Review

Personalized Medicine

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A pharmacist's role in the individualization of treatment of HIV patients

The pharmacological treatment of HIV is complex and varies considerably among patients, as does the response of patients to therapy, requiring treatment plans that are closely tailored to individual needs. Pharmacists can take an active role in individualizing care by employing their knowledge of pharmacokinetics and pharmacogenetics and by interacting directly with patients in counseling sessions. These strategies promote the following: maintenance of plasma concentrations of antiretroviral agents within therapeutic ranges, prediction of pharmacological response of patients with certain genetic characteristics, and clinical control of HIV through the correct use of antiretroviral treatments. Together, these strategies can be used to tailor antiretroviral therapy to individual patients, thus improving treatment efficacy and safety.

First draft submitted: 20 October 2015; Accepted for publication: 8 December 2015; Published online: 23 March 2016

Keywords: HIV • personalized medicine • pharmaceutical care • pharmacist's role • pharmacogenetics • pharmacokinetics

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AIDS was first identified in the USA in the summer of 1981, when the CDC announced the presence of unexplained pneumonia from the *Pneumocystis jirovecii* fungus (previously known as *Pneumocystis carinii*) and Kaposi sarcoma in five previously healthy homosexual men in New York and Los Angeles [1].

In the decades following this discovery, several treatment strategies have been developed to prolong the life expectancy and improve the quality of life of patients infected with HIV, the virus that causes AIDS. Nevertheless, it is still not possible to cure HIV infection, and patients today require prolonged pharmacological treatment that is complicated by adverse effects, drug resistance, drug interactions and the requirement for optimal and long-term adherence [2]. Furthermore, a patient's treatment plan may periodically change due to the appearance of drug toxicity and resistance resulting from mutations in the virus. These periodic treatment changes produce considerable uncertainty for clinicians and patients.

In addition to striving toward the development of a vaccine, therapeutic researchers have focused on finding new drugs or combinations of drugs that are less toxic, more cost effective and more tolerable to patients [3]. To achieve these goals, clinicians have implemented a number of strategies, including simplifying therapy [4,5], conducting genetic testing [6], and resistance testing [7] and maintaining antiretroviral plasma concentration within a range that has been deemed appropriate for each patient through personalized dosages [8].

Pharmacokinetics (PKs), pharmacodynamics (PDs) and pharmacogenetics must be carefully considered during antiretroviral treatment in order to reduce the variability of patient responses and determine the precise concentrations of antiretroviral agents needed to prohibit the replication

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of HIV [9–11]. Through therapeutic drug monitoring (TDM) of antiretroviral agents, it is possible to adjust dosages to maintain plasma concentrations within a therapeutic range, improving efficacy and reducing toxicity. Pharmacogenetics can help predict the pharmacological response in patients meeting certain genetic criteria, allowing clinicians to tailor antiretroviral therapy (ART) to individual patients. Additionally, adherence to ART affects the degree and duration of antiviral response [12–14], making patient education regarding the importance of adherence a key component of care.

This article reviews three principal tools that can be used by pharmacists to individualize HIV treatment: TDM, pharmacogenetics and personalized pharmaceutical care. Used together, these tools promote the optimized dosing of ART and improved clinical results.

PKs in the treatment of HIV patients

Monitoring antiretroviral plasma concentrations [15,16] plays a key role in the optimization of HIV treatment as evidenced by the relationship between drug exposure and efficacy and toxicity [17,18]. The primary objective of TDM in HIV patients is to tailor the dosage of antiretroviral agents for each patient in order to maximize the benefit of the prescribed treatment [19]. In some patients, TDM can be used to reduce the probability of drug toxicity, while in others it can be used to achieve desired therapeutic outcomes.

According to studies [20,21], 35–61% of patients receiving a standard dose of an antiretroviral agent do not achieve adequate plasma concentrations of the antiretroviral. The tendency to prescribe doses that are either too high or too low can be remedied by tailoring dosage according to the PK behavior of the drug in each patient.

Indications for TDM of antiretroviral agents

Treatment effectiveness can be reduced as a consequence of patient-related factors (e.g., lack of adherence and drug intolerance), drug-related factors (e.g., PK and PDs characteristics) and factors related to the virus (e.g., high levels of replication and mutation or the existence of latent reservoirs of virus). TDM can play a role in responding to each of these types of factors [4,5].

According to consensus documents [4–5,22–23], TDM is indicated for the treatment of HIV in order to promote adherence to ART, identify and control interactions, avoid toxicity, determine the initial ART treatment scheme and its modifications, establish unofficial or rescue doses, and optimize therapy in patients with renal or hepatic insufficiency, as well as in overweight, pregnant and/or pediatric patients. Given the evidence of TDM's effectiveness in meeting these objectives, many healthcare centers use TDM only in cases in which meeting these objectives is desired.

Antiretroviral agents suited for TDM

Generally speaking, dosage adjustments based on plasma concentration require the availability of tools capable of accurately measuring and analyzing plasma concentrations and are justified under certain pharmacological, PK and clinical criteria. These criteria include the availability of population PK data, high interpatient and low intrapatient variability in the relationship between dose and serum concentration, a close correlation between the plasma concentration of the agent and the concentration at the site of action, existence of a therapeutic range of plasma concentrations associated with maximum efficacy and minimal toxicity and a pharmacological effect dependent on plasma concentration [24].

The consensus among clinical pharmacists in the Europe and the USA [4,22] promotes the implementation of TDM for treatment with protease inhibitors (PIs) [25–27] and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [28–31]. Nevertheless, information regarding the relationship between concentrations and toxicities in these classes of antiretroviral agents is scarce; therefore, clinicians should consult up-to-date information regarding the therapeutic ranges for these agents.

In the case of entry inhibitors, only the CCR5 receptor antagonist maraviroc (MVC) has been demonstrated that minimal concentrations can be an important predictor of virological success [32]. However, clinical experience with TDM and MVC remains limited, as does the evidence available regarding TDM and integrase inhibitors (IIs). While there has been some evidence involving raltegravir (RAL) [33,34], it is not sufficient to make a concentration recommendation.

For nucleoside analog reverse transcriptase inhibitors (NARTIs), there is no solid or applicable evidence to date on PK/PD relationships in routine clinical practice. NARTIs are prodrugs that must be phosphorylated within cells in order to be activated; therefore, there is not a clear correlation between blood concentrations of these compounds and antiretroviral activity and potential toxicity [35]. Furthermore, these agents require a complex analytical technique and are associated with high intrapatient variability, complicating their use in clinical practice [5].

PK parameters

To date and for practical purposes, the minimum concentration at equilibrium (C^{ss}_{min}) appears to be the best PK indicator of suppression of viral replication accord-

ing to consensus among researchers [15,19,23,36–44]; however, the parameters of area under the curve and maximum concentration at equilibrium (C^{ss}_{max}) have also shown an acceptable correlation with clinical response [38–40]. When evaluating toxicity, measuring C^{ss}_{max} is preferred, as this parameter is more likely to be related with the presence of adverse effects.

Due to the difficulty associated with precisely measuring C^{ss}_{max} or C^{ss}_{min}, an estimation using the Bayesian method is most commonly used. In the context of clinical PKs, Bayes' theorem permits the identification of a quantitative relationship between the probability a priori of presenting certain values of PK parameters and the probability posteriori, once the concentrations of the drug are known [45]. Furthermore, the Bayesian method controls for diverse variables that influence the PK profile of a drug, such as pharmacological interactions.

Table 1 lists the principal PK parameters of each antiretroviral class that is suited for TDM; these parameters are updated periodically by the Liverpool HIV Pharmacology Group [43]. The characteristics that most influence PKs are also described for each family.

Non-nucleoside reverse transcriptase inhibitors

This class of antiretroviral agents has the benefit of a long half-life and low intrapatient variability. Monitoring these agents is particularly useful because dose adjustments help to avoid the rapid appearance of mutations that promote resistance [46], assuring longer lasting viral suppression. TDM also leads to a reduction of concentration-dependent side effects [4].

Protease inhibitors

This class of antiretroviral agents is characterized by low bioavailability, high affinity for plasma proteins and an extensive metabolism by the CYP3A4 enzyme [42]. Using a strategy called PK potentiation, PIs are typically administered along with ritonavir (RTV) or cobicistat (COBI), which inhibits the metabolic enzyme that metabolizes the PIs. RTV is a PI and it is administered in small doses (100–400 mg) for its inhibitory effect on the CYP450 enzyme, including predominately CYP3A4 and CYP2D6, and on P-gp. Due to this inhibitory effect, it is possible to obtain higher minimum concentrations of the antiretroviral agents and prolong their plasma half-lives [47]. This allows for lower and less frequent doses of the PIs, including at a frequency of once a day in the case of darunavir and atazanavir (ATV) [48,49].

With saquinavir (SQV) and lopinavir, the principal effect of RTV is to increase the bioavailability of PIs, while with amprenavir and indinavir (IDV), the principal effect is to prolong the PI's half-life [47].

COBI is a substrate and potent inhibitor of CYP3A, as well as a substrate and weaker inhibitor of CYP2D6; it is used in combination with elvitegravir (EVG). It is also used as a booster of some PIs as an alternative to RTV due to its ability to inhibit the membrane transporters P-gp, BCRP, OATP1B1 and OATP1B3 [50,51]. Both RTV and COBI interact with a high number of other drugs that are metabolized by the enzymes inhibited by the boosters.

Integrase inhibitors

This class of antiretroviral agents has been developed relatively recently with the exception of RAL; therefore, information on the PKs of these agents is limited. RAL and EVG are metabolized by UGT1A1, of which RAL is a weak inhibitor. EVG is also metabolized by the isoenzymes CYP3A and UGT1A3 and is weak inducer of CYP2C9. As previously mentioned, EVG is often boosted by COBI.

Dolutegravir (DTG) is also metabolized by UGT1A1 with minor contribution by CYP3A and is a substrate of P-gp. It is associated with few drug interactions [52]. While there are limited data available on TDM with DTG, its PK profile appears to be characterized by low variability [53]. A new II called cabotegravir may become the first long-acting parenteral drug of this class [54].

CCR5 receptor antagonists

MVC is one of the most sensitive metabolites of CYP3A4 with no significant involvement of the other CYP450 isoenzymes. MVC has a linear PK profile and therefore C^{ss}_{min} can be used as a reliable indicator of adequate drug dose [55].

Therapeutic index

The therapeutic index is the ratio between the maximum tolerated concentration and the minimum effective concentration [56]. Using PK/PD models, relationships between C^{ss}_{min} and virological failure [36–37,57–59] and between C^{ss}_{max} and toxicity have been established for a number of pharmacological classes [38–40]. These relationships are valid for naive patients, in other words, those who have not previously been treated by ART and are theoretically without resistance.

For patients previously treated with ART, the therapeutic index is more difficult to establish, given that it cannot be extrapolated from one group of patients to another [60]. Table 2 shows the consensus values of therapeutic indices for the majority of antiretroviral agents [23,27,61–63]. While therapeutic indices have not yet been established for DTG, EVG and rilpivirina (RPV), techniques for quantifying the plasma concentration of EVG and RPV have been validated [64,65].

Table 1. The principal pharmacokinetic parameters of each antiretroviral class.

Drug	Bioavailability (%)	Volume of distribution (l)	Plasma half-live (h)	Protein binding (%)	Renal excretion (unchanged, %)	Transporters	Main metabolizers routes
Protease inhibitors							
Atazanavir	68	NA	6.5 (8.6 with RTV)	86	7	P-gP, MRP, BCRP	CYP3A4
Darunavir	37; 82 (with RTV)	131 ± 49.9 (with RTV)	15 (with RTV)	95	1.2	P-gP	CYP3A4
Fosamprenavir	NA	6†	7.7 (15–23 with RTV)	90	<1	P-gP	CYP3A4
Indinavir	65	1.74†	1.4–2.2	60	<20	P-gP, MRP1	CYP3A4
Lopinavir	NA	NA	5–6	98–99	<3	P-gP, MRP1, MRP2, hOATP	CYP3A4
Nelfinavir	70–80	2–7†	3.5-5	>98	1–2	P-gP, MRP1, MRP2	CYP3A4, CYP2C19, CYP2D6
RTV	NA	20–40	3–5	98–99	3.5	P-gP, MRP1	CYP3A4, CYP2D6
Saquinavir	4	700	7–12	97	1–3	P-gP, MRP1, MRP2, hOATP	CYP3A4
Tipranavir	NA	NA	5.5–6	>99.9	<5	P-gP	CYP3A
Non-nucleoside reverse transcriptase inhibitors							
Delavirdine	85	0.8–1.0†	5.8	98	<5	NA	CYP3A4, CYP2D6
Efavirenz	NA	252	55	>99	<1	NA	CYP3A4, CYP2B6
Etravirine	NA	NA	41	99.9	<1.2	NA	CYP3A4, CYP2C9, CYP2C19
Nevirapine	91–93	1.1–1.3†	25–30	60	<3	NA	CYP3A4, CYP2B6
Rilpivirine	NA	152	50	99.7	<1	NA	CYP3A, CYP2A19
Other classes							
Dolutegravir	NA	17.4	14	99	<1	P-gP, BCRP	UGT1A1, CYP3A
Elvitegravir	NA	NA	12.9	98–99	7 with RTV	NA	CYP3A, UGT1A1, UGT1A3
Maraviroc	23–33	194	13.2	76	8–23	P-gP	CYP3A4
Raltegravir	NA	NA	9	83	9	NA	UGT1A1

†l/kg.
NA: Data not available; P-gP: P-glycoprotein; RTV: Ritonavir.

Table 2. The consensus values of therapeutic indices for each antiretroviral agent.

Drug	MEC (μg/ml)			MTC (μg/ml) upper limit
	Lower limit		Upper limit	
	Naive patients	Pretreated patients		
Protease inhibitors				
Amprenavir (fosamprenavir)	0.4	1.2	–	–
Atazanavir	0.15	0.15	–	–
Darunavir	0.55	2.2	–	–
Indinavir	0.1	0.75	1	10
Lopinavir	1.0	5	8	–
Nelfinavir	0,8	–	–	–
Saquinavir	0.1	0.1	–	–
Tipranavir	–	20.5	–	–
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz	1	–	4	–
Etravirine	–	0.052	–	–
Nevirapine	3	–	8	–
Other classes				
Maraviroc	0.025	0.050	–	–
Raltegravir	–	0.015	–	–

MEC: Minimum effective concentration; MTC: Maximum tolerated concentration.

Pharmacogenetics in the treatment of HIV patients

Like PKs, pharmacogenetics is an applied clinical research methodology that has as its objective: the maximization of effectiveness and minimization of toxicity by tailoring treatment to individual patients [66]. Pharmacogenetics research explores the mechanisms by which variability in patient outcomes can be explained by genetic characteristics. The principal sources of variability in the human genome are SNPs. While 10 million SNPs have been identified, it is estimated that 20 million exist, equating roughly to one SNP per 100–300 nucleotides [67–69].

Patients undergoing ART for HIV/AIDS present a high level of variability in immune system recovery, as well as adverse drug events (ADEs). Given this variability, it is believed that individuals are genetically predisposed to developing certain ADEs. Accordingly, pharmacogenetics in ART has as its objectives to identify correlations between genotypes and clinical phenotypes, to identify patients at high risk of suffering ADEs or experiencing different treatment responses, to tailor treatment to individual patients – in other words, determine the right drug at the right dose for the right patient – and to improve the efficacy of antiretroviral agents and decrease the intensify of ADEs.

Recent advances in pharmacogenetics and pharmacogenomics have allowed for the identification of genetic markers that influence patient response to pharmacological agents and drug toxicity. Given these advances, in the near future it may be possible to tailor ART to individual patients considering their genetic profiles.

Pharmacogenetics in the response to ART

Variability in patient response to pharmacological agents has both PK and PDs components. Consequently, genetic variations in certain proteins involved in the transport, metabolism and mechanism of action of antiretroviral agents can influence both the efficacy and toxicity of these drugs.

Polymorphisms in drug-metabolizing enzymes

Polymorphisms in drug-metabolizing enzymes may have the following consequences: increase or decrease of the effective dose, lengthening or shortening of the duration of therapeutic effect, ADEs, drug toxicity and drug–drug interactions.

CYP450

The principal isoenzymes involved in the metabolism of antiretroviral agents are CYP1A2, CYP3A4, CYP3A5, CYP2C19, CYP2D6, CYP2A6 and CYP2B6. The

majority of polymorphisms are rare in the general population, and some are found only in certain ethnic groups.

Subclass CYP1A2

CYP1A2 is an important metabolizing enzyme in the liver, comprising approximately 13% of all CYP proteins. There are over 100 substrates identified for CYP1A2, including many clinically important drugs, procarcinogens and endogenous substrates. However, compared with other CYPs, there have been relatively few reports of pharmacogenetics relationships. However, a recent study suggests that the *CYP1A2* g.-163C>A polymorphism is associated with HIV disease progression in Zimbabwean HIV-infected patients treated with nevirapine (NVP) [70].

Subclasses CYP3A4 & CYP3A5

PIs are the principal class of antiretroviral agents metabolized by CYP3A4. PIs are also potent inhibitors of this enzyme. Additionally, some NARTIs are metabolized by these isoenzymes but to a lesser degree. The most relevant polymorphisms *CYP3A4*1B* (-392 A>G), *CYP3A5*3* (6986 A>G) and *CYP3A5*6* (14690 G>A) and their relationships with the PKs of efavirenz (EFV), nelfinavir (NFV), IDV, SQV and lopinavir/RTV have been evaluated in various studies. Studies to date have not yet demonstrated a significant effect of these polymorphisms on the PKs of EFV or NFV [71,72]. However, an association between *CYP3A5*3* and a decrease in the urinary excretion of SQV has been found but additional studies are needed to confirm this effect [73].

Subclass CYP2C19

Currently, the most relevant polymorphisms are *CYP2C19*2* and *CYP2C19*3*, which are responsible for 95% of the slow metabolizer phenotypes. These polymorphisms are more frequent in whites (3–13%) than in Asians or blacks. Regarding the PKs of antiretroviral agents, only *CYP2C19*2* (681G>A) and its involvement in the metabolism of EFV, etravirine (ETR) and NFV have been studied. In the case of EFV, no relationship has been found; however, plasma concentrations of NFV were found to be higher in individuals who were heterozygotes or homozygotes for the rare allele [72]. In the case of ETR, patients carrying the allele *CYP2C19*2* presented a 23% lower clearance compared with patients who were not carriers [74].

Subclass CYP2D6

The *CYP2D6* gene is highly polymorphic. Due to its genetic polymorphisms, it is possible to find individuals with different metabolizing capacities with race being one of the key factors influencing this variability. In this subclass only nonfunctional SNPs, which include *CYP2D6*3* (2549 A>del), *CYP2D6*4* (1846 G>A) and *CYP2D6*6* (1707 T>del), and their relationship with the PKs of EFV and NFV have been studied. The results of these studies demonstrate that individuals who are homozygotes or heterozygotes for these polymorphisms present elevated plasma concentrations of both drugs [75].

Subclasses CYP2B6 & CYP2A6

The isoenzyme CYP2B6 is involved primarily in the metabolism of NNRTIs and presents various genetic polymorphisms with higher frequency in blacks. Numerous SNPs have been identified in the gene that codes for CYP2B6 that are related with an increase in plasma concentrations of EFV and NVP. Those that have shown a higher clinical relevance include *CYP2B6*6* (516G>T) and *CYP2B6*16* (983 T>C), which can produce a 75% decrease in enzyme activity [76,77].

UDP-glucuronyl transferase (UGT or UDPGT)

Within this class, UGT1A1 is the specific enzyme that catalyzes the conjugation of bilirubin. In the case of antiretroviral agents, a number of polymorphisms have been studied to confirm their relationship with hyperbilirubinemia, a condition present in a considerable percentage of patients treated with ATV or IDV. The results of these studies show that the polymorphism most closely related with hyperbilirubinemia is *UGT1A1*28*, which reduces the activity of the enzyme in individuals who are homozygotes for the rare allele [78]. Recently, genetic polymorphisms of the isoenzyme UGT2B7 have also been studied. This enzyme has been observed to be the principal enzyme involved in the *N*-glucuronidation of EFV [79].

Polymorphisms in transporter proteins

Transporter proteins play a role in the oral absorption of drugs, as well as in their passage through the digestive system, the blood–brain barrier, excretion of bile and urine, and in the access to certain tissues.

P-glycoprotein

Key polymorphisms include 3435 C>T and 2677 G>T/A, which are associated with a decrease in the expression of P-gp. A number of studies have been conducted with the aim of establishing a relationship between these polymorphisms and the PKs of various PIs and EFV; however, the results of these studies have not been conclusive [80,81].

Multidrug resistance proteins

Multidrug resistance proteins (MRPs) are coded by the genes *ABCC1*, *ABCC2*, *ABCC3* and *ABCC4*.

MRP1 and MRP2 are charged with the transport of organic anions, including PIs, while MRP4 and MRP5 are charged with the transport of adefovir, tenofovir (TDF) and various NNRTIs (lamivudine, stavudine, among others). The most relevant polymorphism is 3463 A>G in the gene that codes for the MRP4 protein, which is related with the PKs of TDF [82].

Transporters of organic anions & cations

The transporters of organic anions and cations have as substrates a number of antiretroviral agents, including TDF, and different NNRTIs and PIs. These transporters are coded by the gene *OAT1* (SLC22A6), whose various polymorphisms, including 453 G>A and 728 G>A, and their relationship with the PKs of TDF have been studied [82]. Nevertheless, researchers have not yet identified a relationship.

The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) [83] is a pharmacogenomics knowledge resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene–drug associations and genotype–phenotype relationships. PharmGKB collects and disseminates knowledge about the impact of human genetic variation in drug response. Table 3 summarizes the most relevant genetic polymorphisms involved in the metabolism and transport of antiretroviral agents as a tool for individualizing HIV therapy in clinical settings (modified and updated version of Álvarez Barco and Rodríguez Nóvoa [84]).

Toxicogenetics of antiretroviral agents & their clinical application

One of the most important advances that has been made in the field of pharmacogenetics has been the identification of genetic markers associated with an individual's risk of developing certain adverse effects of ART. Accordingly, genetic markers have been identified that are related with the risk of developing neurotoxicity with EFV, hypersensitive reactions to abacavir (ABC) and NVP, hyperbilirubinemia with ATV and IDV, peripheral neuropathy and lactic acidosis with NARTIs, and renal toxicity with TDF. Table 3 summarizes the key polymorphisms in enzyme metabolizers and transporters that are related with adverse effects of antiretroviral agents [84].

Some of the most relevant gene-variant associations include:

- The hypersensitivity reaction to ABC is strongly associated with the presence of the *HLA-B*5701* allele and is the best example of the usefulness of employing pharmacogenetics in clinical settings. The mechanism underlying ABC hypersensitivity syndrome is related to the change in the *HLA-B*5701* protein product. ABC binds with exquisite specificity to *HLA-B*5701*, changing the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides that can bind to *HLA-B*5701*. In this way, ABC guides the selection of new endogenous peptides, inducing a marked alteration in 'immunological self'. The resultant peptide-centric 'altered self' activates ABC-specific T-cells, thereby driving polyclonal CD8 T-cell activation and a systemic reaction manifesting as a hypersensitivity reaction [85]. The genetic test for this allele has been demonstrated to be cost effective, and current guidelines for ART recommend screening for *HLA-B*5701* prior to initiating treatment with ABC [4,5]. However, among sub-Saharan black Africans, *HLA-B*5701* is virtually absent [86], so for this group, genetic testing is not recommended;

- In the case of ATV, the most relevant polymorphisms are those affecting UGT1A1 and P-gp activity. Polymorphisms in the P-gp influence ATV plasma concentrations, which are related with clinical response and increases in bilirubin plasma levels [78,87,104,133]. This is particularly important when ATV is administered in those pretreated patients for whom greater ATV concentrations may be required to inhibit virus replication, as well as in those patients with Gilbert's syndrome. Genotyping for *UGT1A1*28* and screening for the *ABCB1* 3435C>T polymorphism would identify HIV-infected individuals at risk of developing hyperbilirubinemia, which could decrease episodes of jaundice;

- Regarding NNRTIs, *CYP2B6* 516G>T, 983T>C, 785A>G and 21563C>T SNPs have been associated with greater EFV plasma exposure and the development of more severe CNS effects in different HIV-infected populations. The identification of patients who are slow metabolizers of EFV would allow for reduced doses, which could prevent toxicity [105–107,125] and the appearance of resistance following drug discontinuation [102]. Being a carrier of the class II allele *HLA-DRB1*0101* has been linked with NVP-associated hepatotoxicity and hypersensitivity reactions in HIV-infected western Australians, especially in those individuals with a CD4 cell count >25% [134];

- In the case of TDF, while the precise mechanism that produces renal tubular dysfunction has yet to be established, it is possible that genetic factors

Table 3. Summary of most relevant genetic variants that affect antiretroviral pharmacokinetics and toxicity.

Antiretroviral drug class	Drug	Gene (protein)	Variants	SNPs	Clinical impact		Clinical relevance	Ref.
					Efficacy	Toxicity		
PIs	ATV	*UGT1A1* (UGT1A1)	*28	8175347	No	Yes	Higher risk of hyperbilirubinemia	[77,85–87]
				887829		Gilbert's syndrome. Increased levels of bilirubin		
		ABCB1 (P-gp)	3435C>T	1045642	Yes	No	ATV minimum effective concentration = 0.15 µg/ml. Risk of subtherapeutic levels in TT carriers	[85,88–89]
			2677G>T	2032585	Lower ATV plasma levels			
		NR1I2 (PXR)	63396C>T	2472677	Yes		Risk of subtherapeutic levels in TT carriers	[90,91]
					Lower ATV plasma levels			
	LPV	*SLCO1B1* (OATP1B1)	521T>C	4149056	Yes	No	–	[92–95]
					Higher LPV plasma levels with CC genotype			
NARTIs	ABC	*HLA-B* *HLA-B*57:01*	NA	–	No	Yes	Abacavir HSR	[96,97]
		HLA complex P5 (HCP5)	335T>G	2395029	No	Yes	Alternative marker for screening of individuals at risk for ABC-HSR	[98–101]
	TDF	*ABCC2* (MRP2)	CATC haplotype (-24, 1249, 3563, 3972) -24CC	717620	No	Yes	*CATC* haplotype associated with greater risk of KTD -*24CC* associated with higher risk of KTD	[102,103]
				2273697	No	Yes		
				8187694				
				3740066				
				717620				
		ABCC4 (MRP4)	3463A>G	1751034	Yes	No	–	[81]
					Higher intracellular TFV-DP			
		ABCC4 (MRP4)	-669C>T	899494	No	Yes	Risk for KTD	[102]
		ABCC10 (MRP7)	Intron-4	9349256	No	Yes	Urine phosphate wasting and β2-microglobulinuria	[102]

ABC: Abacavir; ATV: Atazanavir; EFV: Efavirenz; HSR: Hypersensitivity reaction; II: Integrase inhibitor; KDF: Kidney tubular dysfunction; LPV: Lopinavir; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NARTIs: Nucleoside analog reverse transcriptase inhibitors; NA: Not applicable; NVP: Nevirapine; P-gP: P-glycoprotein; PIs: Protease inhibitors; RAL: Raltegravir; TDF: Tenofovir.
Data taken from [84].

Table 3. Summary of most relevant genetic variants that affect antiretroviral pharmacokinetics and toxicity (cont.).

Antiretroviral drug class	Drug	Gene (protein)	Variants	SNPs	Clinical impact		Clinical relevance	Ref.
					Efficacy	Toxicity		
NNRTI	EFV	*CYP2B6* (CYP2B6)	516G>T	3745274	Yes Higher plasma levels	Yes CNS adverse effects	EFV range: 1-4 µg/ml TT genotype associated with more risk for CNS adverse events	[104–108]
			785A>G	2279343	Yes Higher plasma levels	Yes CNS adverse effects	Genotype 516/983 associated with increased CNS events	[108–112]
			983T>C	28399499	Yes Higher plasma levels	Yes CNS adverse effects	Genotype 516/983 associated with increased CNS events	[108,111–112]
			*1/*1 haplotype		Yes Lower plasma levels	No	In patients receiving antituberculosis treatment	[113]
		ABCB1 (P-gp)	3435C>T	1045642	Controversial influence in plasma EFV levels	Yes Higher HDL-cholesterol in Spanish populations	Decreased likelihood of virologic failure and decreased emergence of resistant virus	[74,114–117]
		CYP2A6	-48T>G	28399433	Yes Higher plasma levels	Yes CNS adverse effects	In black and white, but not in Hispanic individuals from the USA	[78]
		UGT2B7	735A>G	28365062	Yes Higher plasma levels	Yes CNS adverse effects	In black and white, but not in Hispanic individuals from the USA	[78]
	NVP	*CYP2B6* (CYP2B6)	516C>T	3745274	Yes Higher plasma levels	No	–	[104,118–120]
			983T>C	28399499	Yes Higher plasma levels	Yes	Stevens–Johnson syndrome or toxic epidermal necrolysis, but no other HSR	[112,121–122]

ABC: Abacavir; ATV: Atazanavir; EFV: Efavirenz; HSR: Hypersensitivity reaction; II: Integrase inhibitor; KDF: Kidney tubular dysfunction; LPV: Lopinavir; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NARTIs: Nucleoside analog reverse transcriptase inhibitors; NA: Not applicable; NVP: Nevirapine; P-gP: P-glycoprotein; PIs: Protease inhibitors; RAL: Raltegravir; TDF: Tenofovir.
Data taken from [84].

Table 3. Summary of most relevant genetic variants that affect antiretroviral pharmacokinetics and toxicity (cont.).

Antiretroviral drug class	Drug	Gene (protein)	Variants	SNPs	Clinical impact		Clinical relevance	Ref.
					Efficacy	Toxicity		
NNRTI (cont.)		*ABCB1* (P-gp)	3435C>T	1045642	No	No	T allele associated with lower risk of hepatotoxicity	[123,124]
		HLA-DR	*HLA-DRB1*0101*	–	No	Yes HSR	Greater risk for HSR	[125,126]
		HLA-C	*HLA*-Cw*8	–	No	Yes HSR	Greater risk for HSR	[127,128]
		HLA-B	*HLA*-B3505	–	No	Yes	NVP skin rash	[129]
II	RAL	*UGT1A1*28* [A(TA7)TAA]	**28*	8175347	No	No	–	[130,131]
		ABCB1 (P-gp)	3435C>T	1045642	Yes	No	T allele is associated with lower RAL plasma exposure	[132]

ABC: Abacavir; ATV: Atazanavir; EFV: Efavirenz; HSR: Hypersensitivity reaction; II: Integrase inhibitor; KDF: Kidney tubular dysfunction; LPV: Lopinavir; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NARTIs: Nucleoside analog reverse transcriptase inhibitors; NA: Not applicable; NVP: Nevirapine; P-gP: P-glycoprotein; PIs: Protease inhibitors; RAL: Raltegravir; TDF: Tenofovir.
Data taken from [84].

may facilitate this dysfunction, whose main clinical consequence is phosphate waste that can ultimately lead to osteopenia and osteoporosis. It has been recently demonstrated that certain genetic polymorphisms in the regions that code for the transporter proteins MRP2 (*ABCC2*) and MRP4 (*ABCC4*) are associated with differences in urinary excretion of TDF and the probability of development renal failure [82,135–136]. In this regard, information derived from pharmacogenetics studies may help to identify the subset of individuals at greater risk for developing more severe renal injury and loss of bone density.

Pharmaceutical care of HIV patients

The objective of pharmaceutical care of HIV patients is to achieve adequate clinical control of the virus through the proper use of prescribed antiretroviral agents [137]. To achieve this objective, a pharmacist should possess deep knowledge of pharmacotherapy, the physiopathology of the disease, the methodology of pharmaceutical care and the methodology of clinical interviewing. However, the acquisition of this knowledge does not guarantee success; it is necessary to possess communication and team-working skills and to assume a proactive, empathetic and convincing attitude. To provide quality care to patients with HIV/AIDS, procedures should be established that promote care that is tailored to the characteristics and needs of each patient.

Pharmaceutical care activities

The American Society of Hospital Pharmacists has established in a document of recommendations of the principal actions that can be taken by pharmacists working as members of clinical care teams [138]. These recommendations are supported by a number of previous documents of consensus and apply to both ambulatory patients in general and HIV patients specifically [139–142]. These documents recommend that pharmacists complete systematic evaluations of drug interactions, adherence and adverse effects, and take actions aimed at detecting, preventing and resolving other problems related with the effectiveness and safety of prescribed medications.

Both ART and strategies to tailor treatments to individual patients have advanced continually over the past 30 years [143], leading to a base of evidence regarding the actions that pharmacists can take to anticipate the needs of their increasingly informed and inquisitive patients [144]. The actions of pharmacists caring for patients with HIV have been associated with improved patient outcomes, including enhanced adherence [145], reduced pill burden and dosing frequency, greater

increases in CD4 cell counts, higher rates of viral suppression [146–148] and reduction of medication errors [149,150].

Promotion of adherence in ART

Patient adherence to prescribed treatment involves a complex process that first includes a patient accepting his/her diagnosis and recognizing the need to take his/her medication correctly. It also requires education to assure that the patient is able to correctly administer the medication and respond to any difficulties that may arise during treatment [151].

Medication adherence is a crucial factor affecting the extent and duration of response to combination ART [4]. Suboptimal adherence to any component of HIV therapy may produce lasting consequences, including increased viral load, development of resistance, reduced efficacy of future combination therapy, increased risk of hospital admission, more rapid progression to AIDS and decreased survival [4,152–153]. Data obtained from studies following patients treated with the first combination therapies used in the treatment of HIV (which included nonpotentiated PIs) showed that obtaining maximum efficacy requires near perfect adherence (>95%) [154]. However, recent studies suggest that with lower levels of adherence (75%), it is still possible to reach the therapeutic index during treatment with NNRTIs or PIs boosted with RTV [155–157]. Despite this, all studies agree that with each increment in adherence level, viral suppression increases and progression of the disease slows. These studies also emphasize the importance of maintaining adherence over the long term.

In a worldwide meta-analysis of 84 observational studies, only 62% of adults with HIV achieved adherence to ART of at least 90% [158]. Therefore, a major goal is to increase adherence rates, and pharmacists are uniquely positioned to help patients achieve this objective. However, a number of factors may complicate a patient's ability to take their combination ART as prescribed; therefore, it is essential that pharmacists recognize these factors and develop strategies to overcome them. Effective strategies may include utilization of once-daily regimens, single-tablet fixed-dose combinations, reminder alarm devices, text message alerts, pill organizers, dose planners and one–one–one support in an interdisciplinary team environment [159,160].

A number of studies [146–148] have shown significant gains in the level of adherence and clinical response of patients participating in dedicated pharmaceutical care programs. Furthermore, a recent meta-analysis [161] that evaluated four randomized controlled trials indicated that improvements in ART adherence and treatment efficacy may be greater in populations with initially lower adherence and greater vulnerability, when these patients participate in pharmaceutical care interventions. Considering this evidence, the implementation of pharmaceutical care programs that include adherence evaluation and long-term personalized care is essential to increasing adherence to ART and improving patient outcomes.

Counseling & patient education

The Global AIDS Program of the WHO defines counseling as the dynamic communication process through which one person helps another in an atmosphere of mutual understanding. This process relies on communication abilities and strategies to facilitate decision-making and problem-solving. Pharmacists need to be aware of these issues and take into account the communication style and literacy level of each patient when providing counseling. The ultimate goal of a counselor is to develop a more personal and trusting relationship with the patient, so that the patient feels comfortable and cared for and thus more willing to discuss any and all issues regarding his or her diseases and treatment in a confidential, nonjudgmental, nonpunitive relationship with the pharmacist [162].

Counseling should address practical topics and include advice, for example, on whether to take a medication with or without food and on which foods could affect absorption. Discussions about the adverse effects of medications should be presented in a balanced manner with emphasis on the benefits of therapy and strategies for managing nuisance side effects. Patients benefit from counseling regarding proactive strategies to minimize the risk of resistance if doses are missed. Written materials can also help patients retain the information [4].

The pharmacist can also be a referral source for other support and educational tools that may be of interest and useful to the patient, such as websites with drug information or other patient-related information and community support groups. Furthermore, a number of mobile applications have been developed that aim to improve adherence by educating patients and facilitating communication with the healthcare team [163–166].

From providing counseling on vitamins, alternative medicine and safer sex practices to educating patients on treatment, aging and lifestyle changes to manage co-morbidities, pharmacists can act as the healthcare providers who consolidate information and relay it simply and efficiently to patients in counseling sessions.

Complementary strategies to individualize care of HIV patients

The pharmacological treatment of HIV is complex and specific to each patient, requiring cooperation

among a multidisciplinary healthcare team. In these teams, pharmacists play an important role, employing knowledge of PKs and pharmacogenetics and interacting directly with patients through pharmaceutical care programs.

As previously mentioned, TDM of antiretroviral agents is useful for detecting drug interactions [167], optimizing patient exposure to the medications, avoiding and controlling adverse effects and maintaining treatment efficacy [168]. Furthermore, TDM is a direct indicator of adherence [151] and can be used in conjunction with other adherence evaluation tools used in routine pharmaceutical care, such as self-administered questionnaires and dispensation records. Pharmaceutical care, by providing the pharmacist with a more exhaustive knowledge of the patient, allows for a more accurate interpretation of plasma concentrations obtained through TDM and for dosage adjustments to optimize treatment. Additionally, pharmaceutical care can promote patient education regarding dosage changes and the need to strictly follow therapy during these times.

Pharmacists can also use information regarding the presence of alleles associated with drug disposition and response to certain antiretroviral agents to guide dosage adjustments and the selection of appropriate alternative therapies [66], leading to better treatment designs and predictive profiles for certain genotype-identified patient subpopulations.

The three tools discussed in this paper are complementary and can be used together to individualize care. For example, pharmaceutical care can serve as the initial point of detection of problems with ART, while TDM and pharmacogenetics can allow pharmacists to identify the causes of the problems and develop solutions tailored to each patient [169]. Furthermore, pharmacogenetics tests combined with TDM and pharmaceutical care can be used to individualize dosing regimens, maximize drug efficacy and enhance drug safety.

Conclusion

Combining PKs, pharmacogenetics and pharmaceutical care in the context of a comprehensive and individualized care program appears to be the most effective strategy for allowing pharmacists to best evaluate the efficacy of the therapeutic plan for each patient. This information, when relayed to the medical care team, can support clinical decision-making aimed at optimizing the efficacy and safety of antiretroviral treatments.

Future perspective

The individualization of ART represents an important component of day-to-day practice in the care of HIV patients, given the diversity of drugs available, viral factors and an increasingly diverse HIV patient population. It is expected that in the future TDM will be a common practice in the control of HIV, especially if the development of new pharmaceuticals fails to keep pace with drug resistance – while the number of antiretroviral agents may appear to be high, the number of effective combinations is considerably more limited.

Nevertheless, TDM has some limitations that require continued research aimed at developing further studies of inhibition coefficients that consider the susceptibility of HIV to treatment; developing improved systems of PK interpretation that consider all components of ART, including polypharmacy; determining the population PK parameters for all antiretroviral agents; and developing pharmacoeconomic evaluations to demonstrate the cases for which TDM is cost-effective in routine clinical practice.

In terms of pharmacogenetic analyses, the International Society of Pharmacogenomics has stated that knowledge of pharmacogenetics is necessary for incorporating personalized treatment into routine clinical practice. Evidence suggests that pharmacogenetics will play an increasingly important role in healthcare services. In fact, some health authorities predict that in the future it will be considered unethical not to conduct genetic testing on patients exposed to certain medications that may provoke adverse reactions depending on patient phenotype [170].

To facilitate translation into clinical practice, it is essential that pharmacists are fully prepared to use pharmacogenetics diagnostic tools; however, insufficient education and the resulting lack of knowledge and contextual awareness of these tools may pose severe barriers to the widespread incorporation of personalized medicine in daily clinical practice [88,171-172]. Other factors, such as ethical considerations, the costs associated with utilizing the tools and the complexities of genetic variation among populations and geographies, will further complicate the incorporation of these data into determining patient risk and treatment decision-making.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Pharmacokinetics in the treatment of HIV patients

- The percentage of patients who do not achieve adequate plasma concentrations when given a standard dose of antiretroviral agents is 35–61%.
- The principal objectives of therapeutic drug monitoring (TDM) of antiretroviral agents are to control patient adherence to antiretroviral treatment (ART), to identify and control drug interactions, to avoid toxicity, to establish unofficial or rescue dosing regimens, and to optimize treatment outcomes for overweight, pregnant and pediatric patients, as well as for patients with hepatic or renal insufficiency.
- Evidence supports the use of TDM for protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Pharmacogenetics in the treatment of HIV patients

- Genetic variations in the proteins involved in the transport, metabolism and mechanism of action of antiretroviral agents can influence the efficacy and toxicity of treatments.
- The objectives of employing pharmacogenetics in ART include to correlate genotypes with clinical phenotypes, to identify patients at higher risk of suffering adverse drug events or different treatment responses, to individualize therapy, to improve efficacy and to reduce the intensity of adverse effects.
- Genetic markers have been identified that are related with the risk of developing neurotoxicity with efavirenz, hypersensitivity reactions with abacavir and nevirapine, hyperbilirubinemia with atazanavir and indinavir, peripheral neuropathy and lactic acidosis with nucleoside analog reverse transcriptase inhibitors and renal toxicity with tenofovir.
- Screening for *HLA-B*5701* is recommended prior to administering abacavir in order to avoid the development of a delayed hypersensitivity reaction.
- It is recommended to evaluate other well-established pharmacogenetics associations, including that of *CYP2B6* 516G>T with greater efavirenz plasma exposure and the development of more severe CNS effects and that of polymorphisms in *UGT1A* with a higher risk of hyperbilirubinemia in patients treated with atazanavir.

Pharmaceutical care of HIV patients

- The systematic evaluation of interactions, adherence and adverse effects, as well as the detection, prevention and resolution of other problems associated with ART are key components of the pharmaceutical care of HIV patients.
- The actions of pharmacists treating HIV patients have been associated with improved patient outcomes, including enhanced adherence, reduced pill burden and dosing frequency, greater increases in CD4 cell counts, higher rates of viral suppression and decreases in medication errors.

Complementary strategies to individualize care of HIV patients

- Pharmaceutical care often serves as the initial point of detection of problems with ART, and TDM and pharmacogenetics allow pharmacists to postulate the causes of these problems and develop solutions based on the characteristics of individual patients.
- Available pharmacogenetics tests can complement TDM and pharmaceutical care to individualize dosing regimens and maximize drug efficacy and safety.

Future perspective

- It is expected that in the future TDM will be a common practice in the control of HIV, especially in cases in which the development of new pharmaceuticals fails to keep pace with the drug resistance.
- Some health authorities predict that in the future, it will be considered unethical not to conduct genetic testing on patients exposed to certain medications that may provoke adverse reactions depending on patient phenotype.
- Combining pharmacokinetics, pharmacogenetics and pharmaceutical care in the context of a comprehensive and individualized care program appears to be the most effective strategy for allowing pharmacists to best evaluate the therapeutic plan for each patient and to support the clinical decision-making of the healthcare team.

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