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Impact of Therapeutic Drug Monitoring of Antiretroviral Drugs in Routine Clinical Management of People Living with HIV: a narrative review

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Abstract

Purpose: The treatment of human immunodeficiency virus (HIV) infection has evolved significantly since the advent of highly active antiretroviral therapy. As a result, a response rate of 90-95 % now represents a realistically achievable target. Given this background, it is difficult to imagine the additional benefits that therapeutic drug monitoring (TDM) could provide in the management of HIV infection.

Methods: This article is not intended to provide a systematic literature review on TDM of antiretroviral agents; rather, the authors aim to discuss the potential added value of TDM in the optimal management of people living with HIV (PLWH) in selected real-life clinical scenarios based on data collected over 10 years by their TDM service.

Results: Some clinical situations, in which the selection of the optimal antiretroviral therapy is challenging, have been identified. These include poorly compliant patients, sub-optimal antiretroviral therapies (in terms of both efficacy and toxicity), polypharmacy with a high risk of drug-drug interactions (DDIs), and different patient populations, such as pregnant women.

Conclusions: The transformation of HIV infection from a near universally fatal illness to a lifelong chronic disease has resulted in an HIV population that is growing and aging, placing new and increasing demands on public programs and health services. Increasingly, the management of comorbidities, polypharmacy, and DDIs and their impact on antiretroviral therapy will have to be undertaken. These clinical settings represent some of the new frontiers for the use of TDM with the goal of achieving optimal prescription and outcome for PLWH.

Key words: HIV; therapeutic drug monitoring; drug-drug interactions; antiretroviral agents

Introduction

The treatment of HIV infection was revolutionized by the advent of highly active antiretroviral therapy (HAART) in the mid-1990s. Now, there are approximately 30 antiretroviral drugs with different mechanisms of action, and most of these are characterized by high potency and good

tolerability. In addition, improved pharmaceutical formulations with several drugs packaged as fixed dose combinations in single tablet regimens enable "one size fits all" once-daily treatments.[1-5] International guidelines support the use of antiretroviral agents, including monitoring these therapies for safety and efficacy.[6,7] As a result, a long-term response rate of 90-95 % represents a realistically achievable target when starting antiretroviral therapy in naïve patients.[8-10] Given this background, it is difficult to imagine the additional benefits that TDM of antiretroviral drug concentrations could provide in the management of HIV infection, given the high success rate of available therapies. Consistently, reviews and systematic meta-analyses have concluded that there is insufficient evidence to recommend routine TDM in all patients.[11-17]

However, an extensive review of the existing literature suggests there are potential concerns about the efficacy and/or tolerability of antiretroviral drugs in selected patients, who may, in turn, benefit from the application of TDM. For example, there are clinical situations in which the identification of the optimal antiretroviral therapy is challenging, such as extensive polypharmacy resulting in a high risk of DDIs; "atypical" patient populations such as elderly or pediatric subjects, pregnant women, or gastrectomized patients; patients with a known or suspected history of poor compliance to therapies and/or the appropriate dosing regimen; or patients with HIV resistant to many of the available antiretroviral agents.[12] It has also been reported that a significant percentage of PLWH may experience severe adverse drug reactions after long term treatment due to the high drug concentrations, eventually requiring a change of the antiretroviral regimen.[18,19]

This article is not intended to provide a systematic literature review on the TDM of antiretroviral agents; rather, we aim to discuss the significant potential for TDM to offer added value to the optimal management of adult PLWH in selected real-life clinical scenarios utilizing data collected by our TDM service over a 10-year period.

ASSESSMENT OF PATIENT ADHERENCE

Adherence to antiretroviral therapies is crucial for maintaining the suppression of HIV replication, which is the most important factor affecting long-term HIV treatment outcomes.[20] However, assessment of drug compliance can be difficult because patients may not always tell the truth when the attending physician asks this specific question. From a clinical standpoint, poor compliance to antiretroviral therapy should be suspected when a patient experiences an increase in the HIV viral load without any apparent reason. However, it is now common practice to check the HIV viral load only every 4 to 6 months; therefore, failure of antiretroviral treatment due to poor compliance is likely to be discovered late, putting the patient at high risk of developing an infection by a strain of HIV that is resistant to one or more classes of antiretroviral agents.

There are many published methods for assessing patients' adherence, such as self-reporting, pharmacy refill checks, and medication event monitoring systems, but a gold standard acceptable to all is not available.[21] TDM has been proposed as an alternative approach to confirm short-term adherence of patients to antiretroviral therapies.[21,22] Accordingly, Calcagno *et al* have recently demonstrated that poor adherence to antiretroviral treatment, as identified by TDM-based approaches, was an independent predictor of virological failure.[23] In particular, they stratified patients as "adherent," "partially adherent," or "non-adherent" by matching the plasma concentrations of ritonavir (used as a booster) with those of protease inhibitors (PIs) and taking into account the terminal half-lives of the different drugs. Based on their findings, the authors concluded that TDM could uncover incomplete compliance with treatment, allowing the identification of patients in need of adherence-promoting interventions. However, it must be noted that most antiretrovirals, with the exception of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), have systemic terminal half-life values ranging from two to 20 hours, allowing a steady-state to be attained rapidly (Table 1). Therefore, for these drugs, TDM is only able to provide reliable estimates of recent compliance with therapies and is not without potential caveats, as exemplified in Figure 1. One way to overcome this limitation could be the execution of unscheduled TDM tests, as

is done at our center in selected cases. When there is a suspicion of poor patient compliance not detected by a previous TDM session, we ask the patient to come to the hospital during an unscheduled visit (i.e., to sign some documents or for other bureaucratic reasons). When the patient arrives, we request him/her for signed informed consent for a TDM analysis (unexpectedly, most patients usually agree even if they are poorly compliant). Nevertheless, if the patient denies his/her consent, the TDM is not performed. Using this approach, we have found that nearly 5 % of patients from our hospital have poor compliance to at least one antiretroviral drug (Cattaneo D, personal communication).

The use of TDM in patients with a history of poor/limited compliance to antiretroviral therapies is of great relevance to prevent the selection of resistance mutations. Indeed, significant relationships have been reported between antiretroviral plasma concentrations and the emergence of HIV-1 resistance mutations at treatment failure. More specifically, undetectable drug trough concentrations were seen only in patients failing raltegravir or nevirapine without integrase inhibitor (INI) or NNRTI resistance mutations; conversely, patients with raltegravir or nevirapine resistance mutations failing antiretroviral therapies had detectable but insufficient trough drug concentrations.[24,25]

Some marketed antiretroviral agents, such as rilpivirine and elvitegravir, and the pharmacokinetic enhancer cobicistat need to be administered with food to increase disposition and maximize efficacy. Therefore, complete adherence to therapy with these drugs requires that patients not only regularly take their pills but also do so according to the recommendations. For instance, a patient who takes rilpivirine or elvitegravir reliably at the same time each day whilst fasting could experience virological failure because of suboptimal drug exposure rather than poor compliance. Therefore, real-life adherence of patients to the recommended dosage information can be verified through TDM. For example, the product monograph of the fixed-dose combination containing elvitegravir, cobicistat, tenofovir, and emtricitabine (Stribild) recommends that the formulation should be administered under fed conditions to optimize drugs exposure.[26] As support for this

concept, Shiomi *et al* have shown that administration under fasting conditions resulted in decreases in the mean area under the curve (AUC) of elvitegravir and tenofovir by 50 % and 28 %, respectively, relative to the administration with a standard breakfast, whereas the bioavailabilities of elvitegravir and tenofovir were comparable when administered with a standard breakfast or a nutritional protein-rich drink.[27] Collectively, these findings suggest that elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate should be administered with food and that the bioavailability of elvitegravir and tenofovir is not affected by the type of meal ingested. It must be acknowledged, however, that such findings were derived from studies in healthy volunteers.

To overcome this potential limitation, we performed TDM for 75 PLWH administered Stribild and demonstrated undetectable serum concentrations in approximately 25 % of patients, all of whom took the drug under fasting conditions (specifically, in the middle of the morning or late in the evening) resulting in a higher than expected rate of virological failure.[28] Similarly, nearly 10 % of approximately 1000 rilpivirine TDM assays performed at our center, over the last five years, resulted in undetectable drug trough concentrations that were, in most cases, related to fasting intake of the drug (Cattaneo D, personal communication). These observations are valid as they are derived from TDM assessments done in PLWH; however, they suffer from the limitation that they may have been biased (at least, in part), by poor patient compliance, which is difficult to assess in real-life settings. The key roles of patient education and patient responsibility to be fully adherent with the optimal dosing instructions provided by healthcare professionals should not be underestimated. Overall, TDM has the capability of providing excellent support to these strategies.

IMPROVEMENT OF ANTIRETROVIRAL TREATMENT TOLERABILITY

Several years ago, we undertook a retrospective analysis of routine TDM of antiretroviral concentrations carried out according to the standard clinical practice at our center and demonstrated that a significant proportion of PLWH (ranging from 20 to 45 %, according to the antiretroviral

drug considered) treated with marketed antiretroviral doses had drug concentrations exceeding the recommended upper therapeutic thresholds.[29] Based on these findings, we proposed that such patients may benefit from a TDM-driven reduction in the antiretroviral dosing with potential advantages in terms of toxicity without loss of efficacy. However, as shown in Table 2, only the low therapeutic threshold concentrations were available for most drugs. The lack of upper threshold values to minimize antiretroviral-related toxicity implies that TDM-driven dose reduction cannot be applied to all antiretroviral agents. There are, however, some important exceptions discussed below. In their seminal work published in 2001, Marzolini *et al* were the first to document a significant association between antiretroviral drug exposure and drug-related toxicity.[30] In particular, they demonstrated that the risk of developing drug-related central nervous system (CNS) toxicity was three times more likely in PLWH with efavirenz concentrations (measured at an average of 14 h after drug intake) exceeding 4000 ng/mL compared with patients with efavirenz concentrations ranging from 1000-4000 ng/mL. Such findings were confirmed by Csajka *et al* in a large, independent cohort of PLWH.[31] These results provided the rationale for a prospective study aimed at investigating the feasibility of TDM-guided adjustments in efavirenz dose reduction.[32] The study demonstrated that the standardized TDM-guided efavirenz dose-reduction strategy over a 24-week period was successful, safe, and yielded efavirenz plasma concentrations within the recommended therapeutic range with improved neuropsychiatric tolerability. Among other NNRTIs, significant associations have been reported between nevirapine trough concentrations and drug-related hepatotoxicity,[33] but not for etravirine or rilpivirine.

Similarly, plasma trough concentrations of HIV PIs and drug-related toxicity, specifically indinavir-associated renal toxicity,[34,35] lopinavir-related dyslipidemia,[36] and atazanavir-related hyperbilirubinemia[37] are well described. More recently, after excluding carriers of the UGT1A1*27 genotype, who are genetically at a higher risk of hyperbilirubinemia for impaired catabolism, we confirmed a significant and direct association between the severity of hyperbilirubinemia and atazanavir plasma trough concentrations and documented, for the first time, that patients with

dyslipidemia or nephrolithiasis had atazanavir concentrations significantly higher than those in patients with no drug-related complications.[38] Darunavir, the most recently marketed PI, has no upper threshold of drug concentrations identified to date. For this drug, the choice between the available options (600 mg plus ritonavir 100 mg twice daily, 800 mg plus ritonavir 100 mg once daily or 800 mg plus cobicistat 150 mg daily) is usually driven by drug resistance testing and not by safety concerns. However, cases of drug-related episodes of diarrhea have been reported in PLWH with darunavir trough concentrations above 4000 ng/mL (Marriott DJE, personal communication).

In routine clinical practice, TDM is not undertaken for nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs). One important exception is tenofovir. Indeed, consistent evidence is available in the literature suggesting that plasma trough concentrations of tenofovir correlate with drug-related renal toxicity in HIV patients treated with the prodrug tenofovir disoproxil fumarate (TDF).[39-41] Female patients and subjects with low body weight are at the highest risk of tenofovir-related renal tubular toxicity when treated with the conventional 300 mg once-daily doses.[39] It was recently reported that the adoption of individualized TDM-guided dosages (i.e., 300 mg every 48 or 72 h) in PLWH at high risk of tenofovir over-exposure resulted in a significant increase in the glomerular filtration rate, three months after dose adjustment whilst maintaining antiviral efficacy.[42]

More recently, a novel prodrug formulation of tenofovir has been marketed, namely, tenofovir alafenamide (TAF).[43,44] Pharmacokinetic studies have demonstrated that the administration of 25 mg TAF resulted in 90 % lower plasma concentrations of tenofovir compared with TDF whilst the intracellular drug exposure was increased. For this reason, the therapeutic window of plasma tenofovir concentrations cannot be applied in PLWH to whom TAF is administered, and, in fact, no therapeutic ranges of tenofovir are available for this novel formulation. In Figure 2, we present the tenofovir plasma trough concentrations measured during outpatient visits at our hospital in patients treated either with TDF or TAF (n=500 for each group). In this real-life setting, the TAF formulation was associated with a considerable reduction in the systemic tenofovir concentrations

compared with the TDF formulation (median [interquartile range]: 14.7 [9.8-20.4] versus 106 [71-153] ng/mL).

Integrase inhibitors (INIs) are the most recently marketed class of antiretroviral agents and are characterized by great potency, allowing a very rapid decline in the HIV viral load a few weeks after starting therapy, a high genetic barrier, and a wide therapeutic window with optimal tolerability. [45,46] For these reasons, TDM is not widely used as a tool to optimize treatment for this drug class. One exception may be the reported CNS toxicity of dolutegravir. This is actually a hot topic with many publications and opinion papers that provide conflicting and inconclusive results on the neurological and psychiatric adverse effects experienced by some patients treated with dolutegravir, which eventually lead to a higher rate of drug discontinuation compared with other INIs.[47,48] From a TDM viewpoint, a couple of studies have recently reported significant associations between high dolutegravir concentrations and some of the reported psychiatric symptoms.[49-51] It is likely that genetics plays an important role, as the concomitant presence of high dolutegravir concentrations and polymorphisms in the SLC22A2 gene (encoding the organic cation transporter-2 (OCT2), which is involved in monoamine clearance in the CNS) has been associated with a set of neuropsychiatric events observed during dolutegravir therapy. There is, however, an overlap in the trough concentrations reported to be associated with dolutegravir CNS toxicity and those measured in patients with optimal treatment tolerability.[52,53] The potential role of dolutegravir metabolites in drug-related CNS toxicity, observed in some patients, cannot be excluded at present.

IMPROVEMENT OF ANTIRETROVIRAL TREATMENT EFFICACY

In 1996, Schapiro *et al* were the first to report a significant, direct correlation between saquinavir plasma concentrations and the decrease in HIV viral load in a small cohort of PLWH receiving saquinavir monotherapy for 24 weeks.[54] Such relationships were subsequently confirmed by other investigators, forming the basis for the potential role of TDM as a tool to improve the efficacy of PI-based antiretroviral therapies.[37,55] Significant associations with virological response were

reported subsequently for the NNRTIs efavirenz and nevirapine.[30,56] It must be emphasized, however, that other studies failed to document such associations, providing conflicting results on the potential role of TDM as a tool to improve antiretroviral efficacy.[57,58] To formally address this issue, a meta-analysis of the available literature on this topic was carried out by the Cochrane investigators in 2009.[16] The authors concluded that their review did not support the routine use of TDM in antiretroviral-naive or -experienced patients on either boosted PI or NNRTI regimens. One of the criticisms raised in the Cochrane meta-analysis was related to the lack of clear-cut therapeutic thresholds of minimum effective antiretroviral drug concentrations applicable not only for naïve patients, but also for antiretroviral-experienced patients who may require higher drug concentrations to treat mutant viruses. To overcome this limitation, it has been proposed to adopt, even for antiretrovirals, specific pharmacokinetic/pharmacodynamic (PK/PD) targets instead of pharmacokinetic-based TDM, as usually done with antibiotics (categorized as AUC/minimum inhibitory concentration, peak/minimum inhibitory concentration, or time above the minimum inhibitory concentration based on their PK/PD characteristics). To address this issue, some investigators have attempted the application of the concept of inhibitory quotient (IQ), which was originally introduced by researchers exploring methods to combine antimicrobial drug concentrations and minimum inhibitory concentrations to develop an approach to select appropriate antimicrobial agents, to optimize antiretroviral therapy (therefore, considering antiretrovirals as T>MIC-dependent antibiotics). As reviewed by Morse *et al*,[59] the phenotypic IQ can be simply defined as the trough concentration divided by the 50 % inhibitory concentration (IC_{50}) or derived using more complex approaches. Some studies suggested that the phenotypic IQ was marginally predictive of virological outcome.[60] One of the more promising approaches is the genotypic IQ (gIQ), defined as the trough concentration of antiretroviral drug divided by the number of viral mutations identified in the single patient.[61-63] The gIQ can be estimated by equally weighing all the mutations or using weighed mutation scores, with the latter approach associated with the most accurate achievement of successful virological response.[61,62] Despite these encouraging results, the

assessment of the IQ (either phenotypic or genotypic) as a tool to improve the antiretroviral response has a very limited application range in day-to-day clinical practice. As HIV is treated with a cocktail of drugs and is dependent of the properties of the virus and the remaining functional immune status of the patients, it would be possible, in the future, to introduce machine learning/artificial intelligence/HAART analysis to find better predictors of the response.

MANAGEMENT OF DRUG-DRUG INTERACTIONS

The improved survival of PLWH has resulted in the increased complexity of medical care to the extent that the growing number of co-morbidities have led to polypharmacy,[64-67] and the burden of taking multiple medications is associated with an increased risk of adverse drug events and DDIs. Some antiretroviral agents: a) are substrates for cytochrome (CYP) 3A4 and 3A5 isoforms (Table 1), which are involved in the metabolism of nearly 40-50 % of all marketed drugs; b) can be administered concomitantly with CYP3A inhibitors (ritonavir or cobicistat), resulting not only in increased disposition of HIV PIs but also in altered disposition of concomitant non-antiretroviral drugs; c) are inducers of cytochrome P450 enzymes (efavirenz or nevirapine); d) can modulate the activity of transmembrane proteins involved in the transport of several drugs. For example, dolutegravir and rilpivirine are inhibitors of OCT2, and ritonavir and cobicistat are inhibitors of apical multidrug and toxin extruder (MATE1). Therefore, antiretroviral drugs can act both as victims and as perpetrators of DDIs when co-administered with other medications. Besides drug metabolism, transport, or elimination, some DDIs involving antiretrovirals as victims can also occur during the absorption phase, as in the case of chelation with mineral supplements or changes in gastric pH.[68,69]

Regardless of the mechanisms, such DDIs may compromise the efficacy or the safety of both the antiretroviral and non-antiretroviral treatments.[70] Indeed, several clinically-relevant DDIs have been reported for antiretroviral drugs (a detailed list of all potential DDIs involving antiretrovirals, as

well as periodical updates on the top-ten DDIs are available in the Liverpool website: www.hiv-druginteractions.org), even resulting in fatal outcomes.[71,72]

The most frequent reason for a TDM request in PLWH are potential DDIs. It is, however, important to remember that TDM is useful only for PK-based DDIs (those involving the capacity of a molecule to interfere with the absorption, distribution, metabolism, or elimination of another drug) but not for PD-based DDIs. In fact, TDM can only help to quantify the effect of a co-medication on the disposition of the drugs for which concentrations can be measured. Conversely, PD interactions may involve the combined (synergistic, agonistic, or antagonistic) effects of two or more molecules on the same pharmacological target or different targets; these interactions, which may be potentiating or inhibitory, are usually not related to systemic drug disposition.

To face the emerging problems of polypharmacy and DDIs, we set up a multidisciplinary Ambulatory Polytherapy Management (*Gestione Ambulatoriale Politerapie:* GAP) outpatient clinic in 2016.[73] As already underlined, in this real-life context, the most important tool for the assessment of DDIs between antiretroviral drugs and co-medications is the one developed by the University of Liverpool. Using this freely available website, it is simple to check potential DDIs. However, some important limitations can be overcome by utilizing TDM. For instance, the DDI scoring system adopted by the University of Liverpool is usually based on results from studies carried out in healthy volunteers, exposed to single doses of potentially interacting agents—two conditions that certainly do not mimic real life. This may result in an under- or over-score of DDIs, as exemplified in our experience with HIV/HCV co-infected patients, outlined below.

Complex DDIs were initially reported between the first HCV direct-acting antiviral agents and HIV PIs, leading to relevant limitations of the therapeutic options for HIV/HCV co-infected patients. However, by applying TDM in a real life context, we found no significant differences in the PK of atazanavir, amprenavir, or tenofovir, measured before versus after treatment with telaprevir,[74] thereby challenging the findings from DDI studies carried out in healthy volunteers. Conversely, our real life data revealed that the concomitant administration of darunavir resulted in a significant

reduction of the trough concentrations of the HCV antiviral agent paritaprevir. Most importantly, the only two HIV/HCV co-infected patients from our cohort who failed to achieve a sustained HCV virological response after 12 weeks of treatment with the regimen of ombitasvir, paritaprevir/ritonavir, and dasabuvir, were those receiving darunavir as part of maintenance antiretroviral therapy.[75] Again, these findings differ from the data obtained from PK studies carried out in healthy volunteers.[76]

As an additional limitation, the Liverpool website does not provide detailed data on DDIs involving complementary and alternative medicines (CAMs), which are even more frequently used by PLWH enjoying a higher level of physical well-being, body care, and beauty. A recent systematic review has demonstrated that among HIV patients, over-the-counter (OTC) products and dietary supplements are the most common forms of CAM therapy and, most importantly, some of these products can cause significant DDIs with antiretroviral agents.[77] In our GAP database, we identified five patients concomitantly receiving stable antiretroviral treatment and CAMs, who experienced virological failure or suboptimal therapeutic response because of DDIs.[78-80] As shown in Table 3, TDM clearly demonstrated that concomitant administration of CAM resulted in sub-therapeutic antiretroviral drug trough concentrations, which increased significantly a few days after use of the interacting agent was ceased. In all cases, the co-medication altered the disposition of the antiretroviral agents acting as an inhibitor of drug absorption (orlistat, naringin, or psyllium) or as an inducer of drug metabolism (guggulsterones). These cases illustrate how the application of TDM of antiretroviral agents in clinical practice can identify potential DDIs with CAMs and explain or prevent therapeutic failure.

For HIV medicine, TDM can be an important tool not only to optimize antiretroviral therapies, but also to adjust non antiretroviral medications administered to PLWH for the treatment of comorbidities.[73] For example, medications affecting the CNS are administered frequently and increasingly to PLWH, thereby increasing the risk of DDIs with antiretroviral drugs. Taking advantage of the availability of a TDM service for the assessment of antipsychotics,

antidepressants, and antiepileptic drug trough concentrations in our laboratory, we assessed the distribution of plasma trough CNS drug concentrations in both PLWH and HIV-negative patients using the reference ranges provided by the *Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie* (AGNP) guidelines.[81,82] Interestingly, we found that 64 % and 55 % of PLWH concomitantly receiving an antiretroviral and antipsychotic or antidepressant drug treatment versus 26 % and 25 % of HIV-negative patients had sub-therapeutic plasma psychotropic drug concentrations (Figure 3, difference statistically significant). Conversely, only 30 % and 28 % of PLWH and HIV-negative patients, respectively, had antiepileptic concentrations below the therapeutic targets (difference not statistically significant). The observed discrepant distribution of plasma concentrations of CNS drugs in PLWH can be interpreted in different ways. First, the majority of our PLWH receiving anti-epileptic agents were treated with traditional drugs, such as carbamazepine, phenytoin, phenobarbital, and levetiracetam, for which the pharmacology and potential risk of DDIs has been well established. Second, the TDM of antiepileptic drugs has been utilized for many years in most of the hospitals for the management of antiepileptic therapies, whereas TDM for the optimization of antidepressant and/or antipsychotic treatments is still in its infancy. Therefore, it is likely that antiepileptic therapies and dosages are better managed in clinical practice both in PLWH and HIV-negative patients compared with psychotropic medications, which may also be under-dosed because of the fear of potential DDIs. The application of TDM to non-antiretroviral medications allows the prompt identification of PLWH with suboptimal treatment.

PREGNANCY AND OTHER CLINICAL CONDITIONS

A survey carried out some years ago in the Netherlands indicated that pregnancy was the most frequent reason for the TDM requests of antiretroviral drugs in clinical practice.[83] This is understandable because pregnancy-associated changes in drug absorption, distribution, metabolism, and excretion are known to occur throughout pregnancy and postpartum (reviewed in [84]). Indeed,

reduced exposure to antiretroviral agents of pregnant women living with HIV has been recently reported for darunavir, rilpivirine, cobicistat, elvitegravir, and dolutegravir.[85-87]

Additionally, the understanding of antiretroviral placental and breastmilk transfer may offer additional insight into the potential role in preventing HIV transmission *in utero* and ensuring safety of *in utero* and breastmilk antiretroviral exposures in infants; furthermore, it may also have implications regarding viral resistance in cases where transmission does occur (reviewed in [88]).

Vertical transmission of HIV infection from mother to child is still a significant problem not only in emerging countries but also in developed countries, highlighting the importance of TDM to optimize maternal and child exposure. Di Biagio *et al* recently reported 79 HIV-1-infected children newly diagnosed after birth in Italy.[89] During the pregnancy, only 15 out of 19 women with a known HIV diagnosis were treated with antiretrovirals, whereas, of 34 women who had received an HIV diagnosis before labor began, only 23 delivered by caesarean section and 17 received intrapartum prophylaxis.

TDM may help to identify the optimal antiretroviral treatment required to prevent vertical transmission, as exemplified by two recent case reports. The first was a woman living with HIV with an extensive drug-resistant virus infection, who was successfully switched from a raltegravir-based regimen to a dolutegravir-based intensified antiretroviral regimen a few days before a scheduled caesarean section because of the still detectable viral load.[90] We assessed the patient's exposure by measuring trough antiretroviral drug concentrations before and after delivery and determined that the concentrations of tenofovir, darunavir, ritonavir, maraviroc, and dolutegravir during the third trimester were 300 %, 35 %, 50 %, 50 %, and 140 % lower, respectively, than post-partum concentrations, with significant differences from the mean values reported in the literature. Important variability was also found in the drug amount that crossed the placental barrier. In our case, the newborn-to-mother ratio for dolutegravir was 4-fold higher than the data reported in literature.[86,87] Similarly, great inter-individual variations in the newborn/mother drug ratio have

been reported for tenofovir (from 0.5 to 1.5), maraviroc (from 0.1 to 0.6), and darunavir (from 0 to 0.8).[90]

The second case reported TDM-guided raltegravir for the prevention of vertical HIV transmission in a premature neonate born to a woman with perinatally acquired HIV and documented resistance to multiple HIV drugs.[91] Using frequent TDM, the authors were able to demonstrate that the half-life of raltegravir changed from 106 h to 15 h in the first 14 days of life of the neonate, requiring prompt and frequent changes in the timing of drug dosing. Although raltegravir-related toxicity was probably not an issue in a short 14-day time period, we believe that this case demonstrates delayed raltegravir elimination in a neonate born at a gestational age of 33 weeks and a need for less frequent raltegravir dosing than in older infants and children. The great variability in drug exposure during the different phases of pregnancy, delivery, and drug placental transfer that have been reported provide a solid rationale for the application of TDM in these clinical settings.

Another important clinical setting, which may benefit from the application of TDM may involve PLWH undergoing dialysis or, in general, those with severe renal insufficiency. In these scenarios, TDM can be an important tool to adjust drug dosage to avoid either loss of efficacy (for antiretroviral drugs eliminated by dialysis) or toxicity (due to drug accumulation).[92,93]

THE FUTURE? LONG-ACTING INJECTABLE ANTIRETROVIRAL FORMULATIONS

The advent of HAART has significantly reduced AIDS-related mortality and morbidity and improved the quality of life of PLWH.[2] However, HIV infection continues to be a major global health threat. Indeed, according to the UNAIDS 2017 report, nearly 38 million people are living with HIV and nearly 1.8 million new HIV infections were recorded last year.[94] These figures underline the need to identify approaches that can guarantee optimal adherence of patients to maintenance antiretroviral therapies, as well as the importance of preventing HIV transmission through the adoption of pre-exposure prophylaxis (PrEP)-based strategies. From a pharmacological viewpoint, both requirements could be accomplished by the availability of long-acting injectable

(LAI) formulations of antiretroviral drugs. LAI antiretroviral agents, being administered on a monthly or less-frequent basis, may provide key advantages in both adherence and convenience for HIV treatment and prevention compared with traditional once-daily formulations.[95-97]

In this regard, the possible role of TDM as a tool for optimizing the frequency of LAI antiretroviral formulations has not yet been studied. However, the preclinical and clinical PrEP data may provide a preliminary rationale for the use of TDM in this clinical setting. In fact, in the ÉCLAIR study, the only patient in the cabotegravir arm acquiring HIV-infection had drug plasma trough concentrations well below the protein-adjusted 90 % inhibitory concentration (i.e., the concentration of drug sufficient to inhibit the drug target, eventually corrected for the amount of drug bound to serum protein).[98] Similarly, the plasma concentrations of rilpivirine measured in an HIV-seroconverter from the SSAT040 study, who received the 300-mg dose of LAI rilpivirine, were below the minimum effective drug concentration.[99] Collectively, these findings raise potential concerns related to the long PK tail of LAI antiretroviral formulations with sub-therapeutic drug concentrations, which may facilitate the emergence of viral resistance. In these scenarios, TDM may be indicated in selected clinical conditions (overweight, pregnancy, when DDIs are suspected, etc.), eventually requiring more versus less frequent LAI administrations. As an example, by performing a retrospective analysis of TDM of olanzapine concentrations in schizophrenic patients on maintenance LAI olanzapine given every 4 weeks, we found that nearly 50 % of them had olanzapine trough concentrations below the minimum effective drug concentrations.[100] In these patients, we adopted individualized schemes based on the administration of LAI every 2 or 3 weeks based on TDM results.

Taken regularly (daily or every weeks as LAI), HAART prevents and suppresses the infection. However, treatment interruption almost invariably leads to rebound viremia in infected individuals due to a long-lived latent reservoir of integrated proviruses. Therefore, HAART must be

administered on a life-long basis. Immunotherapy may be an alternative or an adjuvant to HAART because, in addition to preventing new infections, anti-HIV-1 antibodies clear the virus, directly kill infected cells, and produce immune complexes that can enhance host immunity to the virus (reviewed in [101]). Presently, the application of TDM in this context remains unaddressed.

Conclusions

The treatment of HIV infection has been revolutionized in the last twenty years and is expected to change further in the near future. The most recent trials have provided the basis for a paradigm shift from the conventional three drug-based to two drug-based antiretroviral combinations. Currently, these new dual regimens are given once daily as oral formulations but, in the near future, will be administered as LAI formulations once every 4-8 weeks or even less frequently. These approaches are expected to maintain a response rate of 90-95 % in treatment-naïve patients. In this scenario, the routine use of TDM is likely to play a small but potentially important role, by limiting the development of resistance in PLWH showing long-tail drug PK, if treated with LAI.

The transformation of HIV from a fatal infection to a chronic disease with a near-normal life span has resulted in a population of PLWH that is growing and aging, placing new and increasing demands on public programs and health services. Projections for 2013-2045 suggest that in the next two decades nearly one third of PLWH will age more than 55-60 years.[102] Accordingly, we will have to increasingly undertake the management of comorbidities, polypharmacy, and DDIs. These clinical settings represent new frontiers for the use of TDM, not only to determine patient compliance and DDIs, but also for the optimization of the overall therapies in aging PLWH with comorbidities. Indeed, in this selected population, the application of TDM (for both antiretroviral and non-antiretroviral agents), together with the large-scale adoption of de-prescribing procedures able to evaluate the appropriateness of prescribed medications,[103-105] would favor the achievement of optimal prescribing in HIV patients—treatment regimens that maximize benefits that matter to the patient and minimize burdens and potential harm.

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Legend to the Figures

Figure 1

Time-course of atazanavir plasma concentrations measured in two PLWH treated with atazanavir/ritonavir 300/100 mg plus tenofovir alafenamide/emtricitabine 10/200 mg once daily. Patient 1 voluntarily decided not to take atazanavir for the last 3 months; however, he started atazanavir two days before the scheduled TDM (results: 440 ng/mL). Patient 2 had optimal adherence to therapy for the last three months; however, he missed the last two doses (pill lost) before the scheduled TDM (results: <20 ng/mL). According to the TDM data, patient 1 and 2 were compliant and noncompliant to antiretroviral therapy, respectively; however, looking at the figure, one clearly sees how the actual situation is exactly the opposite. Shaded lines represent the minimum effective atazanavir trough concentration (set at 150 ng/mL).

Figure 2

Box-plot of tenofovir plasma trough concentrations in PLWH given tenofovir disoproxil fumarate or tenofovir alafenamide (n=500 for each group).

Figure 3

Distribution of trough antipsychotic, antidepressant, and antiepileptic drug concentrations below, within, and above the reference ranges of the AGNP consensus guidelines [81,82] in PLWH versus HIV-negative patients.

Table 1. Systemic terminal half-life ($T_{1/2}$), metabolic pathways, and potential mechanisms for drug-drug interactions of marketed antiretroviral drugs

Drug	**$T_{1/2}$ (hours)**	**Metabolism**	**Modulation of metabolic enzymes and drug transport proteins**
Tenofovir	18	None	Inhibitor: MRP1, MRP2, MRP3
Abacavir	1.5	ADH	Inhibitor: BCRP, MRP1, MRP2
Lamivudine	7	None	Inhibitor: MRP1, MRP2, MRP3
Emtricitabine	10	None	Inhibitor: MRP1, MRP2, MRP3
Didanosine	2	Xanthine oxidase	None
Zidovudine	2	None	None
Doravirine	21	CYP3A	None
Efavirenz	45	CYP3A, 2B6	Inhibitor: CYP3A, 2C9, 2C19, BCRP, MRP
Etravirine	41	CYP3A, 2C9/19	Inducer: CYP3A, inhibitor of CYP2C9, 2C19
Nevirapine	30	CYP3A, 2B6	Inhibitor/inducer: CYP3A, CYP2B6, MRP
Rilpivirine	45	CYP3A (2C19)	None
Amprenavir	11	CYP3A	Inhibitor: P-gp, BCRP
Atazanavir	9	CYP3A	Inducer: P-gp; inhibitor: UGT, BCRP
Darunavir	15	CYP3A	Inducer: CYP2C9; inhibitor: P-gp, BCRP
Indinavir	2	CYP3A	Inhibitor: P-gp, OATP
Lopinavir	6	CYP3A	Inhibitor: BCRP
Saquinavir	12	CYP3A	Inhibitor: P-gp, OATP
Tipranavir	6	CYP3A	Inducer: CYP2C19; Inhibitor: CYP3A, 2D6
Bictegravir	18	CYP3A, UGT	Inhibitor: OCT2, MATE1
Cabotegravir	31	UGT	Inhibitor: OAT1, OAT3
Dolutegravir	14	UGT (CYP3A)	Inhibitor: OCT2
Elvitegravir	11	CYP3A (UGT)	Inducer<. CYP2C9; inhibitor: OATP
Raltegravir	9 (14)*	UGT	None
Maraviroc	14	CYP3A	None
Enfuvirtide	4	None	None
Ritonavir	5	CYP3A, 2D6	Inducer: UGT, CYP1A2, 2C8, 2C9, 2C19 Inhibitor: CYP3A, 2D6, P-gp, BCRP
Cobicistat	4	CYP3A, 2D6	Inhibitor: CYP3A, 2D6, P-gp, BCRP

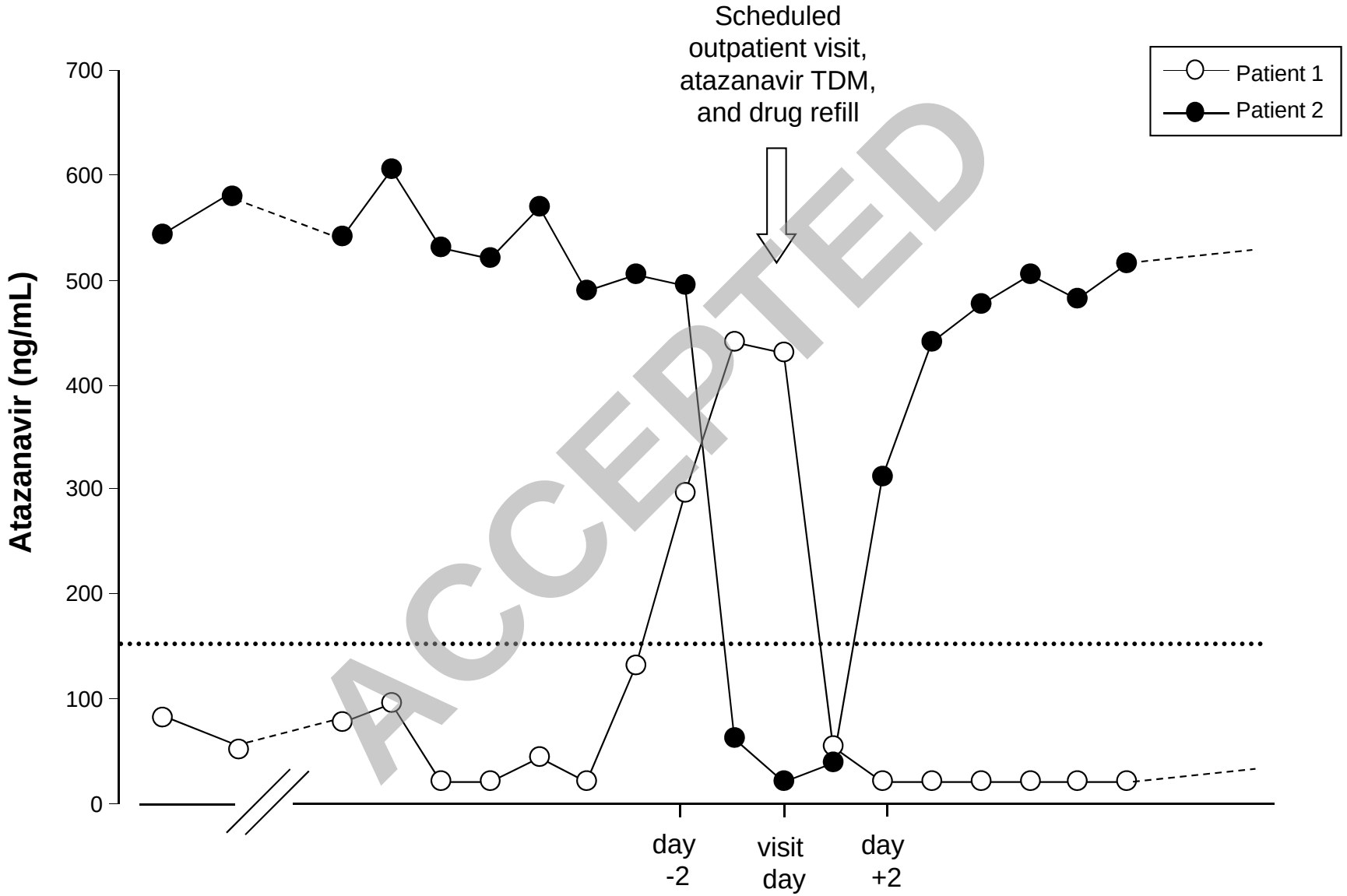
*Once daily formulation; CYP: cytochrome; ADH: alcohol dehydrogenase; UGT: uridine diphosphate glucuronosyl transferase; P-gp: p-glycoprotein; MRP: multidrug resistance protein; BCRP: breast cancer resistance protein; OATP: organic-anion-transporting polypeptide; MATE: multidrug and toxin extrusion; OAT: organic anion transporter.

Table 2. Therapeutic ranges adopted in our laboratory for the optimization of efficacy and safety of antiretroviral drugs. These ranges were retrieved from available literature (summarized in [29]) for tenofovir, efavirenz, etravirine, nevirapine, amprenavir, atazanavir, indinapir, lopinavir, saquinavir, tipranavir, and maraviroc. For the other drugs, the lower therapeutic thresholds are protein-adjusted 90% inhibitory concentrations.

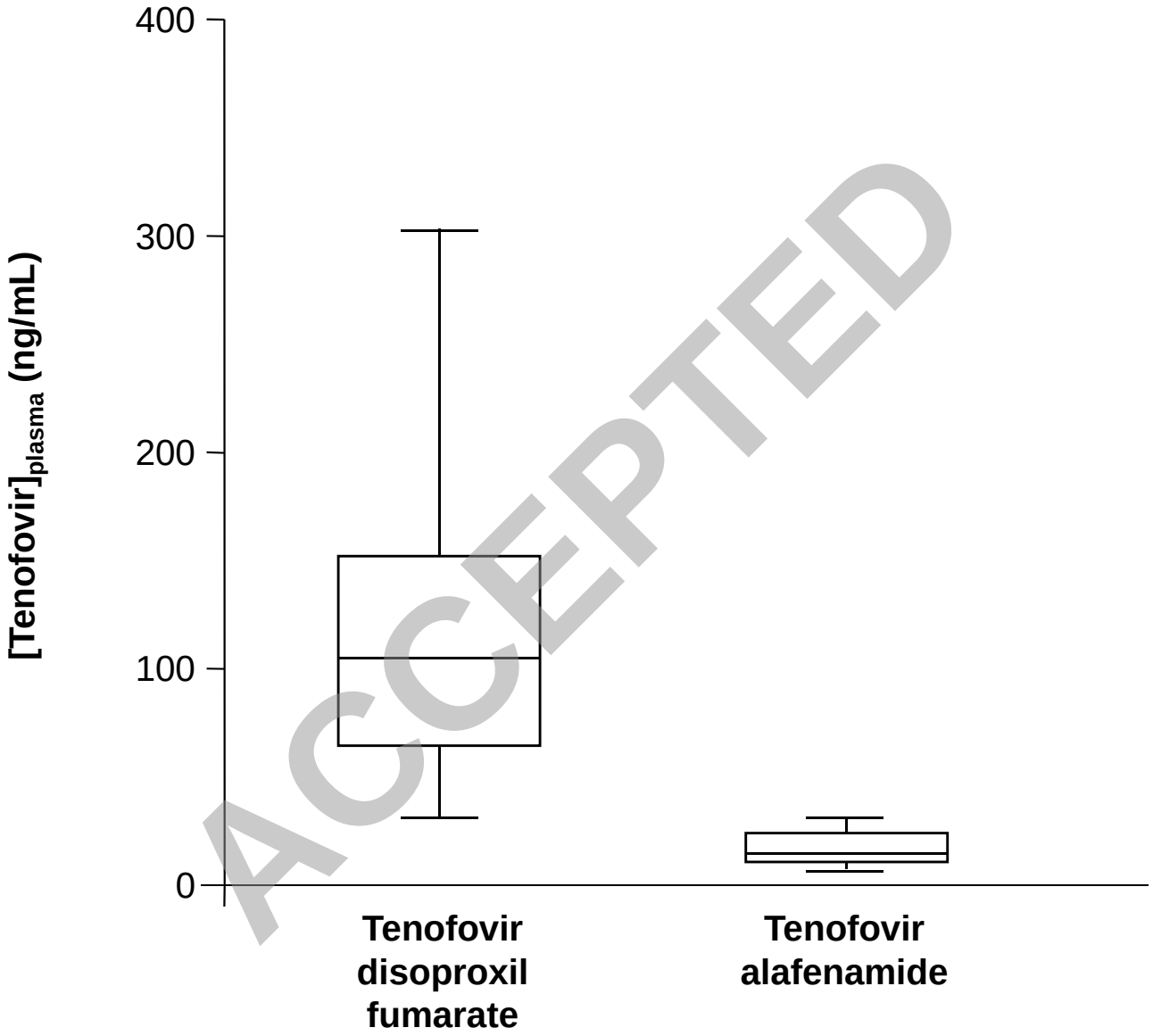
Drug	**Sampling time**	**Therapeutic ranges (ng/mL)**
Tenofovir from TDF	Trough	40-180
Efavirenz	12-h after intake	1000-4000
Etravirine	Trough	>300
Nevirapine	Trough	3000-6000
Rilpivirine	Trough	>20
Amprenavir	Trough	>400
Atazanavir	Trough	150-800
Darunavir	Trough	>550
Indinavir	Trough	150-550
Lopinavir	Trough	1000-7000
Saquinavir	Trough	100-250
Tipranavir	Trough	>20500
Dolutegravir	Trough	>64
Elvitegravir	Trough	>45
Raltegravir	Trough*	>40
Maraviroc	Trough	>50
*Consider the assessment of the area under the curve given the poor predictive value of raltegravir trough concentrations; TDF: tenofovir disoproxil fumarate		

Table 3. Five patients experiencing virological failure while taking complementary and alternative medicines (CAMs)

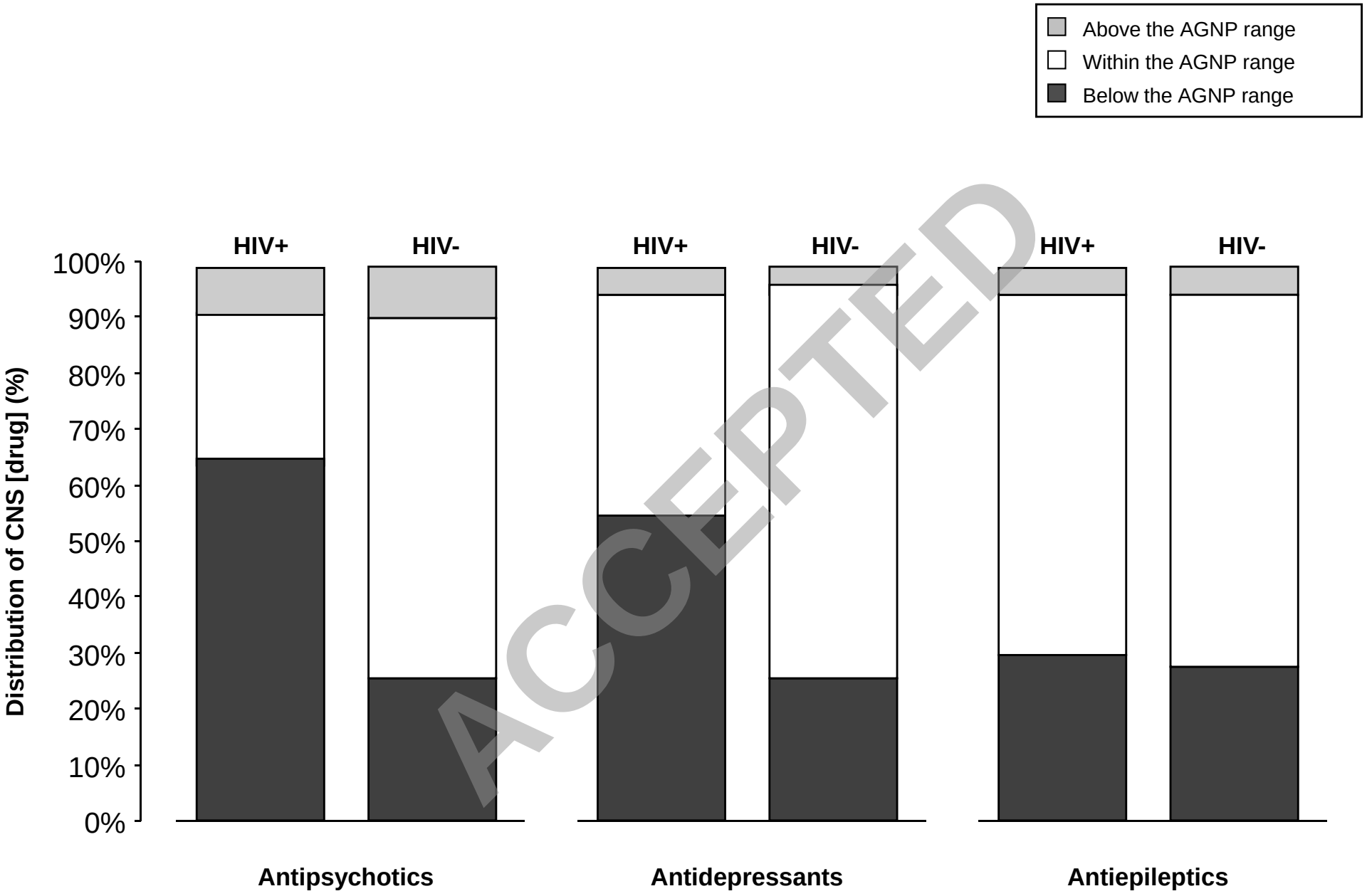
Sex, age	**Interacting agent**	**First TDM**	**Second TDM***	**Reference**
Female, 43 years	Orlistat 60 mg, three times a day	atazanavir: 50 ng/mL	atazanavir: 195 ng/mL	[79]
Female, 39 years	Orlistat 60 mg, three times a day	efavirenz: <150 ng/mL	efavirenz: 3795 ng/mL	[78]
Female, 40 years	Sinetrol 450 mg, two times a day	atazanavir: 85 ng/mL	atazanavir: 719 ng/mL	[78]
Male, 44 years	Lipidyum 6.5 g daily	Not available	Not available	[78]
Male, 45 years	CUT4 HIM plus 4 g, four times a day	elvitegravir: 56 ng/mL	elvitegravir: 653 ng/mL	[80]
*The second TDM was performed after stopping the CAM (patients 1-4) or before starting the CAM (patient 5)				



- Figure 1 -



- Figure 2 -



- Figure 3 -