ABC, according to FDA recommendations, international HIV guidelines and even CPIC (Clinical Pharmacogenetics Implementation Consortium) [17,31,27].

Cns Neurotoxicity And/Or Qt Interval Prolongation Associated with Genetic Polymorphisms in Cyp2b6 In Patients Undergoing Efavirenz Treatment

Several studies show that there is a correlation between EFV neurotoxicity, CYP2B6 genotypes and slow metabolizers, e.g., the study by Kwara et al, evaluated the plasma concentration of efavirenz in 97 patients with HIV and CYP2B6 c.516TT genotype, describing a greater association in these genotypes and an increase in the plasma concentration of efanvirenz.Also the study by Sanchez et al [44-50]., presented similar results, identifying the CYP2B6 gene in 128 HIV patients as the main factor influencing increased plasma concentrations of EFV, which is associated with an increased risk of neurotoxicity and increased risk of QT prolongation by inhibition of the hERG gene (EFV at concentrations >0.4 µg/mL $p < 0.05$) [47,51-53].

Rash, Hepatotoxicity or Therapeutic Failure of Nevirapine, Associated with Genetic Polymorphisms in Cyp2b6 And Hla-Drb

Dickinson et al, observed a significant relationship between CYP2B6 c.983T, which directly affects NVP plasma levels related to therapeutic failure. However, it would not be necessary to adapt the dose of NVP according to ethnicity, as this would not reduce the risk of therapeutic failure or toxicity [54-56]. The association of HLADRB1*0101 with hypersensitivity to nevirapine is also associated with skin rash and hepatotoxicity the latter occurs within the first 12 weeks in 80% of patients with HLA-DRB1*0102, HLA-B*5801 These results suggest an association of HLA DRB class I and II alleles with nevirapine hepatotoxicity [55,57].

abcc-Associated Tenofovir Nephrotoxicity or Nephroprotection

According to the study by Dr Rungtivasuwan et al all polymorphisms were in HardyWeinberg equilibrium (x2, $p > 0.05$), however, in the multivariate analysis there was an independent association with a higher plasma concentration of tenofovir (p 0.05) in patients with low body weight, low glomerular filtration rate, concomitant use of ritonavir-boosted protease inhibitors or the ABCC4 4131T-G variant (TG or GG genotype). On the other hand, the study by Dr. Nishijima et alshowed in univariate and multivariate analyses a significant association between nephrotoxicity and the CC genotype at position -24 CC ([OR], 20.08; 95 % CI, 1.711-235.7; $P = 0.017$) and the AA genotype at position 1249 (OR 16.21; 95 % CI, 1.630-161.1; $P = 0.017$) of ABCC2. Multivariate analysis showed a higher adjusted OR for patients with both homozygotes (adjusted OR, 38.44; 95 % CI, 2.051-720.4; $P = 0.015$). These studies with their results suggest that patients carrying ABCC2 and ABCC4 gene polymorphisms may have part of the risk of developing tenofovir-associated tubulopathy [58-61].

Hyperbilirubinemia Due to Atazanavir, Associated with Polymorphisms in The Ugt1a1 And Abcb1 Genes

Of the 321 HIV patients evaluated in the study by Leger et al 4.6% had discontinuation of atazanavir-associated therapy due to hyperbilirubinemia. Among patients initiating atazanavir/ritonavir regimens, the slow metabolizing UGT1A1 rs88787829 T/T genotype was associated with increased discontinuation of atazanavir (higher risk in Caucasians than in blacks) [34,62-66]. The study of Johnson et al, also associated hyperbilirubinemia with hemoglobin levels and the presence of rs887829 UGT1A1[64,66].

Highest Systemic Concentrations of Lopinavir and Darunavir Associated with Genetic Polymorphisms in Slco

Hartkoorn et al evaluated the substrate specificities of these transporters on lopinavir pharmacokinetics in 349 patients with HIV, and established the genotype for the SNPs SLCO1A2, SLCO1B1 and SLCO1B3, showing an association between the 521T>C polymorphism of the SLCO1B1 gene and a significant increase in lopinavir plasma concentrations, although it was only observed in this gene and not in other functional variants such as SLCO1A2 and SLCO1B3. Kohlrausch et al showed evidence of an association between high lopinavir plasma concentrations and SLCO1B1-521T>C genotypes (P=0.03). The results of Lubomirov et al, also found two functional SNPs in SLCO1B1 and one functional SNP in ABCC2 associated with pharmacokinetic outcomes. Although the subanalysis confirmed that some of the significant variation in LPV clearance was attributed to fluctuation in ritonavir levels, the results of the subanalysis did not show any significant variation in the pharmacokinetic results was also associated with patients homozygous for the SLCO1B1 gene variant rs11045819 and other variants. On the other hand, it was evidenced that darunavir clearance was 12% lower

in patients with SLCO3A1 rs8027174 GT/TT genotypes, while homozygosity for the rs4294800-A allele was associated with a 2.5-fold higher central distribution volume, so that body weight influenced darunavir clearance, while alpha 1 acid glycoprotein concentrations influenced the volume of distrubution. In addition, SLCO3A1 polymorphism and darunavir pharmacokinetics were associated, possibly mediated by altered darunavir distribution [67-72].

Hypertriglyceridemia and Ritonavir-Associated Adipogenesis Linked to Apo

The study by Tarr et al conducted over three years in 329 patients in Switzerland, confirmed an association between single nucleotide polymorphisms (SNPs) in apolipoprotein C-III (APOC3) and hyperlipidemia. A group of patients carrying both APOC3 and APOE variants (5.8%) had a higher risk of severe hypertriglyceridemia due to ritonavir treatment. It has also been associated with increased adipogenesis, energy metabolism, and changes in arm fat [68,69,73-75].

Elevated Systemic Concentrations of Dolutegravir and Raltegravir Associated with Ugt1a1 And Other Biomarkers

Among these polymorphisms are those of UGT1A1 (uridine diphosphate glucuronosyltransferase 1) and the cytochrome P450 family CYP3A4, which metabolize dolutegravir and raltegravir in the liver [76-81]. In the study by Yagura et al it was found that plasma concentrations of dolutegravir in patients homozygous for UGT1A1 were significantly higher than those in patients carrying the normal allele (median, 1.43 and 0.82 µg/ml, respectively, $p = 0.0054$) [78]. Heterozygous patients also showed significantly higher values than those with the normal allele. Furthermore, according to these results, subjects carrying the UGT1A16, UGT1A128 alleles, or both, exhibit a higher cumulative incidence of adverse events than those carrying normal alleles ($p = 0.0454$) The study by Neely et al, described that certain UGT1A1 variants increase plasma concentrations of raltegravir [78,82]. It has also been shown that some UGT1A1*28 polymorphisms have a significant impact on raltegravir metabolism, characterized by higher plasma concentrations and a lower metabolic ratio [83]. Although this pharmacokinetic effect does not correlate with clinical adverse events, this association continues to be investigated.

Sleep Disorders With Elvitegravir77associated With Cyp3a4, Cyp2c8, And Other Biomarkers

Murrell et al, evaluated three integrase inhibitors, including elvitegravir, in 88 patients over 18 years of age [77]. The correlation between CYP and other related alleles (CYP3A4*22 rs35599367) describes an association of adverse events in the central nervous system (CNS) and gastrointestinal (GI) systems with certain CYP SNPs. For example, sleep disorders were 4.3% more frequent in these patients and may correlate with other studies showing slightly higher rates of around 15%, although still lower than with other integrase inhibitors [84,85].

Discussion

We observed that most of the studies included in this review provide clinically relevant information for daily practice, involving 11 antiretroviral medications. Although most studies have a limited number of patients and some measurement biases, their results are plausible, particularly due to the correlation between therapeutic response and genetic polymorphisms, as well as support from key regulatory agencies [17]. This highlights that certain genetic variations—such as genes coding for drug transport proteins, receptor expression or inhibition, or enzymatic metabolism systems—can significantly affect the efficacy and safety of antiretroviral regimens [86-88]. Other relevant variables include viral resistance, treatment adherence, drug distribution, and comorbidities.

Although there is strong evidence that pharmacogenomic monitoring may be associated with better clinical outcomes in HIV treatment, it is not yet a standard practice. The main barriers include the cost of biomarker testing, the time required, and the lack of expertise to properly conduct and interpret these tests [16]. Additionally, one of the major limitations of pharmacogenomic studies evaluating antiretroviral biomarkers is HAART therapy, meaning that combining two or more drugs may alter their pharmacological behavior—especially due to drug interactions and metabolomic effects which can introduce measurement bias or confounding, potentially explaining some of the inconsistent findings across studies [20,21]. Nevertheless, most results from this review align with the updated recommendations in drug labeling from regulatory agencies such as the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency of Japan (PMDA), and the United States Food and Drug Administration (FDA) the latter of which includes over 400 medications with proposed pharmacogenomic biomarker labeling [89,17].

Based on our findings, we see that abacavir (ABC), a nucleoside reverse transcriptase inhibitor used in HIV patients, has shown high efficacy and an acceptable toxicity profile for HIV treatment. However, one of its main known adverse events is hypersensitivity reaction (HSR), associated with ethnic and genetic background, and triggered by the human leukocyte antigen HLA-B57:01.25 On the other hand, studies on efavirenz show variable pharmacokinetic outcomes across ethnic groups, leading to conflicting results and diverse interpretations regarding the relationship between clinical outcomes and the genetic profiles of different populations Nonetheless, most evidence suggests that pharmacogenetic monitoring of CYP2B6 genotypes can be useful to predict and prevent elevated plasma concentrations of efavirenz, which are associated with increased HDL levels (linked to the ABCB1 genetic variant), or greater risk of QT interval prolongation (CYP2B66 allele), through inhibition of the hERG gene [18,25,44,45,53,52]. Individualized dosing of EFV based on therapeutic drug monitoring and CYP2B6 516G>T genotyping may enhance clinical care while reducing costs 18. Nevirapine, another non-nucleoside reverse transcriptase inhibitor used in combination with other ARTs, has shown pharmacogenomic associations with CYP2B6 and HLADRB1*0101, both linked to hypersensitivity and hepatotoxicity

Tenofovir disoproxil fumarate is a nucleotide reverse transcriptase inhibitor that is primarily eliminated via the kidneys through the multidrug resistance proteins MRP2 and MRP4, encoded by the ABCC2 and ABCC4 genes, respectively [55,57]. These proteins are expressed in the S2 segment of the proximal convoluted tubule and are believed to play a role in renal function when exposed to tenofovir. As one of the most widely used antiretroviral agents in HIV treatment regimens, close monitoring is crucial to avoid potential kidney damage. Therefore, stricter future monitoring and close renal surveillance are justified for patients treated with tenofovir, as well as pharmacogenetic monitoring of ABCC2 and ABCC4 polymorphisms, which appear to be associated with nephrotoxicity or nephroprotection [58-62]. Moreover, some authors, such as Dr. Wiriyakosol59 et al consider these types of monitoring to be cost-effective, helping to prevent imminent risk of renal failure [59].

Regarding protease inhibitors such as atazanavir, it is sometimes associated with hyperbilirubinemia, which can lead to early discontinuation of therapy. Therefore, UGT1A1*28 and CYP2B6 c.516G>T play a role in the development of moderate to severe hyperbilirubinemia. Other protease inhibitors that have been associated with elevated plasma concentrations and SLCO genetic polymorphisms (SoLute Carrier Organic) include lopinavir and darunavir. Organic anion-transporting polypeptides (OATP1B1 and OATP3B3), encoded by SLCO genes, are key hepatic transporters of several antiretroviral drugs. Thus, protease inhibitors are substrates for OATP1A2, OATP1B1, and OATP1B3, and these polypeptides are expected to play a fundamental role in the near future for the monitoring of protease inhibitors. In fact, the higher risk of adverse events in these patients (e.g., diarrhea) could be mitigated through the implementation of clinical pharmacokinetic software to individualize dosing in each patient[71], suggesting a link between SLCO3A1 polymorphisms and the pharmacokinetics of protease inhibitors [68-72].

Integrase inhibitors (IIs) such as dolutegravir or raltegravir have been associated with different behaviors depending on the patient's polymorphisms and increased plasma levels Another integrase inhibitor is elvitegravir, which is the least studied in pharmacogenomics to date, but may also be associated with adverse events and CYP-related polymorphisms, similar to other IIs Table 3 lists five antiretroviral drugs under pharmacogenomic monitoring according to the FDA, four of which match the findings of our review [80,81,85,17].

Drug	**Biomarker (Allele or SNP)**	**Phenotypic Implication**	**ATC**
Abacavir	HLA-B* (5701/5703)	HSS	J05AF06
Efavirenz	CYP2B6 (516TT / 516GT)	Adverse event	J05AG03
Dolutegravir	UGT1A1 (*28)	Dose/frequency	J05AX12
Raltegravir	UGT1A1 (*28/*28)	Dose/frequency	J05AX08

HLA-B: Human Leukocyte Antigen HSS: Hypersensitivity UGT1A1: uridine diphosphate glucuronosyltransferase 1. IFNL3: Interferon lambda 3. ATC: Anatomical, Therapeutic, Chemical/ Anatomical, Therapeutic Classification System. IL28B: gene now called IFNL3.

Table 3

The inclusion criteria regarding the article selection period and the use of MeSH-EMTREE terms for active compounds limited the scope of studies included in this review, which could restrict some conclusions. Additionally, in this regard, biomarkers for zidovudine (ABCC4/MRP4), UGT2B7*1C, and lamivudine (ABCC4/MRP4) were not included, although they have also been shown to influence plasma levels [45,87,90].

Despite the limitations of pharmacogenomic studies, these findings open new possibilities for integrating pharmacogenomics into clinical practice—not only for HIV, but also for other key therapies with similar implications—paving the way toward a more personalized and comprehensive approach to precision medicine (Figure 2) 26,91-94].

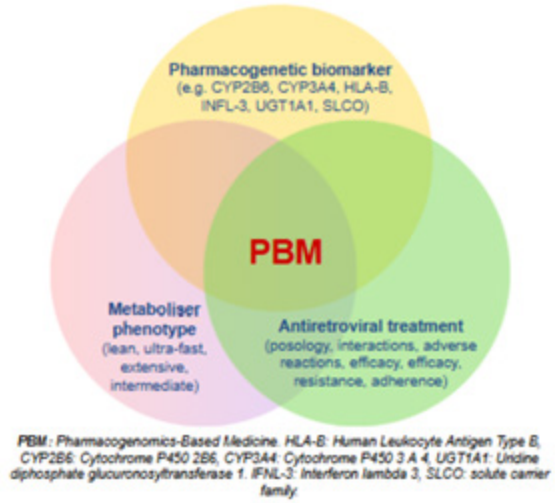

Figure 2

Conclusions

New technologies and the availability of cost-effective, next-generation methods for conducting and interpreting pharmacogenetic testing in HIV are rapidly advancing. As a result, the pharmacogenomic future of HIV and precision medicine appears promising, bringing us closer to genomics-based decision-making with more accurate and predictable outcomes. In this context, abacavir, efavirenz, dolutegravir, raltegravir, ritonavir, and tenofovir should be monitored through genomics-based medicine. However, the numerous genetic variants and the complexity of the disease and its treatment underscore the need for further studies that go beyond pharmacokinetic and pharmacodynamic variations and genetic mutations. Future research should also address viral resistance, viral reservoir mechanisms, specific individual genetic traits, pharmacoeconomics, pharmacodynamics, and levels of adherence to ART in order to confirm the correlation between these genetic polymorphisms and treatment responses—thus revealing new pathways forward [95].

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