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The Role of Therapeutic Drug Monitoring and Pharmacogenetic Testing in the Management of HIV Infection: A Review

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Abstract

One of the less acknowledged tools in the international guidelines of combination antiretroviral therapy (cART) for HIV-1 infection is therapeutic drug monitoring (TDM). Yet anywhere there is a Clinical Pharmacology Unit or other facility for measuring plasma drug concentrations, physicians often measure the plasma levels of antiretrovirals as well as of comedications and find it useful. The aim of this article is to provide an overview of how relevant it is for a clinician to assess individual drug levels. Moreover we wanted to investigate to what extent the field is already assisted by web-based tools (i.e.: drug interaction charts). Finally we tried to look how pharmacogenetics may reduce the need for TDM, and whether this diagnostics is cost-effective.

We searched PubMed by "drug interactions and HIV", "drug level and HIV", "therapeutic drug monitoring", and we investigated the Liverpool Drug Interaction website, the DHHS Guidelines website, the UCSF website, and the AETC online Guide for HIV/AIDS Clinical care. Furthermore, we assessed the role that the main national and international guidelines for antiretroviral treatment attributed to TDM and searched for the various clinical subsets in which drug monitoring is particularly relevant.

Finally, we suggest that cross-sectional studies of subjects failing therapy or experiencing drug-related adverse events, as well as longitudinal studies of particular conditions, may show the importance of problem-targeted rather than routine TDM.

Keywords: Therapeutic drug monitoring; HIV; Antiretroviral; Drug interactions; Pharmacogenetics

Introduction

Rationale and technical aspects of therapeutic drug monitoring

Therapeutic drug monitoring (TDM) is defined as the clinical laboratory measurement of the levels of drugs in plasma, serum or blood of patients that, with appropriate medical interpretation, will directly influence drug prescribing procedures [1]. TDM is also referred to as the individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range or window [2].

The indications for drug monitoring include toxicity, efficacy, compliance, drug-drug interactions, and therapy monitoring, as the data obtained may correlate better with drugs' concentrations than they do with standardized dosing.

The contribution of pharmacokinetic variability to differences in dose requirements can be identified by measuring the drug concentration at the steady state and modifying the dose in order to attain a desired concentration known to be associated with efficacy. Nevertheless, there is substantial inter-individual pharmacodynamic variability at a given plasma concentration [3], hence a range of concentrations rather than a single level is usually targeted [4].

The bulk of the knowledge of clinical pharmacology of antiretrovirals essentially concerns the classes of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The plasma concentrations of these drugs are believed, in fact, to be in a state of substantial equilibrium with the intracellular concentrations [5]; consequently the measurement of the first should provide a good surrogate of the second. Nucleoside/nucleotide reverse transcriptase inhibitors, N_tRTIs, require intracellular phosphorylation to be activated, so that the plasma pharmacokinetic parameters don't reflect the real intracellular metabolism and activity of the drug [6]. In parallel with the pharmacodynamics of antibiotics, PIs and NNRTIs acknowledge a time-dependence mechanism. This means that for the total duration of the dose interval, plasma concentrations must be higher than the minimum inhibitory concentration (MIC) of the activity of the virus (IC_{50} o IC_{90}) [7]. Hence the importance of determining the C_{trough} or the lowest concentration of the drug in the blood that is measured after a dose. To perform a correct analysis a multidisciplinary approach is required, with accurate and complete collaboration by all figures involved patients, clinicians, nurses, and pharmacologist.

If plasma drug concentration measurements are to be of any value, attention must be paid to the timing of blood sampling, the type of blood sample, the measurement technique, and the interpretation of results. First, it is essential to collect the blood sample for measuring the drug concentration at the correct time after dosing. Errors in the timing of sampling are responsible for the greatest number of errors in interpreting the results.

Currently, fluorescence polarization immunoassay (FPIA), enzyme immunoassay (EMIT), and enzyme-linked immunosorbant assay (ELISA) [8] have widely replaced the old radioimmunoassay or high-performance liquid chromatography (HPLC) procedures [9], being much quicker and much cheaper.

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The complexity of the antiretroviral landscape

The number of drugs and drug classes available to treat HIV-1 infection has greatly expanded since 1989, and given the rapid evolution of research wide differences across countries exist either on when to start therapy or on how to combine drugs. In fact, beside some particularly stringent guidelines [10], in some parts of the world we can find up to 120 different regimens, especially arising from switches to the first-line regimens due to toxicity or viral failure [11]. In general, the more regimens a patient has failed due to tolerability or viral failure, the more complex and expensive the regimen becomes, and drug interactions among antiretrovirals are frequent.

Up to date antiretroviral drugs are grouped into four main classes, with individual differences in absorption, metabolism, diffusion volume, toxicity and interactions.

Nucleoside analogues/Nucleotides (NAs, N_tRTIs): N_tRTIs are key components of cART regimens, and are often referred to as the "backbone" of HIV treatment [12]. Indeed, these are drugs with relatively low interaction potential. Only tenofovir decreases plasma levels of protease inhibitors and is itself boosted in such combinations [13]. Thymidine analogues and dideoxynucleosides sum their neurotoxicity to many cancer agents. Dideoxynucleosides, citidine analogues and tenofovir are excreted by the kidney and compete with aminoglycosides, pentamidine, amphoterycin B, cidofovir, flucytosine, cisplatin, capecitabine, hydroxyurea, probenecid, ibandronic acid and others. Drug dosage reduction with reduced creatinine clearance is defined by a specific algorithm [14]. This may pose problems in case of fixed-dose combinations in which drugs with different renal elimination coexist.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): NNRTIs are inducers of hepatic P-cytochrome 450 (CYP450), isoenzime 2B6, 2C9 and 2C19 (efavirenz [15]), and 3A4 (efavirenz, nevirapine, rilpivirine, [16] and etravirine [17]), and their absorption and distribution is affected by the drug transporter P-glycoprotein (P-gp) [18]. NNRTIs, except rilpivirine, interact with protease inhibitors, maraviroc, analgesics, antihelmintics, antiarrhythmics, rifamycins, anticoagulants, anticonvulsivants, antipsychotics, antidepressants, antidiabetics, antifungals, simeprevir, anxiolytics, calcium channel blockers, contraceptives, cytotoxics, erectile dysfunctional agents, steroids and many other agents. Rilpivirine is deeply affected by the concomitant intake of proton pump inhibitors [19]. NNRTIs have a long elimination half-life, therefore the TDM significance does not change significantly between the C_{trough} and any other timepoint of the curve. The investigation about efavirenz dose recently has suggested that for 16 years we might have been using exceedingly high doses of the drug [20].

Boosted protease inhibitors (bPIs): All the currently available PIs are metabolized mainly by CYP450, in particular the CYP3A4 isoenzyme group. With the co-administration of a CYP3A4 inhibitor, ritonavir or cobicistat (and to a lesser extent atazanavir and fluconazole), plasma exposure of these agents is increased, elevating the genetic barrier to resistance (boosting).

This also frequently causes a boosting effect of concomitant medications equally metabolized via the CYP3A4 isoenzymes (i.e.: rifamycins, tacrolimus, sildenafil) increasing the risk of toxicity, or blocks the activation of other drugs through hepatic metabolism. Inducers of CYP3A4 may in turn lower PI concentrations, though this effect is partially reversed by the action of the boosters. PIs share therefore a high drug interaction profile, including many antiretrovirals [21].

When toxicity issues are raised, also a mini-AUC (i.e.: points 0, 1 hour, 2, 3, and 4 hours) may help to understand whether the C_{max} and overall exposure exceed safety limits.

In the future PIs may be made of deuterium, a heavier relative of hydrogen that may slow hepatic elimination, prolonging the drug half-life without the use of a boosting agent.

Integrase strand transfer inhibitors (INSTIs): Raltegravir, the first drug to be approved, is primarily glucuronidated by uridine glucuronosyl transferase (UGT) 1A1, and has limited drug interactions [22], although some reciprocal influence with PIs has been suggested [23,24] . Raltegravir however has a high inter- and intra-patient pharmacokinetic variability and needs at least a mini-AUC as described above for correct assessment [25], as the C_{trough} levels may be poorly indicative [26].

Dolutegravir also is metabolized via UGT1A1 with a minor contribution by CYP3A, and is a substrate for P-glycoprotein, with very few dug-drug interactions [27], the only relevant one being with metformine, whose exposure results nearly doubled by co-administration [28]. There are at present few data on dolutegravir TDM, but it's pharmacokinetics appears to be characterized by low variability [29].

Elvitegravir undergoes extensive primary metabolism by hepatic and intestinal CYP3A and secondary metabolism by UGT1A1/3, and requires enhancement by ritonavir [30] or cobicistat, therefore it shares most drug-drug interactions with the bPI class. Elvitegravir 85 mg/cobicistat 150 mg coadministered with atazanavir results in comparable elvitegravir exposure with an 83% increase in C_{24h} compared to elvitegravir 150mg/cobicistat 150 mg [31].

In the near future, a new INSTI, cabotegravir may become the first long-acting parenteral drug of this class, a very attractive perspective.

Fusion and attachment inhibitors (FIs): Maraviroc: Maraviroc is one of the most sensitive metabolites of CYP3A4 with no significant involvement of the other CYP450 isoenzimes, and has a weak, poorly significant inhibition on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 and 3A5 [32]. Maraviroc has a linear pharmacokinetics and therefore, C^{trough} can be considered a reliable indicator of adequate drug dose [33,34]. bPIs and NNRTIs have a major effect on the plasma concentrations of this drug and require halving or doubling the standard dose [35].

Fusion and attachment inhibitors (FIs): Enfuvirtide: Enfuvirtide is a synthetic peptide that binds to HIV-1 glycoprotein 41, blocking the fusion of viral and cellular membranes. It exhibits a small volume of distribution (5.48 L), low systemic clearance (1.4 L/h), high plasma protein binding (92%), and high bioavailability (84.3%). Less than 17% of it is deaminated to a minimally active metabolite, and both are primarily eliminated via catabolism to amino acid residues. Following subcutaneous administration, enfuvirtide is almost completely absorbed, with a slow and protracted subcutaneous absorption, resulting in relatively flat steady-state plasma concentration-time profiles. Enfuvirtide did not influence concentrations of drugs metabolised by CYP3A4, CYP2D6 or N-acetyltransferase, and had only minimal effects on those metabolised by CYP1A2, CYP2E1 or CYP2C19 [36].

The relevance of drug monitoring and interactions

It is important to understand the benefits and limitations of TDM

in order to understand it's utility. TDM can be used to:

- Confirm antiviral effect or reveal pharmacologic or adherence causes of failure
- Establish dose-related drug toxicity
- Aid dosing in some populations.

Where the correlation between blood concentration and therapeutic activity is known, TDM can establish whether the drug dose is sufficient for the effect to be achieved.

The first demonstration of the importance of drug levels in HIV infection came from the Viradapt study in the year 2000 [37], in which plasma levels of protease inhibitors independently correlated with viral suppression after genotype-guided or standard rules-guided switch for treatment failure. Patients who switched based on genotypic data had better viral control, but having optimal drug concentrations was more important than the knowledge of resistance mutations. The mean change in HIV-1 RNA after 48 weeks of treatment (regardless of the availability of genotypic resistance test results) was -0.36 $\log_{10}$ in the patients with suboptimal concentrations compared with -1.28 $\log_{10}$ in the patients with optimal concentrations (p = 0.0048).

These data were confirmed by a smaller prospective 52-week study [38] and by the larger ATHENA randomized, controlled clinical trial [39]. In this trial, patients receiving either nelfinavir or indinavir in association with two nucleoside analogues were assigned to the TDM or to the control arm. At week 48, the TDM arm had fewer drug discontinuations (17,4% vs 39,7%) and a significantly higher proportion of subjects having HIV-1 RNA < 500 copies/mL (78,2 vs 55,1%).

Two other trials on the other hand failed to confirm the benefits of TDM. In the PharmAdapt study, patients initiating treatment with protease inhibitor–containing regimens were randomised to receive either TDM or standard of care [40]. There was no apparent benefit of TDM at 12 weeks in terms of virological suppression; however, only 25% of the participants in the intervention arm underwent dose modification based on TDM.

Similarly, in the GENOPHAR study, which randomised patients to receive either TDM or standard of care, there was no apparent better virological response in the TDM arm at the intent-to-treat analysis [41]. In this study, dosage adjustments based on TDM were made for only 19% of the intervention group.

In 2008, a Cochrane analysis stated that given the poverty of trials routine TDM is not supported as a tool to improve antiretroviral therapy in naïve patients, however TDM in treatment-naive participants on a PI-based ART regimen, particularly if unboosted by ritonavir, may improve virological outcomes [42].

Moreover, the C_{min} reported, i.e. in the DHHS guidelines, applies to fully sensitive virus, while when resistance-associated mutations (RAMs) arise, inhibitory quotient, *drug* C_{trough}/*viral* IC_{50} ratio, becomes the relevant parameter, however IC_{50} is a phenotypic measure, so genotypic prediction of the degree of reduced sensitivity is being developed [43].

A retrospective cohort analysis from our hospital evaluating the pharmacoeconomic impact of routine TDM in a large clinical setting showed that after one year of follow-up subjects in the TDM group maintained a higher rate of viral suppression compared to non-TDM (85,3% vs 81,4%) and the TDM group had a great reduction of hospitalization-related costs (€688 versus €293) [44]. Moreover, further analysis conducted on 1807 determinations showed that nearly 40% of patients treated with atazanavir, lopinavir and nevirapine had concentrations exceeding the upper therapeutic limits, while 15% of all patients had subtherapeutic drug levels. In particular, the mean interpatient variability was moderate for nevirapine, efavirenz, lopinavir and darunavir (46.3%, 62.9%, 65.7% and 67.8%, respectively), and high for etravirine, maraviroc, tenofovir and atazanavir (90.2%, 93.6%, 96.2% and 100.5%, respectively), suggesting that at least some medications may be frequently overdosed with the risk of increasing the side effects [45].

Finally, while atazanavir, darunavir, lopinavir, etravirine, nevirapine and efavirenz allow some dose modification, other tablets have to be broken, thus loosing dose precision. The fixed-dose combinations are the most untouchable regimens, in particular the QUAD pill: either you tolerate it or you reject it.

The role of adherence

Strict adherence to HAART is crucial in order to maintain a low viral load, prevent the development of drug-resistant virus [46], improve survival and reduce the risk of HIV transmission [47]. Adherence is second only to CD4 T cell count in predicting progression to AIDS and death [48] and suboptimal adherence to antiretrovirals (<95%) is associated with a higher risk for hospitalization [49]. In this setting, TDM can evaluate recent non-adherence but not chronic suboptimal adherence [50]. It may be useful in the setting of a reticent patient failing without resistance mutations. On the other hand the use of TDM may enhance adherence, making the patient more aware of the importance of the treatment [51,52].

Therapeutic drug monitoring in particular clinical settings

TDM may be useful in various recommended situations such as treatment initiation, suspicion of poor compliance, clinically relevant drug–drug interactions, prevention of toxicity, pregnancy, coinfection with tuberculosis or HCV, transplantation, older age or dose-regimen changes. Here we describe more in detail some of the most relevant subsets.

Pregnancy: Pregnant women present significant pharmacokinetic changes especially during the third trimester, that can lead to underexposure to certain antiretrovirals. Drug absorption can be modified by nausea and vomiting and by reduced gastric emptying and small intestine motility due to increased progesterone levels. The increased volume distribution (increased total body water) can impair drug distribution and plasma albumin and alpha-acid glycoprotein concentrations, potentially affecting protein binding. Pregnancy also affects drug metabolism. In particular, the expression of cytochrome P-450 (CYP) isoforms is highly variable during gestation, with potential consequences for the metabolism of many drugs. The activity of CYP2A6, CYP2C9, CYP2D6, CYP3A4 and uridine diphosphate glucuronosyltransferase (UGT) is increased during pregnancy, whereas the activity of CYP1A2 and CYP2C19 is decreased. Finally, increased renal blood flow may enhance the clearance of some drugs excreted via the kidney [53-55]. Increased progesterone levels during pregnancy may be implicated in the augmented CYP3A activity, potentially reducing blood concentration of PIs. Some studies have demonstrated a reduction in PIs exposure in pregnant women compared with non-pregnant controls [56-61] or in pregnant women before delivery compared with postpartum [62-64]. Data regarding nevirapine plasma concentration changes during pregnancy is conflicting, probably due to the small population samples evaluated and the high inter-individual

variability [65,66]. For newer compounds and efavirenz, limited or no data on pharmacokinetics during pregnancy is available [67,68]. Since an undetectable HIV viremia is a powerful predictive factor of low mother to child transmission, the right exposure to HAART during pregnancy is essential. Therefore, systematic TDM during late pregnancy should be considered to enable dose adjustment to be performed when necessary [69] (Figure 1).

Tuberculosis (TB): TB treatment in HIV patients is complicated by significant drug–drug interactions between TB and antiretroviral drugs. Rifamycins, essential components of the TB treatment, are potent inducers of the cytochrome CYP pathway, leading to reduced plasma concentrations of some classes of antiretrovirals [70,71]. On the other hand, HIV patients can present a reduction in antitubercular drug absorption due to enteropathy and diarrhoea caused by parasitic infections or by HIV itself [72]. TDM may thereby be an useful tool in HIV patients affected by TB infection, as early detection of low drug exposure may improve treatment response and prevent development of further drug resistance [73,74]. The inductive effect of rifampicin is most marked on the CYP3A and CYP2C subfamilies and leads to a reduction in PI serum levels by 35–92 % [75-78]. Coadministration of rifampicin and PIs is thereby contraindicated as it may lead to loss of virologic response and possible cross-resistance to PIs or to the backbone. Also the concomitant administration of rifampicin and non-nucleoside inhibitors is contraindicated due to a possible reduction in NNRTIs blood concentrations. This interaction is stronger for nevirapine, rilpivirine and etravirine [79-83]. Coadministration of rifampicin with efavirenz leads to a minor reduction in efavirenz blood concentration in comparison with the other NNRTIs, since efavirenz is largely cleared by CYP2B6 and, to a lesser extent, by CYP3A4. In some cases, anyway, increasing efavirenz dose to 800 mg/day should be necessary to achieve sufficient blood concentration [1,2,3]. Rifampicin is also an inducer of the UGT1A1 enzymes and interferes with drugs, such as integrase inhibitors, that are metabolized by this pathway. Coadministration of rifampicin with INSTIs decreases raltegravir AUC by 40%, C_{max} by 38% and C_{min} by 61% and dolutegravir AUC by 54%, C_{max} by 43% and C_{trough} by 72%, respectively. If co-administration with rifampicin is unavoidable, a double dose of raltegravir and dolutegravir can be considered [87-89]. Rifabutin has no significant effect on antiretroviral plasma concentrations, but it's own blood concentrations can be affected by HIV drugs. Only coadministration of rilpivirine and rifabutin should be avoided due to the effect of rifabutin on rilpivirine metabolism (decrease of AUC, C_{min} and C_{max} by 42%, 48% and 31%) [90]. Both PIs and NNRTIs may impair rifabutin hepatic metabolism, leading to increased serum concentrations and risk of adverse effect and to reduced serum concentrations and loss of efficacy, respectively. Many studies were conducted to identify the most appropriate rifabutin dose with PIs but the comparison between daily and three times weekly rifabutin 150 mg in association with PIs led to conflicting results [91-95]. Daily dose of rifabutin should be instead increased by 50% when administered with efavirenz, since coadministration of rifabutin 300 mg and efavirenz decreased rifabutin AUC, C_{max} and C_{min} by 38%, 32% and 45% [96]. Maraviroc also is expected to be substantially reduced by rifampicin and rifapentine and, to a lesser extent, by rifabutin [97]. In case of extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis, a new drug is now ready, bedaquiline, which has not shown up to date in pharmacokinetic studies on healthy volunteers,

	PK in pregnancy
Zidovudine (AZT), Didanosine (ddI), 3TC/FTC, Abacavir (ABC)	PK is not significantly altered in pregnancy
Tenofovir (TDF)	AUC is lower in 3rd trimester than postpartum but trough levels are adequate
Efavirenz (EFV)	AUC decreased during 3rd trimester, compared with postpartum, but generally exceeded target exposure
Nevirapine (NVP)	PK is not significantly altered in pregnancy
Etravirine (ETV)	Limited PK data in pregnancy (n = 4) suggest no significant differences from non-pregnant adults, not enough to make dose recommendations
Rilpivirine (RPV)	No PK studies in human pregnancy, no dosing recommendation can be made
Atazanavir (ATV) Atazanavir/ritonavir (ATV/r)	Since ATV concentrations are reduced during pregnancy, unboosted ATV is not recommended. Although 400 mg ATV plus 100 mg RTV once daily with food during the 2nd and 3rd trimesters results in plasma levels equivalent to those in non-pregnant adults on standard dosing, the package insert recommends increased ATV dosing only for ARV-experienced pregnant women in the 2nd and 3rd trimesters also receiving either TDF or an H2-receptor antagonist
Darunavir/ritonavir (DRV/r)	Decreased exposure in pregnancy; once-daily dosing is not recommended during pregnancy. Twice-daily dosing is recommended for all pregnant women
Fosamprenavir/ritonavir (FPV/r) Saquinavir/ritonavir (SQV/r)	Fosamprenavir AUC is reduced during the 3rd trimester. However, trough concentrations achieved during the 3rd trimester were adequate for patients without PI resistance mutations. Also SQV exposure may be reduced in pregnancy but still sufficient
Lopinavir/ritonavir (LPV/r)	PK studies suggest increased dose (LPV 600 mg plus RTV 150 mg twice daily without regard to meals) should be used in 2nd and 3rd trimesters, especially in PI-experienced patients. If standard dosing is used, monitor virologic response and LPV drug levels, if available. No data to address if drug levels are adequate with once-daily dosing in pregnancy
Elvitegravir/c/Tenofovir/FTC	Limited PK data in human pregnancy, insufficient to make dosing recommendation
Raltegravir	Limited PK data suggest PK is not significantly altered in pregnancy, therefore no dose modification is required
Dolutegravir	No PK data in human pregnancy, insufficient to make dosing recommendation
Maraviroc	Limited PK data in human pregnancy, insufficient to make dosing recommendation

Figure 1: pharmacokinetic impact of pregnancy on antiretrovirals and dose recommendations.

neither interactions with a strong CYP3A inhibitor such as lopinavir, nor with an inducer, such as nevirapine [98]. However no studies have been published of its' use in HIV-MDR TB up to date.

HCV: The management of HCV infection in HIV-positive patients is complex, as the second and third generation diractly acting antivirals (DAAs) have shown promising results in terms of efficacy and tolerability, and a good pharmacokinetic profile. The drug - drug interaction potential in HIV/HCV co-infection mostly regards the use of HCV NS3 protease inhibitors. Telaprevir, boceprevir and simeprevir interact with CYP3A as inhibitors and substrates, with potential interaction and increased concentrations of drugs metabolized through this pathway. Sofosbuvir is an HCV NS5B RNA-dependent RNA polymerase uridine analogue nucleotide inhibitor, metabolized to the active triphosphate through a series of intracellular reactions. It is also a substrate for P-glycoprotein and breast cancer resistance protein (BCRP). Since neither sofosbuvir nor its active metabolite (GS-331007) are substrates for or inducers of CYP450 enzymes or UGT, pharmacokinetic studies showed few and clinically irrelevant interactions between sofosbuvir and antiretrovirals, not requiring dose adjustments. Sofosbuvir concentrations may be deeply rediced in the coadministration of with nelfinavir and tipranavir, which therefore should be avoided. Simeprevir is an HCV NS3/4A protease inhibitor, metabolized by the CYP3A. It mildly inhibits the intestinal but not the hepatic CYP3A enzymes and inhibits the hepatic CYP1A29 enzymes. Simeprevir can be coadministered with tenofovir, rilpivirine and raltegravir without dose modifications [99], while the combination with efavirenz or darunavir is not recommended. Efavirenz leads to a reduction in simeprevir AUC, C_{max} and C_{min} by 71%, 51% and 91%, respectively. RTV-boosted darunavir is the only protease inhibitor studied with simeprevir. When coadminestered with DRV/r, simeprevir C_{max}, AUC and C_{min} increased by 1.79-, 2.59- and 4.58-fold. Data are not available on the other RTV-boosted HIV protease inhibitors, but similar effect is expected. Daclatasvir is a HCV NS5A replication complex inhibitor. It is a substrate for CYP3A4 and P glycoprotein, and moderately inhibits P-glycoprotein and OATP1B1. Coadministration of atazanavir/ritonavir and daclatasvir (60 mg once daily) increased daclatasvir AUC, C_{max} and C_{min} by 110%, 35% and 265%, respectively. The dose of daclatasvir should be thereby reduced to 30 mg once daily when coadministered with atazanavir/ritonavir. The coadministration of efavirenz and daclatasvir (60 or 120 mg once daily) decreased daclatasvir AUC, C_{max} and C_{min} by 32%, 17% and 59%, respectively (results dose-normalized to 60 mg dose). The dose of daclatasvir should be increased to 90 mg once daily when coadministered with efavirenz [100]. Considering the possible interactions, TDM may be useful in the management of HIV/HCV coinfected patients (See figure 2) .

Transplantation: As transplantation in the HIV population becomes increasingly feasible there is a need to optimize the pharmacologic management of this population. Most studies report a higher rate

Anti-HIV drugs	Ribavirin	Sofosbuvir/Ledipasvir	Simeprevir	Daclatasvir	Dasabuvir/Parataprevir/ Ombutasvir/Ritonavir
Zidovudine (AZT)	▼AZT fosforilation	Ok	Ok	Ok	Ok
Didanosine (ddI)	▲intracellular ddI, fatal hepatitis reported	Ok	Ok	Ok	Ok
3TC/FTC	Ok	Ok	Ok	Ok	Ok
Abacavir (ABC)	Ok	Ok	Ok	Ok	Ok
Tenofovir (TDF)	Ok	▲ TDF AUC >40%, consider alternative	Ok	Ok	Ok
Rilpivirine (RPV)	Ok	Ok	Ok	Ok	▲ RPV AUC, ▲ cardiac risk
Efavirenz (EFV)	Ok	▼Ledipasvir PK by 34%	▼ Simeprevir AUC by 71%	▼ Daclatasvir AUC by 32%, increase to 90 mg	Contraindicated, no data
Etravirine (ETV) / Nevirapine (NVP)	Ok	Ok	▼ Simeprevir AUC likely	▼ Daclatasvir AUC likely	Possible ▼ DAA AUC
Atazanavir (ATV)	Ok	Not unboosted	▲ Simeprevir AUC	Not unboosted	Ok
Darunavir (DRV)	Ok	Not unboosted	▲ Simeprevir AUC	Not unboosted	▼ Darunavir AUC by 43-48%
ATV/r	Ok	▲Ledipasvir AUC 113%, ▲ATV AUC 33%	▲ Simeprevir AUC	▲ Daclatasvir AUC by 110%, reduce to 30 mg	▲ Paritaprevir AUC
DRV/r	Ok	Ok	▲ Simeprevir AUC	Ok	Contraindicated, no data
Lopinavir/r	Ok	Ok	▲ Simeprevir AUC	Ok	Contraindicated, no data
FPV(r),SQV(r), ATV/c, DRV/c	Ok	Ok	▲ Simeprevir AUC	▲ Daclatasvir AUC	Contraindicated, no data
Elvitegravir/c/TDF/FTC	Ok	▲ TDF and Ledipasvir	▲ Simeprevir AUC likely	▲ Daclatasvir AUC likely	Contraindicated, no data
Raltegravir (RAL)	Ok	Ok	Ok	Ok	Ok
Dolutegravir (DTG)	Ok	Ok	▲Dolutegravir AUC 33% no dose adjustment	No dose adjustment required, not studied	No dose adjustment required, not studied
Maraviroc (MVC)	Ok	Ok	Ok	Ok	▲ MVC AUC likely

Figure 2: Interactions between antiretrovirals and anti-HCV DAAs.

of acute rejection in HIV positive patients in comparison with non-HIV-infected patients, possibly due to drug interactions resulting in altered exposure to immune suppressants [101]. It is very important thereby to perform close TDM because of the narrow therapeutic window of immune suppressants. Tacrolimus is a potent calcineurin inhibitor used in solid transplantation and metabolized by CYP3A and P-glycoprotein. Protease inhibitors, especially ritonavir reduce tacrolimus clearance and bowel efflux with high risk of overdose and toxicity [102,103]. Non nucleoside inhibitors on the other hand have a less potent impact than PIs but may potentially reduce tacrolimus blood concentration [104,105]. Cyclosporine is another calcineurin inhibitor, with a similar pharmacokinetic profile [106-108] actually used as alternative choice to tacrolimus because of a higher rate of acute rejection. Mycophenolate is an immunosuppressive drug, metabolized mainly by glucuronidation in the liver. Atazanavir inhibits UDP-glucuronosyltransferase and, theoretically, leads to an increase in blood mycophenolate mofetil levels, whereas ritonavir induces glucuronidation and could reduce blood mycophenolate mofetil levels. However, clinically important drug–drug interactions between mycophenolate mofetil and the antiretroviral agents have not been reported [109,110]. Everolimus and sirolimus are inhibitors of the mammalian target of rapamycin (mTOR), and are also used as cytotoxic anticancer agents. They are metabolized by CYP3A and P-glycoprotein and their blood concentration may be altered by antiretroviral coadministration [111]. Caution is urged also in using corticosteroids for the possible drug-drug interactions between steroids metabolized by CYP3A and antiretrovirals [112,113]. In this setting, assessing not only antiretroviral drug concentrations but particularly immune suppressants' plasma levels is particularly useful.

Web-based tools for the physician

In recent years web-based tools have been developed to help the physicians make decisions about the appropriate ARV drugs according to the patient's complexity.

The University of Liverpool offered one of the first web-based system able to assist clinicians. It includes a drug interaction chart (with the possibility to download an interaction app for mobile devices), treatment selector tables and a special section on pharmacology resources, which offers special information about every single ARV drug [20].

The University of California at San Francisco has created a database of antiretroviral drug interactions with the possibility to search the information by antiretroviral drug or interacting drug or drug class [114].

The Office of the Medical Director, New York State Department of Health AIDS Institute in collaboration with the John Hopkins University propose an in-depth review of the main drug-drug interactions, divided into drug classes, and explain the different pharmacokinetic and pharmacodynamic mechanisms [115].

The DHHS guidelines show updated online tables concerning different pharmacological aspects: concomitant use of selected antiretroviral drugs and all drugs for treatment of hepatitis C, drugs that should not be used with antiretroviral agents, interactions between the different drugs of different classes used for HIV and any other drug, antiretroviral dosing recommendations in patients with renal or hepatic insufficiency [116]. Other available tables concern trough concentrations of antiretroviral drugs for patients who have drug-susceptible virus and for treatment-experienced patients with virologic failure [117].

The International Association of Providers of AIDS Care (IAPAC) summarizes the main pharmacological patterns of the antiretroviral drugs [118].

The interactions between antiretroviral drugs and recreational drugs are specifically addressed by the National AIDS Manual [119].

The University of California at San Diego has developed a computer-based system for modeling and interpreting plasma lopinavir and efavirenz concentrations for TDM [120].

The role of genetic factors

Pharmacogenetics analyses the genetic basis for the inter-individual variation in the body disposition of drugs. The initial candidate genes studies, in which genetic variants of host factors that were already known to play a role in HIV-infection were tested, have lead to genome wide association studies (GWAS), in which the whole genome is studied. Generally a minority of the population has a disposition to accumulate or to rapidly metabolize a certain drug, but these can be at risk of toxicity or failure if the drug is not avoided or correctly dosed.

This aspect started to influence antiretroviral therapy decisions when a clear association of HLA-B*5701 with hypersensitivity reactions to abacavir was discovered [121]. Tenofovir renal toxicity has also been linked with a series of genetic variants of proximal tubular cellular transporters [122-124], although currently information about the effect of genetic polymorphisms on the risk of renal toxicity using tenofovir is still matter of controversy. Nevirapine-related hypersensitivity reactions are more common in subjects harbouring HLA-Cw*8 [125], HLA-DR B1*0101 [126], and HLA-B 3505 [127], although the causality relationship is not as stringent as with abacavir.

More relevant to our issue, other polymorphisms are related to exceedingly high or low antiretroviral drug concentrations. Subjects homozygous for the CYP2B6*6 [128], CYP2B6*16 [129], CYP2B6*18 [130], CYP2B6*27 or CYP2B6*28 alleles [131] have higher levels of efavirenz and risk of toxicity or resistance after drug discontinuation, due to the slow elimination rate. Lopinavir accumulation is possible in subjects harboring the 521CC polymorphism in the OATP1B1 intracellular transporter [132]. On the contrary, ABCB1 and PXR polymorphisms are correlated with a risk of sub-therapeutic atazanavir and raltegravir concentrations [133-135].

In general, with the exception of abacavir, efavirenz and atazanavir, most pharmacogenetic correlations still deserve studies to clarify the precise genetic base and mechanisms that generate the phenotype, in order to have more predictive tests.

However, those genotypes that predict alterations in metabolism may benefit of a simple therapeutic drug monitoring, i.e.: after two weeks of therapy, drug levels may guide dosage adjustment. More often pharmacogenetic analyses are requested in patients experiencing adverse events, together with drug monitoring, to clear out whether or not there is a genetic basis to justify dose reduction. Drug levels should be retested after two weeks of dose reduction.

The above mentioned polymorphisms become particularly relevant when the patients need other medications that share metabolic or excretion pathways, especially if their therapeutic range is narrow, as it may happen with anticancer chemotherapy [136].

The place of Therapeutic Drug Monitoring in the Guidelines

The main international guidelines state that TDM for antiretroviral agents is not recommended for routine use in the management of the HIV-infected patients (CIII) [10,137-143]. This is likely due to the lack of large prospective studies, the lack of established therapeutic ranges of concentrations for all antiretroviral (ARV) drugs, the intra-patient variability in drug concentrations, the lack of widespread availability of clinical laboratories that perform this kind of exam, and the shortage of experts able to assist and translate the data for a clinical use. Even the British guidelines recommend against the unselected use of TDM [10], though recognizing that it may aid the management of vulnerable populations or complex clinical situations. The Italian guidelines underline that in a recent pharmacoeconomic analysis it as been suggested that TDM allows a cost reduction.

The DHHS and Italian guidelines distinguish the possible use of TDM in the different ARV classes. As for PIs, NNRTIs and INSTIs, thanks to the presence of various publications, it has been possible to suggest different trough concentrations for patients who have drug-susceptible virus and for treatment-experienced patients with virologic failure (in particular for darunavir, etravirine and raltegravir). As for CCR5 antagonists, clinical experience in the use of TDM for maraviroc is very limited, even if its C_{trough} has been shown to be an important predictor of virologic success in studies conducted in ART-experienced persons. As for NRTIs, plasma or intracellular TDM can just be considered a research tool. The Spanish guidelines consider TDM just for NNRTIs and PIs.

The guidelines suggest different situations in which it can be useful to perform TDM, in particular drug-drug or drug-food interactions, impaired gastrointestinal or hepatic or renal function, pregnant women, heavily pretreated patients experiencing virologic failure, use of alternative dosing regimens and ARV combinations, concentration-dependent and drug-associated toxicities, lack of expected virologic response in medication-adherent persons [10]. Some guidelines suggest to use TDM also for children and in patients with altered body mass index (BMI).

Discussion

Although assisted by various and well-developed web-based tools, the physician often needs to know whether the patient is taking well his therapy, to what extent unavoidable comedications impact on exposure to antiretrovirals, how much of the inter-patient variability can be predicted by pharmacogenetic tests and how drug levels can be altered by organ impairment, absorption problems and many other concomitant conditions. Wherever the machinery is present, testing antiretroviral drug concentrations is relatively cheap (60% the price of CD4+ T-cell count assessment and less than 50% that of HIV-1 RT-PCR). Not all drugs are listed neither in the guidelines nor in the beautiful websites related to drug toxicity and interactions. Also single-SNP, pharmacogenetic tests are comparable as cost with HIV-1 RT PCR, but need not to be repeated during the life course. In the frequent cases of subjects taking herbs, recreational drugs or other out-of-pharmacy drugs, TDM may represent a safe way to control unexpected interactions before virologic failure occurs. Looking at studies on naïve patients we may say that probably about 80% of them would not need TDM, at least during the first 2 years, but when we consider studies of experienced or salvage subjects, pharmacogenetic and pharmacokinetic tests are really helpful.

Conclusions

The use of pharmacogenetic tests and of TDM in the management of HIV infection is an area that deserves more studies and more research, as the gap between the guidelines and the clinical usefulness is wide. Centers having a Clinical Pharmacology Unit may serve larger areas, covering those hospitals or services that cannot afford creating their own facilities.

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