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The Dual Role of Pharmacogenetics in HIV Treatment: Mutations and Polymorphisms Regulating Antiretroviral Drug Resistance and Disposition

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Abstract——**Significant intra- and interindividual variability has been observed in response to use of pharmacological agents in treatment of HIV infection. Treatment of HIV infection is limited by high rates of adverse drug reactions and development of resistance in a significant proportion of patients as a result of suboptimal drug concentrations. The efficacy of antiretroviral therapy is challenged by the emergence of resistant HIV-1 mutants with reduced susceptibility to antiretroviral drugs. Moreover, pharmacotherapy of patients infected with HIV is challenging because a great number of comorbidities increase polypharmacy and the risk for drug-drug interactions. Drug-metabolizing enzymes and drug transporters regulate drug access to the systemic circulation, target cells, and sanctuary sites. These factors, which determine drug exposure, along with the emergence of mutations conferring resistance to HIV medications, could explain variability in efficacy and adverse drug reactions associated with antiretroviral drugs. In this review, the major factors affecting the disposition of antiretroviral drugs, including key drug-metabolizing enzymes and membrane drug transporters, are outlined. Genetic polymorphisms affecting the activity and/or the expression of cytochromes P450 or UGT isozymes and membrane drug transport proteins are highlighted and include such examples as the association of neurotoxicity with efavirenz, nephrotoxicity with tenofovir, hepatotoxicity with nevirapine, and hyperbilirubinemia with indinavir and atazanavir. Mechanisms of drug resistance conferred by specific viral mutations are also reviewed, with particular attention to replicative viral fitness and transmitted HIV drug resistance with the objectives of providing a better understanding of mechanisms involved in HIV drug resistance and helping health care providers to better manage interpatient variability in drug efficacy and toxicity.**

I. Introduction

The widespread use of highly active antiretroviral therapy (HAART[1]) has dramatically decreased progression to AIDS and death (Palella et al., 1998; Porter et al., 2003). In developed countries, the use of HAART has made it possible to change the natural history of HIV infection into a chronic disease that now requires long-term antiretroviral treatment (Mahungu et al., 2009b). Notwithstanding the benefits of HAART, wide intra- and intersubject variability have been observed both in response to therapy and in the adverse effects of certain antiretroviral drugs. Indeed, response to HAART is highly complex and often limited by the development of short- or long-term toxicities and the emergence of antiretroviral drug resistance. This variability can be explained by factors that regulate the availability of drugs (pharmacokinetics), effects on the host (host pharmacodynamics), and the activity of the virus itself (viral pharmacodynamics).

The effectiveness of therapy is affected by viral sensitivity to a drug. Mutagenesis is a constant process in the viral genome; as such, mutations occur at each replication cycle, thereby enabling the virus to easily adapt. HIV resistance to antiretroviral drugs is an evolutionary phenomenon that favors the selection of viral strains that can become better adapted to survive. Furthermore, transmitted HIV drug resistance is an emerging phenomenon with important clinical implications that can compromise initial antiretroviral therapy.

In addition to viral mutations, other factors may also contribute to treatment failure. Poor adherence is likely to be the most important cause of treatment failure, but intersubject variability in pharmacokinetics also plays an important role. In fact, interindividual variability in the pharmacokinetics of antiretroviral drugs can play a role in treatment failure or toxicity, either directly, because subtherapeutic drug levels can increase the risk of a poor virologic response, or indirectly, when high (toxic) drug levels produce significant intolerability, leading to poor adherence (Cressey and Lallemant, 2007). Variability between patients in relation to the bioavailability and distribution of antiretroviral drug regimens is probably driven by genetic and environmental factors such as drug-drug interactions, drug-food interactions, sex, and body weight. In particular, drug-drug interactions and genetic polymorphisms in drug-metabolizing enzymes and drug transporters contribute to wide variability in drug pharmacokinetics, response to therapy, and toxicity.

This article provides an overview of current knowledge on pharmacogenetic factors that are associated with both the target (i.e., the virus), and the host, which might account for intra- and interindividual variability in responsiveness to antiretroviral therapy. In particular, this article seeks to provide a better understanding of processes related to HIV drug-resistant variants and

[1] Abbreviations: ABC, ATP binding cassette; dsDNA, double-stranded DNA; HAART, highly active antiretroviral therapy; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter, novel type; P450, cytochrome P450; SLC, solute carrier; SLCO, solute carrier organic anion; SNP, single-nucleotide polymorphism; TAM, thymidine analog mutation.

to antiretroviral metabolism and transport. A better understanding of such processes is crucial to determining optimal pharmacotherapy for patients infected with HIV. The fact that HIV can now be considered a chronic disease state makes the management of multiple drugs a significant challenge. The first section of this article summarizes issues related to mechanisms of viral replication and the clinical implications of HIV drug-resistant variants. In the second part, key antiretroviral drug-metabolizing events, notably oxidation by the cytochrome P450 (P450) system, conjugation by UDP-glucuronyltransferase (UGT) enzymes, and the effects of drug transporters are presented, with particular emphasis on the genetic polymorphisms that influence the activities of these systems. A few examples illustrating the relationship between genetic polymorphisms in the genes coding for antiretroviral metabolizing enzymes (P450s and UGTs) and transporters and related toxicities are provided.

II. Role of Pharmacogenetics Associated with HIV

A. The Age of Reason of HIV Therapy

The AIDS epidemic has come of age. With the development of new antiretroviral drugs and the rising significance of variable patient responses to antiretroviral treatment, individual patient considerations have gained a prominent role. The genetic characteristics of those infected and the genotypic and phenotypic characteristics of the virus can condition the response to antiretroviral treatment. Host and virus genetic variability are key toward understanding different host responses, to infection, the efficacy of host restriction factors, immune responses, and pharmacokinetics.

B. HIV Epidemic

In 1981, the first signs of the epidemic emerged when a group of homosexual patients were diagnosed with various types of opportunistic infections, Kaposi's sarcoma, and pneumonia in New York, San Francisco, and Los Angeles (Weiss, 2008). The identification of a retrovirus as the infectious agent followed and was confirmed by many laboratories (Barré-Sinoussi et al., 1983; Levy et al., 1984; Popovic et al., 1984; Vilmer et al., 1984). Shortly after, the epidemic was acknowledged worldwide as the effect of HIV became apparent in many countries in what has become the most challenging and devastating health problem in recent memory.

More than 33.3 million people are infected with HIV worldwide, and the virus has resulted in the death of nearly 30 million people (World Health Organization, 2011). The most affected region worldwide is sub-Saharan Africa, where 22.5 million people are infected with HIV-1 (World Health Organization, 2011).

C. HIV Origin

In 1983, HIV, a human gammaretrovirus, was identified as being responsible for AIDS. According to estimates, HIV-1 and HIV-2, a related virus, spread to the human population at the beginning of the 20th century; as such, they are relatively new human pathogens (Bailes et al., 2003). The transmission of these viruses to humans has been traced in the case of HIV-1 to at least three events from chimpanzees and to more numerous events in the case of HIV-2 from green sooty mangabeys (Damond et al., 2004; Santiago et al., 2005; Keele et al., 2006). It is believed that HIV had to overcome many limiting steps, including acquisition of viral genes, to be able to adapt to the human species (Heeney et al., 2006).

D. HIV Replication Cycle

HIV primarily targets lymphocytes and macrophages using CD4 as a receptor and means of infection (Fig. 1). Coreceptors were also shown to vary among HIV viruses and were identified as chemokine receptors. In vivo, only two chemokine receptors, CCR5 and CXCR4, were shown to mediate entry (Alkhatib et al., 1996; Feng et al., 1996; Berger et al., 1999).

Primary isolates of HIV derived from macrophages and peripheral blood mononuclear cells were shown to interact with the CCR5 receptor. As the disease progresses, HIV variants apparently adapt toward infection of immortalized CD4-positive T-cell lines, and they usually also use the CXCR4 receptor as a coreceptor along with CD4 for infection (Weiss, 2002). Some primary isolates of HIV have been shown to be dual-tropic. Moreover, there is to some extent a subtype dependence concerning the frequency and development of different tropisms (Abebe et al., 1999; Ping et al., 1999).

The binding to CD4, the viral receptor, induces conformational changes in gp120, the surface glycoprotein, causing it to expose a hydrophobic domain in gp41, the transmembrane protein that affects membrane fusion (Weiss, 2002). These conformational changes mediate the interaction with the coreceptors, which in turn allows the exposure of the fusion domain of gp41 (viral glycoprotein). Multiple gp120 and gp41 proteins are arranged in trimers at the viral membrane, allowing multiple interactions of the virus with the cell (Berger et al., 1999).

After virus entry, the capsid liberates viral RNA into the cytoplasm. This seems to be regulated by T-cell receptor-interacting molecule 5α, a cellular protein that might restrict viral replication by inhibiting the amount of capsid that can be liberated into the cytoplasm (Arhel, 2010; Pertel et al., 2011). Two molecules of viral genomic RNA and various proteins required for replication and integration are found in the viral capsid.

Reverse transcription is executed by the viral polymerase, reverse transcriptase, capable of using two distinct templates. Initially it uses genomic viral RNA to

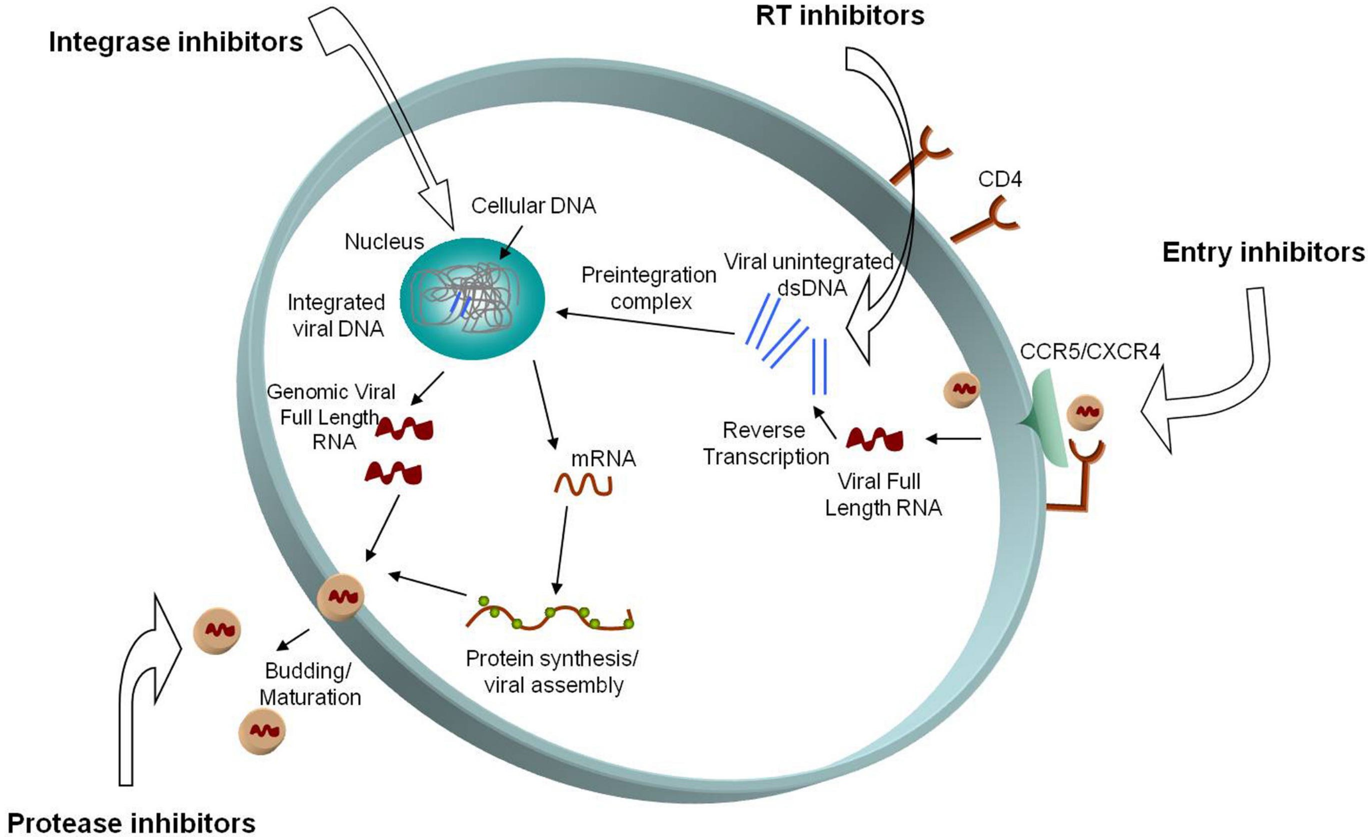

FIG. 1. Depiction of the HIV life cycle and antiretroviral drug targets.

synthesize a single-stranded DNA that is then used as a template by reverse transcriptase to synthesize double-stranded DNA (dsDNA) (Fig. 1). The viral genomic RNA is degraded by an RNase activity also present in the reverse transcriptase enzyme, therefore allowing the single-stranded DNA molecule to be used as a template for dsDNA synthesis (Zucker et al., 2001).

After reverse transcription, viral dsDNA is associated in the preintegration complex. It is believed that the preintegration complex is flexible and that its cellular and viral protein composition varies during its migration toward the nucleus (Arhel, 2010). The transport of the preintegration complex to the nuclear membrane is thought to be mediated through the TNPO3 nuclear pore (Zaitseva et al., 2009; Arhel, 2010; Ocwieja et al., 2011). Once in the nucleus, the viral DNA is tethered to the chromatin by the action of a cellular protein, lens epithelium-derived growth factor/p75 (Van Maele et al., 2006). Although integration occurs randomly in the cellular genome, it has been shown that HIV DNA is tethered to less condensed chromatin regions (Brady et al., 2009; Ocwieja et al., 2011).

Integration is an irreversible process enacted by the viral protein integrase that introduces the viral dsDNA into cellular chromatin. After integration, small gaps in the chromatin DNA resulting from integrase enzymatic activity are readily fixed by cellular proteins, and the viral DNA is finally incorporated into the cellular genome.

The stability of viral reversed-transcribed dsDNA that is not integrated remains debatable (Wu, 2004). However, such intermediates are detected in circular or linear isoforms in the nucleus as well as the cytoplasm (Wu, 2004). Although unintegrated viral DNA has been shown to mediate expression of viral regulatory proteins and to cause the depletion of major histocompatibility complex and viral receptors, the infectivity of such intermediates is still debatable (Wu, 2004; Sloan et al., 2010, 2011).

The synthesis of full-length HIV genomic RNA depends on the cellular transcription machinery. Transcribed HIV RNA is spliced and shorter mRNA molecules are transported through nuclear pores to the cytoplasm in similar fashion as cellular mRNA molecules (Cullen, 1998, 2003). Viral proteins are synthesized in a way that exploits the cellular translation mechanism. Tat, a viral accessory protein, is synthesized and accumulates in the cytoplasm, is transported to the nucleus, and increases HIV RNA transcription (Cullen, 1993, 1998; Zucker et al., 2001; Romani et al., 2010). Rev, also a viral accessory protein, is synthesized in the cytoplasm and transported to the nucleus, where it mediates the transport of full-length HIV RNA to the cytoplasm (Cullen, 1998, 2003).

Once the viral RNA and viral polyproteins have accumulated in the cytoplasm, viral particle formation occurs, and full-length nonspliced HIV RNA is encapsidated and budded from the cell. Tetherin/bone marrow stromal cell antigen 2, a membrane cellular protein, is a cellular restriction factor that inhibits the capacity of newly formed virus to reinfect (Andrew and Strebel, 2010; Evans et al., 2010). HIV possesses an accessory protein, Vpu, that is capable of counteracting this cellular restriction mechanism.

The viral particle, once budded, is immature and noninfectious. The viral protease enzyme mediates its maturation, is responsible for the cleavage of capsid proteins, and renders the particle infectious (Debouck et al., 1987; Kohl et al., 1988; Ridky and Leis, 1995).

E. HIV Variability

High viral diversity is the result of the mutation-prone nature of the reverse transcriptase enzyme. A high rate of spontaneous mutation in HIV has been attributed to the absence of a $3' \rightarrow 5'$ exonuclease proofreading mechanism (Coffin, 1995; Turner et al., 2003). It is estimated that reverse transcriptase introduces a miss-incorporation of a nucleotide once in every 10,000 base pairs (i.e., once in every replication cycle) (Coffin, 1995; Brenner et al., 2002). Therefore, a patient will have all possible combinations of HIV nucleotide changes shortly after HIV infection (Coffin, 1995). Understanding the inter- and intrahost variability of the virus as well as genetic differences among patients is essential toward improvement of treatment outcomes.

F. Resistance and Fitness

The first inhibitors of viral replication were directed against reverse transcriptase and were nucleoside reverse transcriptase inhibitors (NRTIs). However, antiretroviral drug treatment has also led to the emergence of drug resistance that potentially causes virological and clinical failure.

Drug resistance arises spontaneously as a result of the error-prone reverse transcriptase and results in the accumulation of single or multiple mutations in the viral genome. Resistance mutations typically occur in the gene targeted by a given antiretroviral drug and cause a reduction in the efficacy of the inhibitor. The acquisition of resistance can be mediated by structural changes in the drug target that reduce the affinity of the drug for the protein.

Genetic barrier for resistance refers to the number of nucleotide changes a virus needs to accumulate to become resistant against a given antiretroviral drug. A high genetic barrier indicates that the virus will need more genetic changes to become resistant, suggesting a more efficient drug in terms of resistance. Because of high variability among viral populations, genetic barriers could be different for various antiretroviral drugs depending on viral genotypes or subtype.

Under selective pressure, resistant viruses are capable of replicating better than sensitive viruses and, therefore, of being positively selected. Nevertheless, resistance mutations may have a negative effect on the function of the protein targeted (reverse transcriptase, protease, integrase etc.), thereby causing a decrease of viral "fitness" (i.e., relative efficiency of replication). Hence, when the virus accumulates resistance mutations, its replication, virulence, and transmission might be impaired compared with wild-type virus in the absence of drug resistance mutations (Turner et al., 2003). The extent of the impairment may depend on the type(s) of mutations and on the viral target mutated.

However, the negative effect of resistance mutations on viral fitness can be minimized as a result of secondary mutations that might reduce the fitness cost of a single mutation. The accumulation of secondary resistance mutations and their effect on viral fitness have been evaluated in the case of many resistance mutations in reverse transcriptase and integrase (Götte and Wainberg, 2000; Brenner et al., 2002; Wainberg, 2004; Fransen et al., 2009). In these examples, a primary mutation may confer resistance, and then a second mutation may increase fitness, allowing a recovery even in the presence of antiretroviral drugs.

G. Reverse Transcriptase as a Drug Target

NRTIs were the first antiretroviral drugs. These agents are nucleoside analogs that lack a 3′-OH moiety in the ribose ring, which distinguishes them from physiological dNTP substrates (Fig. 2A). They mediate reverse transcriptase inhibition through incorporation into the nascent DNA strand during reverse transcription. This incorporation causes the termination of transcription, thereby blocking viral replication (Gulnik et al., 1995; Götte and Wainberg, 2000). Nucleotide reverse transcriptase inhibitors (e.g., tenofovir) act by the same mechanism as NRTIs.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit reverse transcription by a different mechanism (i.e., through binding to noncatalytic enzyme sites). Unlike the NRTIs, the NNRTIs do not require phosphorylation for activity and do not integrate into growing DNA strands. NNRTI inhibition is usually mediated through steric hindrance that impedes structural changes in HIV reverse transcriptase (Götte and Wainberg, 2000). The key chemical components of NNRTIs have been developed based on structures and molecular models of reverse transcriptase (Fig. 2B). Ensuing chemical modifications to these components produced NNRTIs with improved activity against NNRTI-resistant HIV mutants. Resistance mutations against both nucleoside and non-nucleoside reverse transcriptase inhibitors have been identified and characterized (Table 1).

There are several major genetic mutational patterns of resistance and cross-resistance that can evolve with the use of nucleoside (or nucleotide) reverse transcriptase inhibitors, including thymidine analog mutations (i.e., TAMs) and nonthymidine mutations such as K65R and M184V. In treated patients, TAMs can emerge in an organized manner, and their accumulation is related to an increasing level of resistance (Boucher et al., 1992). TAMs were commonly selected by zidovudine- and stavudine-based regimens, but evidence shows that these mutations are also associated with resistance to other NRTI agents (Shafer, 2002). In fact, there is broad cross-resistance within the NRTI class. The magnitude of phenotypic and clinical resistance to other NRTIs seems to be related to the number of TAMs. Consequently, specific patterns of TAMs could have different effects on treatment responses. On the other hand, the K65R muta-

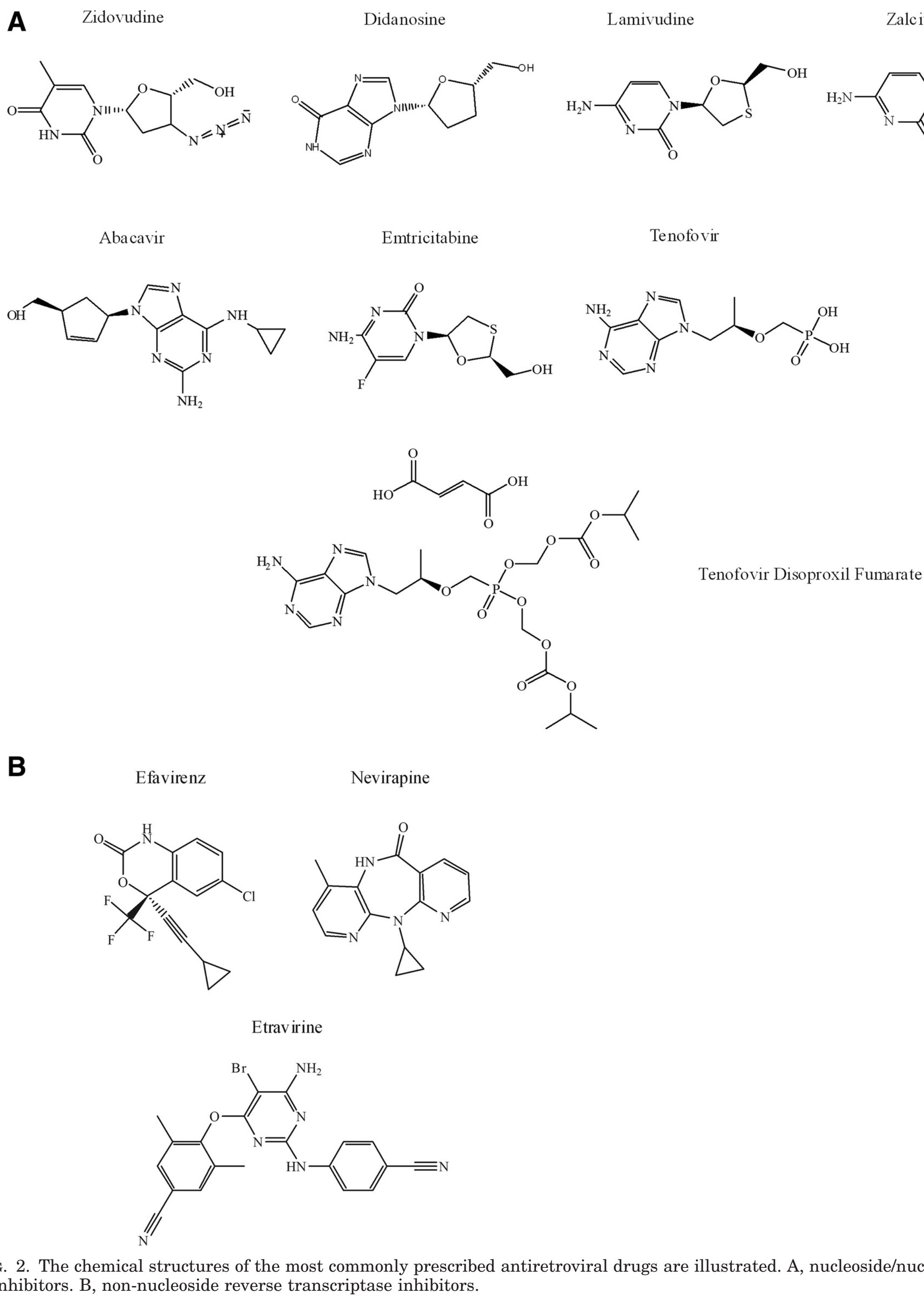

FIG. 2. The chemical structures of the most commonly prescribed antiretroviral drugs are illustrated. A, nucleoside/nucleotide reverse transcriptase inhibitors. B, non-nucleoside reverse transcriptase inhibitors.

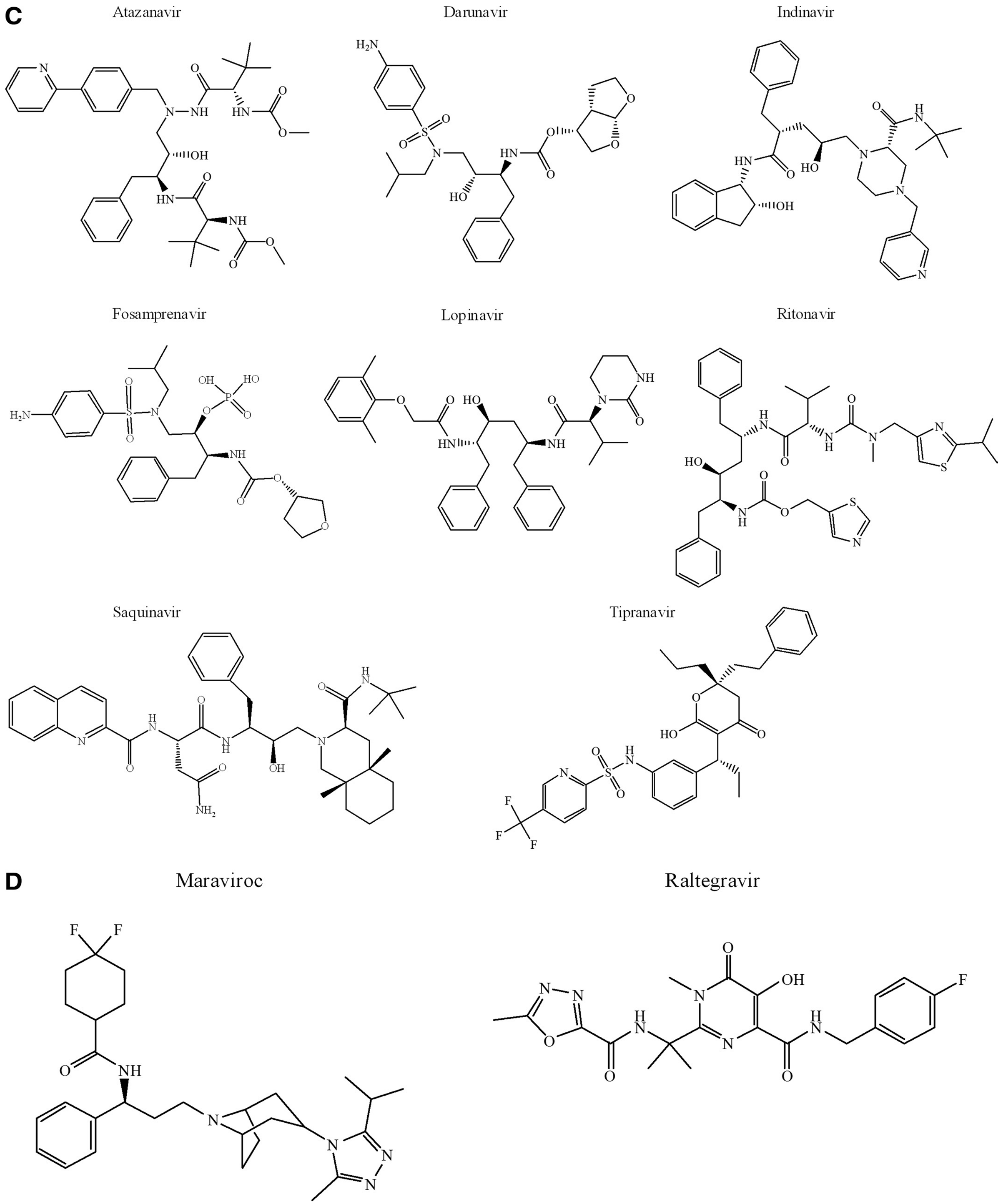

FIG. 2. Continued. C, protease inhibitors. D, maraviroc and raltegravir.

tion is associated with cross-resistance in all agents from this class except zidovudine. Low genetic barrier NRTI analogs, requiring a single-point mutation to confer high-level resistance, include lamivudine and emtricitabine, whereas most nondeoxycytidine NRTIs, such as thymidine analogs, didanosine, aba-

TABLE 1

List of the main resistance mutations against the most commonly used antiretroviral drugs

Reverse Transcriptase Mutations	Antiretroviral Drug
M41L	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
A62V	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
D67N	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
K65R/N	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF, stavudine
T69D/Ins	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
K70R/E/G	Stavudine, zidovudine
L74V/I	Abacavir, didanosine
V75I/T/M	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine
F77L	Abacavir, didanosine, stavudine, zidovudine
Y115F	Abacavir, tenofovir/tenofovir DF
F116Y	Abacavir, didanosine, stavudine, zidovudine
Q151M	Lamivudine, emtricitabine, abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
M184V/I	Lamivudine, emtricitabine, abacavir, didanosine
L210W	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
T215F/Y	Abacavir, didanosine, tenofovir/tenofovir DF, stavudine, zidovudine
K219Q/E	Stavudine, zidovudine
Non-nucleoside reverse transcriptase inhibitors	
A98G	Nevirapine, delavirdine, etravirine
L100I	Nevirapine, delavirdine, etravirine
K101E/P	Nevirapine, delavirdine, etravirine
K103N/S	Nevirapine, delavirdine, etravirine
V106A/M	Nevirapine, delavirdine, etravirine
V108I	Nevirapine, delavirdine, etravirine
V179D/E/F	Nevirapine, delavirdine, etravirine
Y181C/I/V	Nevirapine, delavirdine, etravirine
Y188L/H/C	Nevirapine, delavirdine, etravirine
G190A/S/E	Nevirapine, delavirdine, etravirine
P225H	Etravirine
F227L/C	Nevirapine, delavirdine, etravirine
M230L	Nevirapine, delavirdine, etravirine
P236L	Delavirdine
K238T	Nevirapine, delavirdine, etravirine
Protease inhibitors	
L23I	Nelfinavir
L24I	Atazanavir/R, fosamprenavir/R, indinavir/R, lopinavir/R, nelfinavir, saquinavir/R
D30N	Nelfinavir
V32I	Darunavir/R, fosamprenavir/R, indinavir/R, lopinavir/R, tipranavir/R
L33F	Atazanavir/R, darunavir/R, fosamprenavir/R, lopinavir/R, nelfinavir, tipranavir/R
M46I/L	Atazanavir/R, fosamprenavir/R, indinavir/R, lopinavir/R, nelfinavir, tipranavir/R
I47V/A	Atazanavir/R, darunavir/R, fosamprenavir/R, indinavir/R, lopinavir/R, nelfinavir, tipranavir/R
G48V/M	Atazanavir/R, Lopinavir/R, nelfinavir, saquinavir/R
I50L/V	Atazanavir/R, darunavir/R, fosamprenavir/R, lopinavir/R
F53L	Atazanavir/R, indinavir/R, nelfinavir, saquinavir/R
I54V/T/A/L/M	Atazanavir/R, darunavir/R, fosamprenavir/R, indinavir/R, lopinavir/R, nelfinavir, saquinavir/R, tipranavir/R
G73S/T	Atazanavir/R, darunavir, fosamprenavir/R, indinavir/R, nelfinavir, saquinavir/R
L76V	Darunavir, fosamprenavir/R, indinavir, lopinavir/R
V82A/T/F/S	Atazanavir/R, fosamprenavir/R, indinavir/R, lopinavir/R, nelfinavir, saquinavir/R, tipranavir/R
I84V/A/C	Atazanavir/R, darunavir, fosamprenavir/R, indinavir, lopinavir/R, nelfinavir, saquinavir/R, tipranavir/R
N88D/S	Atazanavir/R, indinavir/R, nelfinavir, saquinavir/R,
L90M	Atazanavir/R, darunavir, fosamprenavir/R, indinavir/R, lopinavir/R, nelfinavir, saquinavir/R, tipranavir/R
Integrase inhibitors	
T66I/A/K	Elvitegravir
E92Q	Raltegravir/elvitegravir
F121Y	Raltegravir/elvitegravir
E138A/K	Raltegravir/elvitegravir
G140S	Raltegravir/elvitegravir
Y143R/C/H	Raltegravir
S147G	Raltegravir/elvitegravir
Q148H/R/K	Raltegravir/elvitegravir
S153Y	Elvitegravir
N155H/S	Raltegravir/elvitegravir
R263K	Elvitegravir

Data from Rhee et al. (2003) and Shafer (2006).

cavir, and the nucleotide reverse transcriptase inhibitor tenofovir, are associated with a moderate genetic barrier for the development of resistance.

Despite the numerous advantages of NNRTI-based regimens on virologic outcomes, their use is limited by their low genetic barrier to resistance. Resistance to the first generation of NNRTIs (nevirapine and efavirenz) is characterized by a rapid selection of viruses that carry one or several mutations in the reverse transcriptase gene that confer high-level resistance to these agents. A single-point mutation in the reverse transcriptase enzyme is often enough to confer high-level loss of drug affinity, which is associated with clinically significant phenotypic resistance. Despite their different structures, nevirapine and efavirenz show marked cross-resistance (De Clercq, 1998). Only some mutations confer strong cross-resistance to all-generations of NNRTIs. Resistance to efavirenz, which is the most commonly prescribed NNRTI, is mainly associated with the K103N reverse transcriptase gene substitution whereas the Y181C mutation more frequently emerges with nevirapine therapy (Miller et al., 1998; Bacheler et al., 2000; Johnson et al., 2010). A second-generation NNRTI agent (i.e., etravirine) has a higher genetic barrier for resistance than the first-generation NNRTIs, requiring multiple mutations for loss of activity (Andries et al., 2004; Vingerhoets et al., 2005; Schiller and Youssef-Bessler, 2009).

H. Protease Inhibitors

Protease inhibitors act on the viral protease, inhibiting the maturation of new viral particles, therefore attacking already formed HIV before initiation of the next cycle of infection.

Most of the protease antagonists are substrate-based inhibitors designed specifically against the viral protease based on its crystal structure. Protease inhibitor drugs are smaller that the natural substrates. Although their chemical structures are different from one another, they occupy a comparable volume within the active binding site. The chemical structures of major protease inhibitor drugs are illustrated in Fig. 2C. Protease inhibitors are substrate based nonhydrolyzable peptide mimetic compounds that target the wild-type enzyme (Ridky and Leis, 1995). Mutations in key residues involved in the substrate-binding pocket result in reduction of van der Waals bonds between the protease active site and the protease inhibitors, thereby reducing the inhibitor's affinity. The mutations causing such changes with regard to any given drug can also affect other protease inhibitors, thereby causing cross-resistance.

Resistance mutations cause a reduction in up to 15-fold in the enzyme's catalytic activity. However, secondary mutations can increase enzymatic activity to levels similar to wild-type (Table 1) (Ridky and Leis, 1995; Doyon et al., 1996). Mutations in the cleavage sites of Gag can compensate for the deleterious effect of a given mutation in vivo and can confer a significant growth advantage in the presence of protease inhibitors (Boden and Markowitz, 1998; MacArthur and Novak, 2008).

As a class, protease inhibitor agents generally present a high genetic barrier against resistant viral strains compared with NRTIs and NNRTIs. In contrast to these drug classes, the virologic activity of protease inhibitors is generally maintained despite the emergence of mutations. Indeed, developing drug resistance to protease inhibitors may require the accumulation of several mutations; most nonboosted protease inhibitors and some boosted protease inhibitors exhibit a moderate genetic barrier to resistance, except for nelfinavir, which is associated with a low genetic barrier to resistance. Boosted protease-inhibitor regimens combine a low-dose of ritonavir with a second protease inhibitor to enhance patient exposure to the latter protease inhibitor agent, whereas the unboosted protease inhibitor-based regimen refers to the administration of a protease inhibitor without the addition of ritonavir. The highest genetic barrier protease inhibitor drugs require many mutations before resistance develops; these include darunavir and tipranavir (De Meyer et al., 2005; Hicks et al., 2006; Clotet et al., 2007).

I. Entry Inhibitors

HIV enters the cell after interaction with the viral receptor CD4 and the coreceptors CXCR4 or CCR5. Maraviroc, an HIV entry inhibitor, prevents the usage of the coreceptor CCR5 and entry of the viral particle to the target cell (MacArthur and Novak, 2008; Donahue et al., 2010) (Fig. 2D). However, maraviroc is incapable of inhibiting infection with viral particles that are not CCR5 tropic.

J. Inhibition of Integration

Integration is a unique and essential step in viral replication and, therefore, was identified as a target for drug development years ago. However, the first integrase inhibitor, raltegravir, was approved by the U.S. Food and Drug Administration only in 2007 (Fig. 2D). The delay was due mainly to the insolubility of HIV integrase and therefore the ability to decipher its structure and to design inhibitors. The effect of the use of integrase inhibitors on viral reservoirs is still debated. Moreover, the high efficacy of raltegravir has been related to its favorable physical-chemical characteristics and to the inhibition of the integrase stage in viral replication (Hazuda et al., 2009; Bar-Magen et al., 2010; Donahue et al., 2010). The two first-generation inhibitors of integration, raltegravir and elvitegravir, show cross-resistance (Table 1). Integrase inhibitors exhibit a relatively low genetic barrier for resistance, in that only one or two mutations are capable of causing marked reductions in susceptibility to raltegravir and elvitegravir (Cooper et al., 2008; Malet et al., 2008; Canducci et al., 2009; Delelis et al., 2010; Hatano et al., 2010; Zolopa et al., 2010). Overall, the genetic barrier to integrase inhibitors is lower than that of the protease inhibitors and most NRTIs. Second-generation integrase inhibitors are still under development and their resistance profiles are still being studied (Bar-Magen et al., 2010).

K. Transmission of Drug-Resistant HIV Variants

The use of combinations of antiretroviral drugs has been remarkably successful in suppressing HIV infection; nevertheless, such benefits can be compromised by the development of drug resistance and, also, by the transmission of drug-resistant HIV strains. HIV resistance to antiretroviral drugs is classified as primary resistance when there is no history of antiretroviral therapy or as secondary resistance, when resistance develops after exposure to antiretroviral drugs. The primary resistance of HIV can be explained by transmitted resistance or infection with a drug-resistant HIV strain, which may happen through sexual, parental, and vertical routes of HIV acquisition.

Transmitted HIV drug resistance is a growing concern, because the presence of low-frequency or minority HIV drug resistance mutations may adversely affect response to antiretroviral therapy. However, evidence regarding the clinical significance of such HIV-resistant strains with regard to first-line regimens is conflicting. Overall, in North America and Western Europe, where the history of the use of antiretroviral therapy is extensive, the prevalence of transmitted drug resistance has been estimated to be between 4 to 16% among HIV-infected persons (Grant et al., 2002; Little et al., 2002; Pillay, 2004; Weinstock et al., 2004; Wensing et al., 2005; Jayaraman et al., 2006; Shet et al., 2006; Vercauteren et al., 2009; Descamps et al., 2010).

Most cases of transmitted HIV resistance mutations involve NRTIs and NNRTIs. Patterns of transmitted HIV resistance are always changing, reflecting the evolution of therapeutic strategies and the introduction of new antiretroviral agents. Cases of transmitted resistance were first described with NRTI drugs, which were the first class of antiretroviral agents in widespread use (Erice et al., 1993). As antiretroviral drug use expanded, a shift toward more transmitted NNRTI resistance ensued after extensive use of this class of drugs (Grant et al., 2002; Shet et al., 2006; Turner and Wainberg, 2006). Transmitted protease inhibitor resistance still remains uncommon, occurring in fewer than ~5% of cases despite widespread use of this class (Ross et al., 2007; Bonura et al., 2010). Most available data on transmitted HIV resistance mutations are from subtype B HIV. It has been proposed that this could be explained by a longer period of antiretroviral therapy use among patients with subtype B viruses rather than any inherent transmission disadvantage or advantage with regard to nonsubtype B. In contrast, it has also been suggested that some HIV subtypes can develop certain mutations at differential rates compared with viruses of subtype B origin. Brenner et al (2006) showed that subtype C viruses exhibit a greater propensity than subtype B to select the K65R mutation in reverse transcriptase.

A pooled analysis from Li et al (2011) reported that the presence of any NNRTI- or NRTI-resistant minority variant was associated with an increased risk of virologic failure (hazard ratio of 2.6). Their analysis from large cohort studies revealed virologic failure in 40% of patients with drug-resistant minority mutations compared with 17% in those without minority variants (Li et al., 2011). They reported that NNRTI-resistant minority variants were associated with more than twice the risk of virologic failure in patients initiating NNRTI-based antiretroviral therapy (Li et al., 2011). In addition, it has been observed, using the most sensitive test to detect resistant minority mutations, that approximately 11 patients would need to be screened before initiation of antiretroviral therapy containing an NNRTI to prevent one case of virologic failure (Johnson et al., 2008; Li et al., 2011). Because NNRTIs are commonly prescribed in first-line regimens, this finding supports a rationale for ultrasensitive screening for HIV drug-resistant variants before initiation of antiretroviral therapy to help identify subjects at higher risk of virologic failure.

III. Role of Pharmacogenetics in Antiretroviral Metabolism and Transport

The observed intersubject variability in the pharmacokinetics of antiretroviral drugs also plays a major role with regard both to the toxicity and the efficacy of these agents. After the administration of standard doses of antiretroviral drugs, large intersubject variability in plasma drug concentrations have been reported (Back et al., 2002; Owen et al., 2006; Cressey and Lallemant, 2007). The enzymes responsible for the metabolism of these agents and the proteins involved in their transport are among the major determinants of what happens to a drug once it is in the body. Host genetic and environmental factors, such as drug-drug interactions, gender, weight, and the presence of comorbidities can influence enzyme and transporter activity and, consequently, the disposition of antiretroviral agents.

A. Pharmacokinetics

The processes that regulate drug absorption, such as the intestinal-hepatic first-pass effect, distribution (systemic and tissue), metabolism and excretion are major determinants of the plasma and tissue concentrations of drugs. The majority of antiretroviral drugs are administered orally and absorbed via intestinal epithelial cells. These cells express a number of membrane bound proteins that act as selective drug transporters that locally determine absorption quantities. Moreover, enterocytes contain large quantities of enzymes that are able to biotransform drugs (Boffito et al., 2003). The fraction of the drug absorbed from the intestine passes to the liver via the mesenteric veins and then by the portal vein to the liver. In hepatocytes, the drug is once again subjected to transport and metabolism processes before it reaches the systemic circulation. Together, these processes define the effect of the first intestinal-hepatic pass that determines a drug's systemic bioavailability.

Once it is in the systemic circulation, and depending on the molecule's inherent physiochemical properties, the drug is distributed to various tissues that enable the antiretroviral agent to reach certain HIV sanctuary sites. This distribution is a function of both the degree of binding with plasma proteins and, in most cases, the antiretroviral's affinity with the influx and efflux transporters expressed in various cell types. Selective expression could result in the accumulation of the drug in a particular tissue and not in another. Moreover, local metabolism could significantly influence the quantity of drug available to intracellular sites of action. These same factors could also explain specific toxicities.

The mechanisms regulating pharmacokinetics are important components of antiretroviral activity and response (Kim, 2003). The large enzyme (P450s, UGTs) and transporters (ABC and SLC families) play a major role in what happens to antiretroviral agents in the body and in the ability of these drugs to reach target reservoir tissues (Fig. 3).

B. Cytochromes P450

Enzymes belonging to the large family of P450s protect the organism by transforming liposoluble molecules into more hydrosoluble ones. P450 isoenzymes make up a superfamily of hemoproteins, of which 57 genes and 58 pseudogenes are known in humans. However, only approximately 30 of them code for a protein (Guengerich et al., 2005). CYP1, CYP2, and CYP3 are the main families involved in the majority of phase 1 biotransformation reactions of clinically used drugs, including many antiretroviral agents. In fact, CP450s are the major enzyme system involved in the metabolism of NNRTIs, protease inhibitors, the CCR5 coreceptor antagonist maraviroc, and the integrase inhibitor elvitegravir (Table 2).

Variable expression and activity of P450s contribute to inter- and intraindividual variations in drug clearance, efficacy, and toxicity. P450 isoforms differ among other ways in their degree of tissue expression, their tissue selectivity, selectivity toward their substrates, and the reactions they catalyze. Each isoform has an affinity for certain substrates; activity can be altered by the coadministration of other substrates and by selective inhibitors or inducers. In addition, polymorphisms in some genes that code for P450 enzymes significantly contribute to interindividual variability in drug response. The next section describes the contribution of P450s as a factor in interindividual variability in the pharmacokinetics of antiretroviral agents.

C. CYP2B6

CYP2B6 is the only identified gene belonging to the CYP2B family in humans. The CYP2B6 protein is mainly expressed in the liver (Hanna et al., 2000; Ortiz de Montellano, 2005). The content of hepatic CYP2B6 varies considerably (20- – 250-fold) (Code et al., 1997; Ekins et al., 1998; Stresser and Kupfer, 1999; Hesse et al., 2000; Zanger et al., 2007). It has also been observed that CYP2B6 activity measured in human liver microsomal preparations varied 20- to 80-fold for substrates such as *S*-mephenytoin, bupropion, and efavirenz (Ekins et al., 1998; Faucette et al., 2000; Desta et al., 2007). CYP2B6 is also found in various extrahepatic tissues such as the brain, kidneys, endometrium, peripheral circulating lymphocytes, and skin (Gervot et al., 1999; Janmohamed et al., 2001; Ding and Kaminsky, 2003). It has been suggested that approximately 3 to 8% of clinically used drugs are fully or partially metabolized by CYP2B6 (Ortiz de Montellano, 2005; Mo et al., 2009). For example, CYP2B6 is largely responsible for the metabolism of bupropion (typical substrate), methadone, cyclophosphamide, ketamine, propofol, and NNRTIs (efavirenz and nevirapine) (Table 2) (Wang and Tompkins, 2008).

The *CYP2B6* gene is highly polymorphic, and this accounts, in part, for wide interindividual variability in the expression and function of this isoenzyme (Lang et al., 2001; Haas et al., 2004; Tsuchiya et al., 2004; Rotger et al., 2005a). To date, more than 28 alleles have been characterized and more than 100 mutations (SNPs) have been described for the *CYP2B6* gene. Among different variants, the *CYP2B6*6* haplotype (*516 G>T*, *785 A>G*) leads to reduced catalytic activity and a significant decrease in protein expression. The frequency of the *CYP2B6*6* mutant allele varies among different ethnic groups: 15 to 40% in Asians, 25% in white persons, and more than 50% in African Americans and black Africans (Lang et al., 2001; Guan et al., 2006; Mehlotra et al., 2006). The *CYP2B6*16* (*785 A>G*; *983 T>C*) or the *CYP2B6*18* (*983 T>C*) variants, which are relatively common in black populations, lead to a decrease in the expression of the corresponding protein without affecting its intrinsic catalytic activity (Wang et al., 2006).

Efavirenz is mainly metabolized by CYP2B6 into 8-hydroxyefavirenz and less so via accessory pathways involving CYP2A6, CYP3A4/5, and UGT2B7 (Mutlib et al., 1999; Ward et al., 2003; Desta et al., 2007). In addition to being a substrate of CYP2B6, efavirenz can induce its own metabolism (self-inducer of CYP2B6) (Robertson et al., 2008; Zhu et al., 2009). This induction may be selective for certain tissues, which would also suggest particular induction mechanisms (Lee et al., 2006). As such, the partial metabolic clearance of efavirenz would be responsible for around 90% of its systemic clearance (Ward et al., 2003). Oral administration of a daily dose of 600 mg of efavirenz is associated with wide interindividual variability in plasma concentrations (Marzolini et al., 2001; Csajka et al., 2003; Ståhle et al., 2004).

Many studies have reported an association between genetic polymorphisms of CYP2B6 and the pharmacokinetics of efavirenz (Haas et al., 2005; Carr et al., 2010; Chen et al., 2010). Tsuchiya et al (2004) reported an increase in efavirenz plasma concentrations among *CYP2B6*6/*6* individuals. Another study also showed an association between the *CYP2B6 516 G>T* variant and 1) an increase in the area under the curve for efavirenz, 2) increased intracellular concentrations of the drug in peripheral blood mononuclear cells, and 3) a higher risk for toxicity in the central nervous system of persons homozygous for the allelic variant (Rotger et al., 2005a). Wang et al. in 2006 showed that the concentrations of steady-state efavirenz were higher in Africans

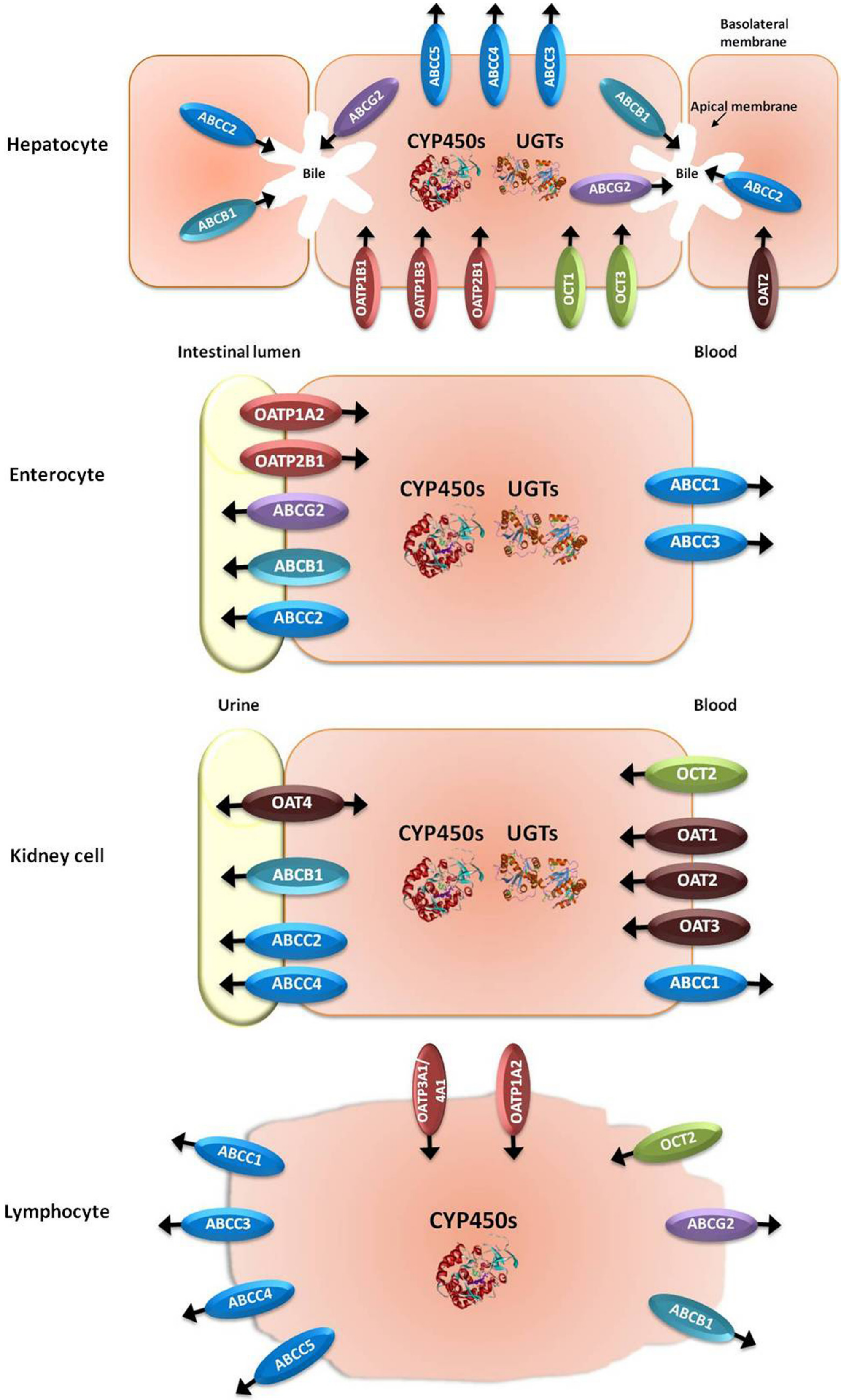

FIG. 3. Membrane drug transporters and drug metabolism systems (P450s and UGTs) involved in the transport and metabolism of antiretroviral drugs expressed in the liver, intestine, kidney, and lymphocytes.

TABLE 2

List of the main drug metabolism enzymes (CYP450 and UGT isoenzymes) and membrane transporters and their effect on the disposition of antiretrovirals

This table is based on available in vitro and in vivo data.

Antiretrovirals	CYP450s and UGTs Substrates	Membrane transporters of drugs				References
		ABC		SLC		
		Substrates	Inhibitors	Substrates	Inhibitors	
NRTIs and NtRTI						
Abacavir	UGT1A1	ABCB1 ABCC4 ABCG2			OCT1 OCT2	Pan et al., 2007; Shaik et al., 2007; Weiss et al., 2007a; Yuen et al., 2008; Minuesa et al., 2009
Didanosine		ABCG2				Wang et al., 2003
Emtricitabine		ABCC1	ABCC2		OCT1 OCT2	Weiss et al., 2007b; Bousquet et al., 2008a; Minuesa et al., 2009
Lamivudine		ABCC4 ABCG2		OCT1 OCT2 OCT3		Leung and Bendayan, 2001; Wang et al., 2003; Anderson et al., 2006; Jung et al., 2008
Stavudine		ABCG2				Wang et al., 2003
Tenofovir/tenofovir DF		ABCB1 ABCC2 ABCC4		OAT1 OAT3 OCT1 OCT2		van Gelder et al., 2002; Mallants et al., 2005; Ray et al., 2006; Minuesa et al., 2009
Zalcitabine				OCT1 OCT2		Schuetz et al., 1999; Jung et al., 2008
Zidovudine	UGT2B7	ABCC4 ABCG2		OAT1 OAT2 OCT1 OCT2		Barbier et al., 2000; Wang et al., 2003; Pan et al., 2007; Minuesa et al., 2009
NNRTIs						
Efavirenz	CYP2B6 UGT2B7		ABCB1 ABCG2 ABCC1/2			Mutlib et al., 1999; Ward et al., 2003; Desta et al., 2007; Storch et al., 2007; Weiss et al., 2007a,b; Bélanger et al., 2009; Bousquet et al., 2009
Etravirine	CYP2C19 CYP3A4/5		ABCB1			Seminari et al., 2008
Nevirapine	CYP2B6 CYP3A4/5					Erickson et al., 1999; Weiss et al., 2007b; Mahungu et al., 2009a
Protease inhibitors						
Atazanavir	CYP3A4/5	ABCB1 ABCC1 ABCC2	ABCG2		OATP2B1	Le Tiec et al., 2005; Roucairol et al., 2007; Weiss et al., 2007a; Bousquet et al., 2008b; Zastre et al., 2009; Kis et al., 2010
Darunavir	CYP3A4/5	ABCB1		OATP1A2 OATP1A3 OATP1B1		Back et al., 2008; Brown et al., 2009; Fujimoto et al., 2009; Kwan et al., 2009; Hartkoorn et al., 2010; König et al., 2010
Indinavir	CYP3A4/5	ABCB1 ABCC1 ABCC2			OCT1 OATP2B1	Chiba et al., 1997; Kim et al., 1998b; Koudriakova et al., 1998; Lee et al., 1998; Hugen et al., 2000; Zhang et al., 2000; Hochman et al., 2001; van der Sandt et al., 2001; Huisman et al., 2002; Campbell et al., 2004; Jorajuria et al., 2004; Hamidi, 2006; Jung et al., 2008; Annaert et al., 2010
Lopinavir	CYP3A4/5	ABCB1 ABCC1 ABCC2	ABCG2	OATP1A2 OATP1A3 OATP1B1	OATP2B1	Kumar et al., 1999; Agarwal et al., 2007; Janneh et al., 2007; Weiss et al., 2007a; Hartkoorn et al., 2010; Kis et al., 2010; van Waterschoot et al., 2010
Nelfinavir	CYP3A4/5 CYP2C19	ABCB1 ABCC1	ABCG2		OCT1 OCT2 OATP2B1	Kim et al., 1998b; Choo et al., 2000; Zhang et al., 2000; Baede-van Dijk et al., 2001; Jones et al., 2001a; Jones et al., 2001b; Gupta et al., 2004; Hirani et al., 2004; Salama et al., 2005; Kaddoumi et al., 2007; Weiss et al., 2007a; Hirt et al., 2008; Jung et al., 2008; Kis et al., 2010
Ritonavir	CYP3A4/5	ABCB1 ABCC1 ABCC2	ABCG2		OCT1 OCT2 OATP2B1	Kumar et al., 1996; Koudriakova et al., 1998; Lee et al., 1998; Zhang et al., 2000; Jones et al., 2001a; Jones et al., 2001b; van der Sandt et al., 2001; Huisman et al., 2002; Gupta et al., 2004; Jung et al., 2008; Zastre et al., 2009; Kis et al., 2010
Saquinavir	CYP3A4/5	ABCB1 ABCC1 ABCC2	ABCG2	OATP1A2 OATP1A3 OATP1B1	OCT1	Fitzsimmons and Collins, 1997; Kim et al., 1998a,b; Kupferschmidt et al., 1998; Lee et al., 1998; Srinivas et al., 1998; Eagling et al., 1999, 2002; Choo et al., 2000; Zhang et al., 2000; Jones et al., 2001a; Meaden et al., 2002; Williams et al., 2002; Campbell et al., 2004; Gupta et al., 2004; Maffeo et al., 2004; Su et al., 2004; Janneh et al., 2005; Park and Sinko, 2005; Weiss et al., 2007a; Jung et al., 2008; Hartkoorn et al., 2010
Tipranavir	CYP3A4/5	ABCB1			OATP2B1	Yeni, 2003; Vourvahis and Kashuba, 2007; Langmann et al., 2008; Kis et al., 2010
CCR5 co-receptor inhibitor						
Maraviroc	CYP3A4/5	ABCB1				Walker et al., 2005; Emmelkamp and Rockstroh, 2007; Abel et al., 2008
Integrase inhibitor						
Raltegravir	UGT1A1	ABCB1		SLC22A6		Kassahun et al., 2007; Moss et al., 2011

who were carriers of the *CYP2B6*16* allelic variant than in other patients (Wang et al., 2006).

Cabrera et al (2009) developed a population pharmacokinetics model to study the effects of various covariables (such as gender, age, weight, duration of antiretroviral treatment and genetic polymorphisms of CYP2B6, CYP3A4, and the ABCB1 transporter) on the pharmacokinetics of efavirenz. Their study reported that the genetic polymorphism of *CYP2B6* could explain around 27% of the variance in efavirenz clearance (Cabrera et al., 2009). This result concurs with results of another study published in 2009 that reported that genetic variations of CYP2B6 contributed to 31% of interindividual variability in mean efavirenz clearance (Arab-Alameddine et al., 2009).

Lubomirov et al (2011) evaluated the association of recognized and proposed genetic markers of toxicity or elevated plasma drug levels over time to antiretroviral discontinuation during the first year of a first-line regimen. They reported an association between various genetics variants with different rates of efavirenz discontinuation. Their analysis indicates that loss of CYP2B6 function (homozygous, loss or decrease of functional alleles; *CYP2B6*6*, **11*, **15*, **18*) with a concomitant reduction of function in accessory metabolic pathways (CYP2A6 and/or CYP3A4) was associated with a higher risk of discontinuation (Lubomirov et al., 2011). Patients having the highest genetic risk score discontinued efavirenz more frequently than those with a lower genetic risk scores (cumulative rates of 72 versus 28%, respectively) (Lubomirov et al., 2011).

It has been suggested that CYP2B6 may be responsible for metabolizing nevirapine into its 3- and 8-hydroxy metabolites (Erickson et al., 1999). Chou et al (2010) suggested that nevirapine clearance can also be influenced by genetic polymorphisms of *CYP2B6 516 G>T*. Although CYP2B6 had a lesser effect with nevirapine than with efavirenz, nevirapine clearance was significantly reduced in HIV-infected Cambodian patients, 1.86 L/h for subjects homozygous for the *CYP2B6 516T* mutation versus 2.95 L/h for subjects with a genotype homozygous for the wild-type allele. Moreover, Mahungu et al (2009a) showed that the *CYP2B6 516 G>T* variant was a significant predictor of nevirapine trough plasma concentrations. The SNP *983 T>C* polymorphism (which is a suspected null allele) has only been identified in Hispanic and African populations (Lang et al., 2004; Klein et al., 2005; Mehlotra et al., 2007). Results from another study showed that heterozygosity for the *CYP2B6 983 T>C* was significantly associated with higher plasma concentrations of nevirapine in black patients (Wyen et al., 2008). One study used a population pharmacokinetic model to assess the complex relationship between drug exposure for efavirenz and nevirapine, weight and genetics (*CYP2B6 516 G>T* and *983 T>C* SNPs). This study confirms the significant impact of *CYP2B6 983 T>C* SNP, patients heterozygous for this allele having a 40% decrease in oral clearance rates (Schipani et al., 2011).

1. Pharmacogenetics and Toxicity Associated with Efavirenz. The administration of efavirenz is associated with adverse reactions in the central nervous system among more than 50% of patients. A prospective study showed that the appearance of acute symptoms in the central nervous system was responsible for 13% of the rate of efavirenz cessation in the two weeks after treatment initiation (Blanch et al., 2001). Although these symptoms (such as dizziness, insomnia, nightmares, lack of concentration and drowsiness) generally appear in the first few days and weeks after efavirenz initiation, they generally tend to disappear over time. However, severe events such as depression, psychosis, mania, and paranoid reactions have also been described in some patients.

The appearance of neuropsychiatric symptoms might be associated with high plasma concentrations of efavirenz. Several studies have confirmed this hypothesis by demonstrating that patients with high plasma concentrations of efavirenz were more likely to experience adverse effects in the central nervous system (Marzolini et al., 2001; Ståhle et al., 2004; Gutiérrez et al., 2005; Hasse et al., 2005; Mathiesen et al., 2006; Lowenhaupt et al., 2007). Consequently, several research groups have studied the relationship between CYP2B6 polymorphisms, the pharmacokinetics of efavirenz, and the appearance of adverse effects in the central nervous system.

Haas et al (2004) studied the relationship among the polymorphisms of the CYP2B6 and CYP3A4 genes and the ABCB1 (*MDR1*) transporter, the appearance of adverse effects in the central nervous system related to efavirenz, and the pharmacokinetics of efavirenz. Their results revealed that the *GT* and *TT* (*CYP2B6 516 G>T*) genotypes were related to adverse symptoms in the central nervous system during the first week of efavirenz use. However, this genotype-phenotype relationship did not persist after 24 weeks of efavirenz. As noted by the authors, these results concur with those of Staszewski et al (1999), who reported that the symptoms tend to disappear over time. Moreover, they showed that the *CYP2B6 516 G>T* genetic polymorphism, the frequency of which is higher in African Americans than in European Americans, was associated with diminished efavirenz clearance and a greater incidence of adverse neuropsychiatric effects at the beginning of the treatment period (Haas et al., 2004). No other association between the other polymorphisms studied (*CYP2B6 C1459T*, *CYP3A4 A-392G*, *CYP3A5 A6986G*, *ABCB1 G2677T*, *ABCB1 C3435T*) and neurological symptoms related to efavirenz use was demonstrated (Haas et al., 2004).

Rotger et al. (2005a) showed an association between the *CYP2B6 516 TT* genotype and the appearance of neuropsychological symptoms in patients receiving efavirenz. These authors reported that the appearance of sleep and mood problems and fatigue was higher in patients homozygous for the mutant allele (*CYP2B6 516 G>T*). The presence of the variant was 2- to 3-fold higher among patients displaying neuropsychological symptoms (such as fatigue and sleep and mood problems) and 2-fold more frequent among patients displaying neurotoxicity. No significant correlation could be established between efavirenz plasma concentrations and the risk of toxicity. However, some adverse effects and their severity were associated with intracellular efavirenz concentrations measured in peripheral blood mononuclear cells. The authors suggested that the intracellular concentrations in peripheral blood mononuclear cells might be a reflection of concentrations in cellular compartments or organs, such as the central nervous system, where adverse toxic effects occur. It should be noted that CYP2B6 is also expressed in neurons and astrocytes in humans (Gervot et al., 1999; Miksys et al., 2003). Consequently, CYP2B6 expression in peripheral compartments such as the brain could influence intratissue concentrations and thereby affect the therapeutic and toxic effects of efavirenz in reservoir tissues.

Mathiesen et al. (2006) and Hasse et al. (2005) reported a significant improvement of central nervous system symptoms after an efavirenz dose reduction in patients previously receiving a normal dose and who displayed severe neuropsychiatric symptoms while having high plasma concentrations of the drug. In these two studies, a genotype analysis revealed that these patients were carriers of the *CYP2B6 516T* genetic polymorphism, which resulted in slow hepatic elimination of efavirenz (Hasse et al., 2005; Mathiesen et al., 2006). The authors concluded that neurotoxicity can be explained in part by very high efavirenz concentrations in patients who are carriers of the *CYP2B6 516 G>T* mutant allele and that reducing the efavirenz dose is a therapeutic option for slow metabolizers who display severe neuropsychiatric effects. This observation was subsequently confirmed in a study assessing the administration of a lower dose of efavirenz and the incidence of neurological effects (Gatanaga et al., 2007). An improvement in central nervous system symptoms associated with efavirenz was observed in 10 of 14 patients who received a lower dose adjusted as a function of the *CYP2B6*6*6* and *CYP2B6*6*26* haplotypes while maintaining efficacy with regard to virological suppression (Gatanaga et al., 2007).

Several studies have noted an association between the *CYP2B6 516G>T* genetic polymorphism and a high risk for central nervous system symptoms stemming from efavirenz use. Generally speaking, carriers of the *CYP2B6 516T* variant, especially those homozygous for the reduced functional allele, seem to have higher plasma concentrations of efavirenz and are much more likely to develop severe neuropsychiatric symptoms (Haas et al., 2004; Hasse et al., 2005; Rotger et al., 2005a; Gatanaga et al., 2007; Lowenhaupt et al., 2007).

Hepatic toxicity is another adverse effect of efavirenz. Yimer et al. (2011) have provided evidence that the *CYP2B6*6* genotype and high plasma efavirenz levels were predictors of increased risk for efavirenz-induced liver injury. In addition, the *CYP2B6*6* allele has been associated with early treatment discontinuation of efavirenz-containing antiretroviral regimens (odds ratio 2.8; $p = 0.006$) and potentially with an increased risk for inhibition of drug interactions (Wyen et al., 2011).

D. CYP2C19

The CYP2C subfamily enzymes account for roughly 20% of all hepatic P450s (Imaoka et al., 1996). CYP2Cs have several genetic polymorphisms that influence drug response. Of the four members of this subfamily, CYP2C19 is of clinical interest for HIV drugs.

In terms of abundance, the CYP2C19 protein is a relatively minor component, accounting for less than 5% of total hepatic P450 proteins. The classic marker of its activity is 4-hydroxylation of *S*-mephenytoin. The number of substrates metabolized by CYP2C19 is also relatively small. Drugs of interest include certain proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole), clopidogrel, citalopram, voriconazole, and the antimalarial drug proguanil/chlorguanide (Desta et al., 2001; Rendic, 2002). Among antiretroviral agents, nelfinavir and etravirine are of interest (Table 2). Nelfinavir is biotransformed mainly by CYP2C19 and to a lesser extent by CYP3A4 into its active metabolite M8.

Several polymorphisms of the *CYP2C19* gene are associated with reduced enzyme activity. In particular, among the genetic variants, the *CYP2C19*2* allele leads to a G>A substitution (position 681), causing a splicing problem, and the *CYP2C19*3* variant produces a premature stop codon. The presence of these alleles can help account for the slow and intermediary metabolic phenotypes associated with CYP2C19. As such, persons homozygous for the *CYP2C19*2* and/or *CYP2C19*3* alleles are considered to be poor CYP2C19 metabolizers, whereas carriers of at least one *CYP2C19*1* wild-type allele are described as normal or intermediate metabolizers. The decrease in CYP2C19 activity seems to be more common among Asians than among whites of European ancestry. Indeed, the frequency of slow CYP2C19 metabolizers is approximately 3 to 5% in white and African populations and 20% in Asian populations (Desta et al., 2002). *CYP2C19*17*, a new allelic variant that is associated with increased gene transcription, has been identified (Sim et al., 2006). Thus, an ultrarapid metabolizer phenotype is observed in carriers of the *CYP2C19*17* allele.

Haas et al. (2005) showed that a slow CYP2C19 metabolizer phenotype was associated with greater plasma exposure to nelfinavir, a decrease in plasma concentration ratios of nelfinavir and its active metabolite M8, and possibly a favorable response in terms of virological suppression. Indeed, previous studies had suggested a comparable efficacy for nelfinavir and its active metabolite M8. As such, the observed reduction of virological failure in carriers of the *CYP2C19*2* variant was unexpected. Another study observed that the number of viral RNA copies was significantly influenced by the CYP2C19 genotype. Only 46% of HIV-infected children homozygous for *CYP2C19*1*1* and receiving nelfinavir displayed virological suppression at 24 weeks compared with 69% of subjects heterozygous for the *CYP2C19*2* allele (Saitoh et al., 2010). Once again, decreased CYP2C19 activity was associated with a better clinical response.

Few data are available concerning the pharmacokinetic contribution of CYP2C19 and the virological response to etravirine. Etravirine metabolism is known to be dependent upon several P450 isoenzymes, such as CYP2C19, CYP2C9, and CYP3A4 (Seminari et al., 2008). Concomitant administration of etravirine and omeprazole, a CYP2C19 substrate, caused a 41% increase in the area under etravirine's plasma concentration curve in subjects who were not seropositive for HIV (Schöller-Gyüre et al., 2008). This drug-drug interaction can be explained by competitive inhibition of CYP2C19 by omeprazole, which leads to a decrease in etravirine metabolism by this isoenzyme. Although this increase is statistically significant, the authors concluded that the interaction was not clinically significant and that no etravirine dose adjustments were required when it was administered with omeprazole. It is noted that etravirine can, in turn, competitively inhibit the metabolism of other CYP2C19 substrates (i.e., substrates with a weaker affinity for this isoenzyme compared with etravirine). Consequently, it is recommended that etravirine administration be avoided with certain drugs such as the prodrug clopidogrel. Unfortunately, there are few, if any, data about the influence of CYP2C19 polymorphisms on the pharmacokinetics of etravirine.

E. CYP3A4/5

CYP3A4 is the major P450 isoenzyme involved in drug metabolism. It is the most abundantly expressed isoenzyme in the liver, where it accounts for 30 to 50% of hepatic P450 content (Guengerich, 1990; de Waziers et al., 1990; Kivistö et al., 1996). The CYP3A4 fraction in the small intestine is even higher (Paine et al., 2006). The presence of this isoenzyme in hepatocytes and enterocytes significantly contributes to presystemic drug metabolism (i.e., the intestinal-hepatic first-pass effect). Consequently, CYP3A4 activity can significantly influence the bioavailability of orally administered drugs and thereby affect their efficacy and toxicity profile. The CYP3A4 isoenzyme contributes to the metabolism of more than 50% of clinical drugs that are cleared by metabolism. These drugs include several HIV antiretroviral agents such as protease inhibitors, maraviroc, NNRTIs, and elvitegravir (Table 2).

Catalytic activity associated with CYP3A4 varies widely in the population. It is quite common to observe up to a 40-fold (even 90-fold) interindividual variation in expression of this protein (de Waziers et al., 1990; Shimada et al., 1994; Paine et al., 1997; Wolbold et al., 2003). Transcriptional induction of this isoenzyme seems to play an important role in interindividual variability.

There is a more than 85% similarity in the amino acid sequences of the CYP3A4 and CYP3A5 genes (Ortiz de Montellano, 2005). These two isoenzymes are homologous in the specificity of their substrates. As such, it is difficult to discern their respective contributions to CYP3A substrate metabolism. CYP3A5 expression has been detected in the kidneys (the predominant isoenzyme), stomach, lungs, prostate, adrenal glands, and more weakly in the liver and small intestine (Kolars et al., 1994; Lown et al., 1994; Anttila et al., 1997; Raunio et al., 1999; Yamakoshi et al., 1999; Koch et al., 2002; Hukkanen et al., 2003). Kuehl et al. (2001) showed that CYP3A5 can account for more than 50% of CYP3As in certain persons who express this isoenzyme.

CYP3A isoenzymes (CYP3A4 and CYP3A5) are involved in many clinically relevant drug-drug interactions (http://ws-ddi.intermed-rx.ca, http://medicine.iupui.edu/clinpharm/ddis/table.aspx), all the more so in patients infected with HIV given the number of drugs to which they are exposed. Schmitt et al. (2009) studied the effect of saquinavir combined with ritonavir on the metabolism of midazolam, a *CYP3A* marker substrate. They observed that maximum concentration, the area under the midazolam concentration curve, and its elimination half-life were increased 4.3-, 12.4-, and 3-fold, respectively, after 2 weeks of treatment with saquinavir/ritonavir (Schmitt et al., 2009). Mertz et al. reported a major drug-drug interaction between tacrolimus and a darunavir/ritonavir combination for which the weekly tacrolimus dose had to be reduced by almost 30-fold to 3.5% of the typically administered dose (Mertz et al., 2009). This interaction was explained by the significant reduction of the hepatic first-pass effect (via the CYP3As and glycoprotein-P) of tacrolimus by protease inhibitors (Mertz et al., 2009). In fact, it is possible to see a decrease in CYP3A activity for drugs with a significant intestinal-hepatic first-pass effect and that cannot reach efficacious concentrations. The use of ritonavir as a booster works in this way and makes it possible to optimize the antiretroviral therapeutic value of other protease inhibitors.

It should also be noted that the concomitant administration of CYP3A inducers has major repercussions on the virological efficacy of certain antiretroviral CYP3A substrates by increasing their clearance. For example, concomitant administration of maraviroc (a CYP3A substrate) with rifampin or efavirenz (CYP3A inducers) causes a significant decrease in the maximum concentration and the area under the maraviroc concentration curve (70 and 50%, respectively) (Abel et al., 2008). In contrast, combining maraviroc with protease inhibitors (saquinavir and lopinavir combined with ritonavir) produces increased exposure of maraviroc because of the competitive inhibition of its metabolism by CYP3A. It is therefore important to understand that adding efavirenz to this cocktail thwarts CYP3A inhibition caused by the effect of protease inhibitors on maraviroc metabolism (Abel et al., 2008). Indeed, Abel et al. (2008) reported that the net effect of combining efavirenz with protease inhibitors on maraviroc exposure remained inhibition, although the magnitude was much less in the presence than in the absence of efavirenz (Abel et al., 2008). It should be noted that protease inhibitors have different pharmacokinetic characteristics, giving them different competitive inhibitor profiles with regard to CYP3A substrates. For example, tipranavir combined with ritonavir has a weaker inhibition potential than agents such as lopinavir (Boffito et al., 2006; Abel et al., 2008). When administered alone, tipranavir induces CYP3A activity, whereas its coadministration with ritonavir results in CYP3A inhibition (MacGregor et al., 2004). Consequently, managing drug-drug interactions with antiretroviral agents requires very specific rather than merely general knowledge of each of the agents involved.

Several genetic variants have been identified in the *CYP3A4* gene. However, the association between these genetic polymorphisms and direct impact on exposure to substrates is often contradictory. In contrast, the presence of genetic polymorphisms directly regulates the expression and variable distribution of CYP3A5 according to ethnic origin. Variability in hepatic CYP3A5 expression is largely attributed to the *CYP3A5*3* mutant allele and, to a lesser extent, to the *CYP3A5*6 and CYP3A5*7* variants. The variant *CYP3A5*3* allele creates an alternate splicing site in mRNA, resulting in aberrant mRNA, which causes the early appearance of a stop codon and a weak to null level of protein expression. Depending upon ethnic origin, its frequency varies: 70 to 95% in white populations (French and European), 71 to 85% in Japanese, 65 to 75% in Chinese, and 20 to 35% in Africans and African Americans (Kuehl et al., 2001; Lee et al., 2003; Xie et al., 2004; Quaranta et al., 2006). This variant allele is more prevalent than the wild-type allele (*CYP3A5*1*) in the majority of populations, with the exception of African Americans, in whom the wild-type allele predominates. The frequency of the wild-type allele is 10 to 30% in white people, 15% in Japanese, 25 to 35% in Chinese, and 50% in African Americans. It has been observed that only those with at least one wild-type allele express significant quantities of the enzyme in the liver. The *CYP3A5*6* allele has been identified in around 13 to 16% of African Americans and is rarely found in white (0 to 4%) or Asian (0%) populations (Kuehl et al., 2001; Lee et al., 2003; Xie et al., 2004).

The *CYP3A5*3* variant has been associated with a decrease in the clearance of various substrates of CYP3As (indinavir and saquinavir) (Fröhlich et al., 2004; Mouly et al., 2005; Anderson et al., 2006). Mouly et al. (2005) assessed the association between the degree of clearance for saquinavir and variants for *CYP3A4* and *CYP3A5* genes in healthy subjects. They showed that *CYP3A5*1* was associated with an increase (2-fold) in the clearance of the drug compared with carriers of the *CYP3A5*3* variant (Mouly et al., 2005). Another study, conducted in 16 subjects, showed that mean plasma levels of saquinavir were decreased by 34% in subjects homozygous for *CYP3A5*1* (Josephson et al., 2007). Similar results were obtained for indinavir. Anderson et al. (2006) showed that subjects with at least one *CYP3A5*1* allele have an increased oral clearance of indinavir (44%) compared with subjects with a *CYP3A5*3*3* genotype. Similar results were also obtained with atazanavir in which plasma levels of the drug were shown to be lower (24 ng/ml) and clearance higher (0.38 $l \cdot h^{-1} \cdot kg^{-1}$) in subjects with at least one *CYP3A5*1* allele compared with subjects homozygous for the *3 variant allele (131 ng/ml and 0.18 $l \cdot h^{-1} \cdot kg^{-1}$, respectively) (Anderson et al., 2009)The coadministration of ritonavir, which inhibits CYP3As, is associated with a blunting of *CP3A5*1* allele effects.

It should be noted that adding ritonavir changes the phenotype associated with CYP3A activities. Consequently, studies assessing the influence of genetics on the pharmacokinetics of antiretroviral agents must ask whether the medication is administered with ritonavir (or another CYP3A inhibitor or inducer) or by itself. In this regard, Estrela et al. (2008) observed that a genetic polymorphism in the *CYP3A5* gene did not influence lopinavir trough concentrations in patients infected with HIV who were receiving lopinavir in combination with ritonavir. Similar observations have been reported with indinavir: when indinavir was administered alone, its clearance was reduced by 31% in patients with a *CYP3A5*3*3* genotype compared with carriers of the *CYP3A5*1*3* genotype (Solas et al., 2007). However, when patients received indinavir with ritonavir, variability in the pharmacokinetics of indinavir was significantly reduced. The authors suggested that recourse to the pharmacokinetics of CYP3A5 may be of little clinical value in the presence of a therapeutic regimen that includes a protease inhibitor, if it is combined with ritonavir. Indeed, administering ritonavir leads to a reduction of intersubject variability because it acts as a phenotypic modulator by decreasing CYP3A metabolic activity. Lubomirov et al. (2010) studied the influence of various mutations on the pharmacokinetics of lopinavir (1380 SNPs were genotyped, including a tag SNP of the CYP3A locus). This model indicates that genetic variations can explain only ≈5% of lopinavir variability in patients receiving lopinavir/ritonavir (Lubomirov et al., 2010).

F. Drug Transporters

One of the causes of the persistence of viral replication despite HAART therapy could be the suboptimal penetration of antiretroviral agents into sanctuary sites such as the central nervous system or into CD4$^+$ target cells. Drug transporters are viewed as one of the major mechanisms that account for suboptimal tissue concentrations of antiretroviral agents (Sankatsing et al., 2004). What happens to drugs regulated by transporters is the result of a dynamic interaction between influx and efflux transporters. The importance and the direction of movement of several drugs are determined by the combined action of transporters expressed at the apical or basolateral surface of the membrane (Fig. 3).

Drug transporters fall into two groups: the ABC superfamily of transporters (ATP-binding cassette proteins) and the SLC superfamily of transporters (solute carrier proteins), for which 49 and 362 genes, respectively, have been identified in the human genome (Hediger et al., 2004; Gillet et al., 2007; He et al., 2009). The membrane proteins of the ABC class use ATP as an energy source, enabling an accumulation of the drug against an electrochemical gradient, whereas SLC transporters catalyze the transport of substrate using an electrochemical gradient (Dean et al., 2001; Jung and Taubert, 2009). The transport proteins of the ABC family include such proteins as ABCB1 transporters (P-glycoprotein), ABCC [multidrug resistance associated proteins (MRPs)] and ABCG2 (breast cancer resistance protein). The transport proteins of the SLC family include OATPs (SLC21/SLCO), OATs, OCTs (SLC22A1–3) and OCTNs (SLC22A4–5).

ABC transporters are found in many epithelial and endothelial cells, where they participate in the absorption and excretion of several drugs. The ABC transporters also act as a barrier by limiting the distribution by extrusion of drugs in certain tissues such as encephalic, placental, and testicular barriers. They also act as a barrier against the accumulation of drugs in certain sites such as leukocytes (Schinkel and Jonker, 2003). For their part, SLC transporters are generally associated with the influx transport of drugs.

Transporters can influence antiretroviral therapy in many ways: 1) bioavailability (intestinal and hepatic transporters); 2) antiretroviral penetration in sanctuary sites (e.g., brain, vaginal mucus, testicles); and 3) access in target cells (lymphocytes).

G. ATP-Binding Cassette Subfamily B Member 1 Transporter (P-Glycoprotein)

The P-glycoprotein transporter coded by the *ABCB1* (*MDR1*) gene is the most studied ABC transporter. This efflux transporter is widely distributed and has significant expression levels in the small intestine, liver, kidneys, and brain (Ho and Kim, 2005). It is also expressed in other tissues, such as the placenta, ovaries, testicles, and lymphocytes (Thiebaut et al., 1987; Cordon-Cardo et al., 1989; Klimecki et al., 1994; Turriziani et al., 2008). ABCB1 expression in lymphocytes has been observed in 20 to 80% of B lymphocytes and 30 to 80% of T cells (Chaudhary et al., 1992; Drach et al., 1992; Klimecki et al., 1994; Ludescher et al., 1998; Köck et al., 2007). It is noteworthy that expression of *ABCB1* is dependent upon cell activation level (Ludescher et al., 1998; Köck et al., 2007).

P-glycoprotein participates in the transport of a wide variety of drugs, including digoxin (often used as a marker substrate), chemotherapeutic agents, immunosuppressive drugs, statins, calcium channel blockers, and antidepressant and antiretroviral agents (Sakaeda et al., 2003). In vitro and in vivo studies have shown that all protease inhibitors display a high affinity for ABCB1 (Table 2) (Kim et al., 1998b; Lee et al., 1998; Jones et al., 2001b; Ronaldson et al., 2004; Fujimoto et al., 2009; Zastre et al., 2009). Maraviroc, abacavir, and raltegravir are among other antiretroviral agents that have also been identified as ABCB1 transporter substrates (Table 2) (Walker et al., 2005; Kassahun et al., 2007; Shaik et al., 2007). It therefore seems clear that ABCB1 transporter expression in peripheral blood mononuclear cells can play an important role in antiretroviral therapy.

In vitro studies in the early 1990s demonstrated a role for ABCB1 transporters in antiretroviral drug resistance. For example, it was shown that suppressing the ABCB1 transporter in CEM cells affected intracellular concentrations of zidovudine and was associated with a decrease in the antiproliferative and antiviral effects of this drug (Antonelli et al., 1992). In addition, Jones et al. (2001a,b) showed that there was less intracellular accumulation of protease inhibitors in cells overexpressing ABCB1 or ABCC1 transporters. Several studies support the idea that intracellular concentrations of several protease inhibitors are influenced by ABCB1's functional activity (Jones et al., 2001a; Meaden et al., 2002; Ford et al., 2004). Moreover, two clinical studies showed a correlation between intracellular concentrations of protease inhibitors and antiviral activity; virological failure was noted only when subtherapeutic intracellular concentrations were observed (Bilello et al., 1996; Nascimbeni et al., 1999).

In general, the role of ABC transporters in in vitro cell-based viral resistance has been well established for protease inhibitors and NRTIs. However, the data indicate that NNRTIs are not affected by the presence of these transporters. Moreover, Janneh et al. (2009) confirmed that intracellular accumulation of efavirenz and nevirapine in lymphocytes was independent of ABCB1 transporter activity.

The presence of polymorphisms in genes coding for drug transporters is associated with a modulation of the pharmacokinetics of the antiretroviral agents they transport. The most common and most studied genetic polymorphism in the *ABCB1* gene is the *3435 C>T* mutation at exon 26. The *ABCB1 3435 C>T* variant is a synonymous mutation; i.e., it affects the genetic code but does not lead to an amino acid change. The frequency of the *3435T* variant varies according to ethnic origin and is estimated to be ~40% in Asians, 60% in Indians, 50% in whites, and 19% in African Americans (Fung and Gottesman, 2009).

Fellay et al. (2002) described the first clinical evidence suggesting that antiretroviral response at the outset of treatment could be influenced by the presence of allelic variants of the *ABCB1* gene. This study showed that patients homozygous for the *ABCB1 C3435T* variant displayed a greater increase in $CD4^+$ cell count 6 months after therapy had started (Fellay et al., 2002). An association between the intracellular exposure of nelfinavir and the *ABCB1 C3435T* variant has been shown (Colombo et al., 2005). The role of ABCB1 in the pharmacokinetics of lopinavir was also shown by van Waterschoot et al., who reported that its plasma concentrations were 9-fold higher in *abcb1 a/b*(−/−) knockout than in wild-type mice (van Waterschoot et al., 2010).

ABC transporters contribute to the efflux of NRTIs. However, it should be noted that several studies have reported contradictory results with regard to the effect of the *ABCB1* polymorphism on virological response. As such, several studies have not found a significant association between the ABCB1 genotype and viral load (Saitoh et al., 2010). Leschziner et al. (2007) reported the existence of several limitations that could explain the contradictory results observed in vitro, ex vivo, and in vivo with regard to the relationship between polymorphisms in the *ABCB1* gene and drug response. Among other things, they concluded that study power, number of patients, genotyping technique, the presence of comorbidities and comedication could influence ABCB1 expression and activity. This situation is similar to that observed with the *CYP3A5* polymorphism. The presence of ritonavir in therapeutic regimens reduces the impact of genetics by modulating patient phenotypes. Consistent with this, an association was reported between the *ABCB1 3435T* polymorphism and virological efficacy only among patients infected with HIV who were receiving antiretroviral therapy that contained a protease inhibitor without a boosting agent (de la Tribonnière et al., 2008).

1. Pharmacogenetics and Hepatotoxicity Associated with Nevirapine. Hypersensitivity reactions and increases in hepatic transaminases are among the most common toxicities associated with nevirapine use. The results of several studies of the safety profile of nevirapine indicate that 2 to 13% of patients receiving this drug develop hepatotoxicity symptoms and that this risk increases in the presence of coinfections such as hepatitis B or C (Sulkowski et al., 2002; Ena et al., 2003; Stern et al., 2003; van Leth et al., 2004; Chu et al., 2010). In general, hepatitis secondary to nevirapine occurs at approximately 12 weeks after the initiation of treatment and is often accompanied by a skin rash. These adverse events require the discontinuation of nevirapine in 2 to 7% of patients (Montaner et al., 1998; Martínez et al., 2001). The human leukocyte antigen class II system and the CD4-dependent immune response associated with nevirapine have been associated with the appearance of hypersensitivity and hepatotoxicity reactions. The absence of a rash or fever in several cases of hepatic toxicity with nevirapine suggests that the latter adverse event does not always involve an immune process and that other mechanisms may be involved.

Two studies reported an association between the *ABCB1* polymorphism (*3435 C>T*) and the overall risk of hepatotoxicity after nevirapine treatment. A case-controlled study by Ritchie et al. (2006) showed that the *ABCB1 3435 C>T* polymorphism was significantly associated with a lower risk of hepatic toxicity in patients receiving an NNRTI. This genotype-phenotype association was confirmed by a randomized study by Haas et al. (2006), which showed that the *ABCB1 3435 T* allele was less frequent in the patient group displaying hepatic toxicity. No significant association with risk of hepatic toxicity with other polymorphisms of potential gene candidates of enzymes involved in the metabolism of nevirapine (CYP2B6 and CYP3A5) was found (Haas et al., 2006; Ritchie et al., 2006). Hence, the polymorphism in the gene coding for ABCB1 bestows protection against hepatic toxicity. The role of ABCB1 in nevirapine transport remains controversial. The mechanism that explains the association between the ABCB1 polymorphism and the reduced risk of hepatotoxicity is not understood and requires mechanistic studies before a genuine association can be confirmed.

H. ATP-Binding Cassette Subfamily C Transporters (Multidrug Resistance-Associated Proteins)

The ABCC transporters (MRP) also play an important role in the distribution of antiretroviral agents (Table 2). As is the case with ABCB1, ABCC transporters actively participate in the efflux of drugs from cells contributing to the drug-resistance phenomenon. The ABCC1, -2, -4, and -5 transporters are among the most important in the ABCC family, with the ability to influence response to antiretroviral agents. Initially detected in pulmonary tumor cells, it is now well established that ABCC1 expression is ubiquitous in human organs (e.g., the testicles, peripheral blood mononuclear cells, and the placenta) (Flens et al., 1996; St-Pierre et al., 2000). It has been reported that ABCC1 and ABCC2 transporter expression was higher in $CD4^+$ cells, followed by $CD8^+$ and $CD19^+$ cells (Oselin et al., 2003). Briefly stated, mRNA or the protein was detected for the various ABCC1, -2, -4, and -5 transporters in monocytes, $CD4^+$ cell lines, and the lymphocytes of patients infected with HIV (Oselin et al., 2003; Zhang et al., 2006; Turriziani et al., 2008; Weiss et al., 2009).

Several in vitro studies have shown that ABCC1 and ABCC2 transporters participate in the transport of protease inhibitors such as lopinavir, atazanavir, ritonavir, saquinavir, and indinavir (Srinivas et al., 1998; Jones et al., 2001b; Huisman et al., 2002; Dallas et al., 2004; Jorajuria et al., 2004; Agarwal et al., 2007; Janneh et al., 2007). Consequently, these transporters could be important modulators of the pharmacokinetics of these drugs by affecting their distribution in the body (van der Sandt et al., 2001; Huisman et al., 2002; Janneh et al., 2005, 2007; Anderson et al., 2006; Zastre et al., 2009). Studies have shown a relationship between intracellular concentrations of protease inhibitors in peripheral blood mononuclear cells and ABCC1 expression (Jones et al., 2001a; van der Sandt et al., 2001; Meaden et al., 2002; Janneh et al., 2005; Agarwal et al., 2007; Zastre et al., 2009). In addition, the efflux of emtricitabine (an NRTI) in lymphocytes by ABCC1 has been demonstrated (Bousquet et al., 2008a). Several in vitro studies have also shown that ABCC4 can transport substrates such as abacavir and zidovudine, whereas stavudine is an ABCC5 substrate (Schuetz et al., 1999; Reid et al., 2003). The efflux of tenofovir can be regulated by several transporters, including ABCC2, -4, and -5 (Reid et al., 2003; Mallants et al., 2005; Ray et al., 2006; Imaoka et al., 2007). For example, Ray et al. (2006) showed that the intracellular concentration of tenofovir was 5-fold lower in cells overexpressing ABCC4. They also found that ABCC4 overexpression in these cells was associated with a 2- to 2.5-fold decrease in cytotoxicity.

Several genetic variants have been identified in the transporter genes belonging to the ABCC family. However, the role of *ABCC1* polymorphisms in systemic and intracellular pharmacokinetics and in virological response has not been clearly established. However, an association has been observed between *ABCC2* genetic variants and the pharmacokinetics of some protease inhibitors. One study reported that oral clearance of indinavir was faster (by 24%) in carriers of a mutation in the promoter region of *ABCC2 −24 C>T* (Anderson et al., 2006).

Polymorphisms in the *ABCC4* gene have been associated with high concentrations of NRTIs, suggesting that this transporter plays a role in the disposition of these drugs. Carriers of the *4131 T>G* variant of the *ABCC4* gene displayed a 20% increase in intracellular concentrations of lamivudine. In addition, the mean concentration of zidovudine was 49% higher in carriers of the *ABCC4 3724 G>A* mutant allele than in subjects homozygous for the wild-type allele (Anderson et al., 2006). The *ABCC4 3463 A>G* polymorphism has been associated with a 35% increase in intracellular concentrations of tenofovir in patients infected with HIV (Kiser et al., 2008). There is still scant information about the genetic role of ABCC3 and ABCC5 transporters and the clinical impact of polymorphisms in these genes.

I. The ATP-Binding Cassette Subfamily G Member 2 Transporter (Breast-Cancer Resistant Protein)

In addition to the ABCB1 (P-glycoprotein) and ABCC (MRP) transporters, the ABCG2 (breast cancer-resistant protein) transporter has also been associated with transport and resistance to certain drugs. The ABCG2 transporter has tissue distribution similar to that of ABCB1. Indeed, it is expressed in the placenta, small intestine, liver, lymphocytes, blood-brain barrier, mammary tissue, and hematopoietic stem cells (Mao and Unadkat, 2005). Whereas NRTIs are substrates subject to efflux by ABCG2, this transporter's activity has been shown to have no effect on protease inhibitors (Table 2). In contrast, it has been reported that several protease inhibitors (e.g., lopinavir, ritonavir, saquinavir, nelfinavir, and, to a lesser extent, atazanavir) and the NNRTI efavirenz are powerful inhibitors of ABCG2 substrate transport (Gupta et al., 2004). No significant inhibition of ABCG2 activity has been observed in the presence of indinavir and amprenavir (Gupta et al., 2004; Weiss et al., 2007a).

Wang et al. (2003, 2004) reported the first evidence of possible ABCG2 involvement in cell resistance to antiretroviral agents belonging to the class of reverse transcriptase inhibitors. The antiviral activities of zidovudine, zalcitabine, didanosine, and stavudine were reduced in MT-4 cells transfected with wild-type ABCG2 (Wang et al., 2004). Moreover, in cells transfected with ABCG2, there was less intracellular accumulation of zidovudine, abacavir, lamivudine, and stavudine, and ABCG2 transporter inhibitors attenuated this effect (Pan et al., 2007; Giri et al., 2008). Giri et al. (2008) showed that plasma levels were reduced and cerebral penetration increased for abacavir in ABCG2 knockout mice. The sequencing of the ABCG2 transporter revealed that many allelic variants could significantly affect its in vivo activity. However, a pharmacogenetics study that included the *C421A* and *G34A* variants, which were associated in vitro with a decrease in ABCG2 activity, found no association of these polymorphisms with intracellular accumulations of zidovudine triphosphate and lamivudine triphosphate (Anderson et al., 2006). The ABCG2 transporter's role in antiretroviral therapy is poorly defined, and studies are needed to establish the contribution of ABCG2 as a modulator of the pharmacokinetics of reverse transcriptase inhibitors and influence on virological response.

J. Solute Carrier Transporters

Recent data suggest a probable role for SLC transporters in the pharmacokinetics of antiretroviral agents (Table 2). Transporters belonging to the SLCO (OATP) family, which are involved in the transport of several endogenous compounds and drugs, play an important role in the influx transport of many compounds, particularly in the intestine, hepatocytes, kidneys, and placenta (Hagenbuch and Gui, 2008). The results of an in vitro study showed that SLCO transporters were an important determinant of the intracellular accumulation of saquinavir and lopinavir in T $CD4^+$ cells and peripheral blood mononuclear cells (Janneh et al., 2008). Using an oocyte transport system, Hartkoorn et al. (2010) assessed the specificity of substrates for various SLC family transporters. Their results demonstrated that protease inhibitors (lopinavir, darunavir, and saquinavir) are substrates for SLCO1A2 (OATP1A2), SLCO1B1 (OATP1B1), and SLCO1B3 (OATP1B3) transporters, although their expression did not affect NNRTI (efavirenz and nevirapine) transport.

Many genetic polymorphisms (40 mutations) have been identified in the *SLO1B1* gene and to a lesser extent in the *SLCO1A2* and *SLCO1B3* genes. Among various genetic variants, *A388G* and *T521C* occur frequently in the population, and their allelic distribution has been observed in various ethnic groups. For example, the estimated distribution of the *T521C* allele is 1% in African Americans, 14% in whites, and 16% in Asians (König et al., 2006). In addition, it has been demonstrated in vitro and in vivo that several *SLCO1B1* genetic variations were associated with a decrease in transporter activity. Moreover, it has been observed that the *SLCO1B1 T521C* polymorphism was significantly associated with higher plasma concentrations of lopinavir in patients homozygous for the mutant allele, which would suggest that the entry of lopinavir into the liver via the SLCO1A2 influx transporter is an important determinant of lopinavir exposure. However, no significant associations between lopinavir concentrations and the polymorphisms of the *SLCO1A2* and *SLO1B3* genes were observed (Hartkoorn et al., 2010). Another study assessed the influence of various genetic variations of the *SLCO1B1* gene (*A338G*, *C463A*, and *T521C*) on lopinavir plasma concentrations in 99 patients infected with HIV who were receiving a lopinavir-ritonavir combination (Kohlrausch et al., 2010). The results showed that lopinavir plasma concentrations were higher in carriers of a mutant allele (*521C*) than in those homozygous for the wild-type allele (*521TT*) (Kohlrausch et al., 2010). No association was observed with the other genetic variants. A pharmacokinetic-pharmacogenetic population analysis revealed that subjects homozygous for the *SLCO1B1*4* (*SLCO1B1 463 C>A*) allele had higher lopinavir clearance (12.6 l/h) than subjects with the reference genotype (5.4 l/h) or carriers of at least one mutant allele for *SLCO1B1* (**5*; *SLCO1B1 521 T>C*), *ABCC2*, or *CYP3A* (3.9 L/h) (Lubomirov et al., 2010). The *SLCO1B1*4* allele is associated with an increased activity of the transporter.

The SLC2 family includes OCT members, the substrates of which can be transported in varying directions depending on the transmembrane concentration gradient. Interactions between OCT transporters and antiretroviral agents have been described with OCT1 and OCT2, which are involved in the transport of several small cationic organic molecules (Table 2). OCT2 is highly expressed in the kidney, whereas OCT1 is highly expressed in the liver. These transporters are of interest for HIV in light of their distribution in target tissues for HIV replication and in sanctuary sites. OCTs have been identified in $CD4^+$ lymphocytes, monocytes, the brain, the testicles, and lymph nodes (Jung and Taubert, 2009). Jung et al. (2008) reported that OCT1 and OCT2 transporter expression in lymph nodes was higher in seropositive patients than in subjects not infected with HIV.

NRTIs such as lamivudine and zalcitabine are OCT1, -2, and -3 substrates (Leung and Bendayan, 2001; Takubo et al., 2002; Jung et al., 2008; Minuesa et al., 2009). In vitro studies have reported that protease inhibitors such as saquinavir, nelfinavir, ritonavir, and indinavir were OCT1 inhibitors (Zhang et al., 2000; Jung et al., 2008). Minuesa et al. (2009) observed transport inhibition by OCT1, OCT2, and OCT3 in the presence of abacavir, emtricitabine, tenofovir, and zidovudine. An interaction between lamivudine and trimethoprim has been described in vitro and in vivo, and the suggested mechanism for this interaction is inhibition by trimethoprim of lamivudine kidney transport by OCT2 (Moore et al., 1996; Leung and Bendayan, 2001; Takubo et al., 2002; Jung et al., 2008). Patients infected with HIV displayed a 43% increase in the area under the concentration curve and a 35% decrease in renal clearance of lamivudine when trimethoprim was coadministered (Moore et al., 1996). The clinical relevance of OCT transporters in monitoring antiretroviral therapy has yet to be clearly defined.

1. Pharmacogenetics of Transporters and Neurotoxicity Associated with Tenofovir

Tenofovir, a nucleoside reverse transcriptase inhibitor, is widely used in HIV treatment because of its favorable efficacy profile, its very good toxicity potential, pharmacokinetics allowing for once-daily administration, and its weak potential for drug-drug interaction (it is neither a substrate, an inhibitor, nor an inducer of P450s). However, several cases of tenofovir-induced nephrotoxicity, including renal proximal tubulopathy, acute renal failure, and Fanconi syndrome, have been reported (Coca and Perazella, 2002; Verhelst et al., 2002; Créput et al., 2003; Karras et al., 2003; Lee and Marosok, 2003; Schaaf et al., 2003; Barrios et al., 2004; Hansen et al., 2004; Rifkin and Perazella, 2004; Mauss et al., 2005; Irizarry-Alvarado et al., 2009; Woodward et al., 2009; Agarwala et al., 2010). Although the incidence of nephrotoxicity is rare (around 2%), proximal renal tubular damage has been observed in several patients with prolonged exposure to tenofovir (Coca and Perazella, 2002; Karras et al., 2003; Rifkin and Perazella, 2004; Saumoy et al., 2004; Padilla et al., 2005). Several factors have been associated with a high risk for renal tubular damage in patients receiving tenofovir: age, low body weight, a pre-existing alteration of renal function, concomitant administration of nephrotoxic drugs, coadministration of didanosine, high tenofovir plasma concentrations, and pharmacogenetic factors (Saumoy et al., 2004; Masiá et al., 2005; Zimmermann et al., 2006; Crane et al., 2007; Nelson et al., 2007).

The exact mechanism of tenofovir-induced renal toxicity is not clearly defined. However, two mechanisms have been proposed: 1) via mitochondrial toxicity (but the potential of tenofovir for interfering with mitochondrial function and inhibiting DNA polymerase-γ is weak), and 2) via interference by tenofovir with normal function of renal cells via its action on transporters expressed in renal cells.

Tenofovir is eliminated by renal excretion through a combination of glomerular filtration and active tubular secretion. The process of active secretion of tenofovir in renal tubular cells involves several membrane transporters belonging to the ABC and SLC superfamilies. Tenofovir entry into renal tubular cells through the basolateral membrane (transport of tenofovir in the blood toward the renal cell) is carried out by OTA organic anion transporters, mainly OAT1 and to a lesser extent OAT3. Inside the renal cells, tenofovir is secreted by ABCC2- and ABCC4-mediated active efflux transport on the apical membrane (carried into the urine) (van Aubel et al., 2002; Mallants et al., 2005; Van Aubel et al., 2005; Ray et al., 2006; Imaoka et al., 2007). Imaoka et al. (2007) showed a greater accumulation of tenofovir in the renal tissues of ABCC4 knockout mice than in control mice. Renal clearance of efflux was also lower in ABCC4 knockout mice (46% less than in control mice). Ray et al. (2006) observed that tenofovir concentrations were 5-fold less in cells overexpressing the ABCC4 protein. They also reported that tenofovir toxicity was reduced by more than 2-fold in cells overexpressing ABCC4 as a result of a lower accumulation of tenofovir in these cells.

Kiser et al. showed that carriers of a *3436G* mutation in the gene coding for ABCC4 displayed lower renal clearance and higher plasma concentrations than carriers of the wild-type allele (Kiser et al., 2008). This study suggests that genetic variations in *ABCC4* could play a role in the intracellular concentration of tenofovir and predispose subjects to renal toxicity (Kiser et al., 2008).

Two studies have reported an association between a polymorphism in the *ABCC4* gene and the risk for renal tubulopathy associated with tenofovir. Izzedine et al. (2006) hypothesized that variations in the genes involved in tenofovir transport could favor its intracellular accumulation and thereby increase the risk of tubular toxicity. They conducted a case-control study of 30 white patients infected with HIV who were receiving tenofovir (13 patients who displayed tenofovir-induced tubular nephropathy and a 17-patient control group who displayed no renal problems). Different variants of the *ABCC4*, *ABCC2*, and *ABCB1* genes were analyzed. The occurrence of tenofovir-induced renal tubulopathy was associated with the ABCC2 1249G>A variant and with the CATC haplotype (defined by the combination of different SNPs at positions −24, 1249, 3563, and 3972 of the *ABCC2* gene) (Izzedine et al., 2006). They also observed that the CGAC haplotype found only in the control group seemed to protect against nephrotoxicity by stimulating increased renal secretion activity (Izzedine et al., 2006).

Rodríguez-Nóvoa et al. (2009) assessed the association between various genetic polymorphisms found in *ABCC4*, *ABCC2*, *ABCB1*, and *SLC22A6* (*OAT1*) and the risk of tenofovir renal toxicity. Their analysis showed a significant association between the *ABCC2 −24C* allele and the risk of renal damage in patients receiving tenofovir. However, this study did not succeed in confirming the association between the CATC haplotype of ABCC2 with the incidence of tenofovir-induced renal tubulopathy (Rodríguez-Nóvoa et al., 2009).

K. Glucuronidation Enzymes

Glucuronidation plays a central role in drug metabolism. Phase II reactions catalyzed by UGTs consist of the transfer of a glucuronic acid molecule to an acceptor molecule. Glucuronidation is an important step in the elimination of several endogenous compounds (e.g., bilirubin, bile acid, and steroid hormones) and certain drugs used in HIV treatment such as zidovudine, raltegravir, abacavir, and efavirenz (Mutlib et al., 1999; Barbier et al., 2000; Ward et al., 2003; Kassahun et al., 2007; Bélanger et al., 2009). The enzymes involved in glucuronidation are grouped into two families (UGT1 and UGT2) and include 19 enzymes having significant conjugative activities in humans. UGT enzymes are for the most part expressed in the liver, and 10 of them display a hepatic expression greater than 1% of total UGTs. There is wide interindividual variation in their expression (Congiu et al., 2002; Izukawa et al., 2009; Court, 2010).

UGT2B7 has been identified as the main isoform involved in the glucuronidation of zidovudine and efavirenz (Trapnell et al., 1998; Barbier et al., 2000; Collier et al., 2004; Kassahun et al., 2007; Bélanger et al., 2009). The *UGT2B7* gene is influenced by genetic polymorphisms, and its variations seem to explain the interindividual variability observed in the kinetics of these antiretroviral agents. Kwara et al. (2009a,b) assessed the impact of genetic polymorphisms in UGT2B7 on the pharmacokinetics of zidovudine and efavirenz. Oral clearance of zidovudine was 196% higher among carriers of the *UGT2B7*1c* allele (gain-in function) than those with the wild-type allele (Kwara et al., 2009a). The area under the zidovudine plasma concentration curve and its elimination half-life were reduced by 57 and 67% in patients with the *UGT2B7*1c* allele (Kwara et al., 2009a). These results were supported by in vitro data showing that the *UGT2B7*1c* allele was associated with higher protein expression and a 48% activity increase (Kwara et al., 2009a). In another study, the same authors reported that in addition to *CYP2B6*, variations in

UGT2B7, the gene responsible for glucuronate *N*-efavirenz formation, influenced efavirenz plasma concentrations (Kwara et al., 2009b). The results of their linear regression analysis suggest that the *UGT2B7*1a* allele explains 10% of total variance in the plasma concentrations of efavirenz (Kwara et al., 2009b). The multivariate regression model suggested that pharmacokinetic data associated with CYP2B6, UGT2B7, and CYP2A6 accounted for more than 60% of the variability in efavirenz concentrations in patients in Ghana infected with HIV (Kwara et al., 2009b). The results of this study support the role of UGT2B7, as well as CYP2B6 and CYP2A6, as predictors of the pharmacokinetic profile of efavirenz.

1. Pharmacokinetics of UDP-Glucuronosyltransferase and the Risk of Atazanavir- and Indinavir-Associated Hyperbilirubinemia. Hyperbilirubinemia is an adverse effect observed in a signification proportion of patients receiving antiretroviral therapy containing atazanavir or indinavir. Unconjugated bilirubin entry into hepatocytes occurs by passive diffusion and by transport facilitated by the OATP1B1 influx transporter (König et al., 2000; Briz et al., 2003). Bilirubin can then become conjugated to glucuronic acid in the hepatocyte and excreted into the bile via the ABCC2 efflux transporter (Tukey and Strassburg, 2000).

Around 25 to 30% and 5 to 25% of patients exposed to atazanavir or to indinavir, respectively, develop hyperbilirubinemia secondary to an increase in unconjugated bilirubin. The clinical condition of 6% of these patients evolves into jaundice (Plosker and Noble, 1999; Busti et al., 2004). This adverse event results from competitive inhibition by atazanavir or indinavir of UGT1A1, the enzyme responsible for bilirubin conjugation and clearance.

Polymorphisms in the *UGT1A1* gene are associated with variations in its enzyme activity. Moreover, hyperbilirubinemia situations occur more often in patients with Gilbert's syndrome, which is associated with a genetic abnormality that alters bilirubin conjugation. This syndrome results from a genetic polymorphism in the promoter region of the *UGT1A1* gene (*UGT1A1*28*, defined by seven repetitions of the TA dinucleotide in the promoter region, *UGT1A1-TA7*). The frequency of the *UGT1A1*28* allele varies according to ethnic group. This variant is expressed less frequently in Asians (Japanese 11% and Chinese 16%) than in whites (36–39%) and African Americans (43%) (Beutler et al., 1998; Ki et al., 2003; Takeuchi et al., 2004). Several studies have shown that the incidence of hyperbilirubinemia in patients exposed to atazanavir or indinavir varies as a function of genotype. Huang et al. (2005) reported that 15% of patients homozygous for the wild-type allele versus 90% of patients homozygous for the *UGT1A1*28* allele developed hyperbilirubinemia. Bilirubin plasma levels and the number of cases of jaundice were higher in the group of patients carrying the two mutant alleles (Zucker et al., 2001; Rotger et al., 2005b; Boyd et al., 2006; Rodríguez-Nóvoa et al., 2007). Rodríguez-Nóvoa et al. (2006) confirmed the relationship between the *UGT1A1*28* genotype and the risk of hyperbilirubinemia with atazanavir and indinavir. They found that the proportion of grade 3 to 4 hyperbilirubinemia was 80% among patients homozygous for the *UGT1A1*28* allele, 29% in heterozygous patients and 18% among patients homozygous for the wild-type allele (Rodríguez-Nóvoa et al., 2006).

Other polymorphisms in the *UGT1A1* gene can also favor the development of hyperbilirubinemia associated with atazanavir and indinavir. The *UGT1A1*6* polymorphism, which is found in Asians (13–23%) and rarely in whites (<.1%), is associated with a 70% in vitro reduction of the rate of bilirubin conjugation and as such mimics Gilbert's syndrome (Bosma et al., 1995; Yamamoto et al., 1998; Takeuchi et al., 2004; Kaniwa et al., 2005; Urawa et al., 2006). Boyd et al. (2006) reported that the risk of severe hyperbilirubinemia with indinavir was correlated with the presence of the *UGT1A1*6* allele in Thai patients.

However, Park et al. (2010) observed a similar prevalence of atazanavir-associated hyperbilirubinemia among Koreans compared with whites, which would suggest that other variants and genes could be involved. It has been suggested that the risk of atazanavir-associated hyperbilirubinemia could be influenced by atazanavir plasma concentrations. The ABCB1 efflux transporter participates in the absorption and distribution of several protease inhibitors, including atazanavir (Marzolini et al., 2004). The results of studies assessing the relationship between polymorphisms in the *ABCB1* gene and atazanavir-associated hyperbilirubinemia are controversial (Ma et al., 2007; Phillips and Mallal, 2008). For example, one study shows that the *ABCB1* polymorphism is associated with lower atazanavir concentrations and a lower risk of atazanavir-associated hyperbilirubinemia, whereas others did not find any associations between atazanavir concentrations and *ABCB1* polymorphisms. Moreover, Park et al. (2010) reported that polymorphisms in *ABCB1 G2677 T/A* and *UGT1A1*28* were significantly associated with the degree of severe hyperbilirubinemia. It is suggested that variants in other genes such as *SLCO1B1* (coding for the influx transporter OATP1B1) that facilitate the entry of unconjugated bilirubin in hepatocytes could also contribute to atazanavir- and indinavir-associated hyperbilirubinemia (Rodríguez-Nóvoa et al., 2006; Ma et al., 2007; Park et al., 2010).

In contrast, Lubomirov et al. (2011) have assessed the association of pharmacogenetic markers with the time to treatment discontinuation during the first year of atazanavir. They reported that individuals homozygous for *UGT1A1* alleles (**28/*28* or **28/*37*) were associated with higher risk of atazanavir discontinuation (adjusted hazard ratio of 9.13) (Lubomirov et al., 2011). First-year cumulative rates of atazanavir discontinuation were 62.5, 23.8, and 14.6% for homozygous, heterozygous, and noncarrier subjects of UGT1A1 genetic variants, respectively (Lubomirov et al., 2011). Thus, in patients with genetic risk (*UGT1A1* genotype score), HIV drug discontinuation was associated with atazanavir toxicity ($p = 0.004$) (Lubomirov et al., 2011).

Although the incidence of discontinuation because of intolerance or toxicity has declined over time as simplified regimens have become more frequent, the major cause of antiretroviral drug discontinuation remain intolerance and toxicity associated with these drugs (Cicconi et al., 2010). A better understanding of mechanisms involved in toxicity and intolerance of antiretroviral drugs can help to improve and reduce first-line treatment discontinuations.

IV. Conclusion

New problems have emerged after improvements in survival rates of patients infected with HIV who received HAART. HIV treatment has entered a new era in which polypharmacy and genetic variations (host and virus) must be taken into account when developing and formulating therapeutic regimens. This now involves a shift toward personalized medicine.

The clinical response to antiretroviral therapy is a mixture of complex interactions involving a multitude of factors. In the past several years, results have provided support for the host-related factors can contribute in a significant way to resistance to antiretroviral agents. In brief, the factors that modulate a drug's cellular exposure are major determinants of the response to antiretroviral therapy and include the enzymes responsible for the metabolism of antiretroviral agents and drug transporters that can limit access to these agents in the systemic circulation, in infected cells, and in HIV sanctuary sites. As such, drug-drug interactions and the presence of genetic polymorphisms involved in drug metabolism or transport significantly contribute to the inter- and intraindividual variability in antiretroviral response. The management of patients receiving HAART is complex and requires familiarity with systems related to virology, P450s, UGTs, and membrane transporters to optimize therapy and minimize adverse.

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