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Management of Polypharmacy and Drug-Drug Interactions in HIV Patients: A 2-year Experience of a Multidisciplinary Outpatient Clinic

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Abstract

HIV-positive patients are treated with various antiretroviral-containing drug combinations to control their underlying disease, which may also be combined with drugs aimed to manage independent or secondary comorbidities. This can expose patients to drug-drug interactions (DDIs) that may lead to suboptimal drug exposure, an increased risk of therapeutic failure or poor tolerability, and a need to adopt alternative therapeutic strategies. Although such undesired responses to pharmacological therapies can be appropriately managed in some situations, the fact that the available information is usually incomplete which makes it difficult (if not impossible) to assess DDIs and the consequent adjustments of polytherapies in clinical practice. For these reasons, we set up our ambulatory polytherapy management (Gestione Ambulatoriale Politerapie [GAP]) outpatient clinic in September 2016 to manage polypharmacy in HIV-infected patients. The main aims of the GAP clinic are to check whether patients are treated with drug combinations that are contraindicated due to known or predictable DDIs; assess the clinical and/or pharmacokinetic relevance of the DDIs; and provide written advice as to how the treatments should be modified if possible. We here describe the results of our 2-year experience in various clinical scenarios. **(AIDS Rev. 2019;21:40-49)**

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Key words

HIV. Drug-drug interactions. Polypharmacy.

Introduction

The improved survival of HIV-infected patients has complicated their medical care insofar as an increasing number of comorbidities have led to polypharmacy[1-3], and the burden of taking multiple medications is associated with an increased risk of adverse drug events, non-adherence to prescriptions, and drug-drug interactions (DDIs). This may compromise the efficacy of both the antiretroviral and non-antiretroviral treatments[4].

The aims of this review are to summarize the mechanisms underlying DDIs and their potential clinical

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relevance and describe the clinical scenarios that we have encountered over the years since we set up our multidisciplinary ambulatory polytherapy management (Gestione Ambulatoriale Politerapie: GAP) outpatient clinic to manage the polypharmacy of HIV-infected patients.

The mechanisms underlying DDIs

The main mechanisms underlying the interactions between two or more substances (drugs, supplements, etc.) are chemicophysical, pharmacokinetic, or pharmacodynamic. Some drugs directly interfere (or react) with each other on the basis of their chemicophysical properties, such as calcium-, aluminum-, magnesium-, or iron-based supplements that interfere with the absorption of integrase inhibitors due to their chelating reactions[5]. However, the most widely studied and clinically understood mechanism is pharmacokinetics (i.e., the capacity of a molecule to interfere with the absorption, distribution, metabolism, or elimination of another drug). The most frequent pharmacokinetic reactions involve the inhibition or induction of drug metabolizing enzymes. The most common are those affecting drug metabolism due to the induction or inhibition of the cytochrome P450 (CYP), leading to abnormal drug exposure; among the different CYP isoforms, CYP3A and CYP2B6 are those most frequently involved in DDIs of antiretroviral drugs[1-4].

Over the past few years, considerable attention has also been given to DDIs involving the transmembrane proteins (such as the well-known efflux pump P-glycoprotein) that act as carriers of various drugs: for example, the inhibition of organic cation transporter 2 (OCT2), which is involved in the renal elimination of metformin, increases the bioavailability of this drug in dolutegravir-treated patients[6]. Pharmacodynamic interactions may involve the combined (synergistic, agonistic or antagonistic) effects of two or more molecules on the same pharmacological target (such as the therapeutic action of naloxone in inhibiting the symptoms of a morphine overdose) or different targets (such as the combined use of two diuretics that act on different tracts of nephrons); these interactions may be potentiating or inhibitory and are clinically highly significant[7].

The relevance of pharmacological interactions

DDIs represent a highly complex aspect of clinical pharmacology because, unfortunately, most of the information produced during the development of a drug is not very useful in determining their clinical relevance. Furthermore, most of what we know about the possible impact of DDIs on humans comes from experimental models or studies of healthy volunteers who are administered a single dose in situations that are very different from the everyday clinical context in which drugs are actually used once they are marketed[8]. Consequently, the information collected in pre-marketing studies should only be considered a starting point for a more comprehensive bedside approach that takes into account all of the other factors that largely govern the risk of DDIs. This risk is directly proportional to the number of drugs received, but it is also necessary to remember that some patients (the elderly, patients with excretory organ deficiency, etc.) are more at risk than others; diseases can mask or modify the manifestations of an interaction; genetic or environmental factors can lead to more or less marked variability in individual drug responses; and the effect of a drug can be quantitatively measured in only a few cases[8-11].

Another critical point is the fact that the scientific literature mainly consists of studies of potential DDIs that can be predicted a priori on the basis of the pharmacological properties of the drugs involved but do not necessarily give rise to clinical problems for patients[12]. The European Medicines Agency or American Food and Drug Administration (FDA) evaluates the entity of a pharmacological interaction on the basis of the linear relationship between pharmacokinetic data and clinical outcomes, but this has been documented only in the case of a minority of drugs and without taking into account their therapeutic index (see examples below). Although a few thousand DDIs have been reported, the number of clinically significant DDIs is much smaller, and these frequently involve drugs with a low therapeutic index, such as oral anticoagulants, some oral antidiabetic drugs, anticonvulsants, antidepressants, anti-arrhythmic drugs (including digoxin), nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin), neuroleptics, many anticancer and immunosuppressive agents, and theophylline[8,13,14].

The sources of information concerning DDIs include a drug's summary of product characteristics and dedicated databases that rate DDIs on the basis of their severity, clinical relevance, or clinical documentation (Table 1)[15-22]. However, it is important to note that it is advisable to consult more than one of these databases because none of them are perfect and there are discrepancies between them, particularly in terms of their

Table 1. Some of the free web databases that can be used to verify possible drug interactions

Link	Notes
https://clinicalweb.marionegri.it/intercheckweb	A database that evaluates prescriptive appropriateness in the elderly by considering various aspects of geriatric pharmacology (it requires individual registration)
https://reference.medscape.com/drug-interactionchecker	A "generalist" database that also includes over-the-counter products, some phytotherapeutic agents, and supplements
https://www.hiv-druginteractions.org	A database verifying interactions between antiretroviral agents (HIV) and between antiretroviral and non-antiretroviral agents
https://www.hep-druginteractions.org	A database verifying interactions between antiviral agents (HCV) and between antiviral and non-antiviral agents
http://www.drugs.com/drug_interactions.html	A "generalist" database
https://cancer-druginteractions.org/checker	A database verifying interactions between antitumoral agents and between antitumoral and non-antitumoral agents
http://healthlibrary.uchospitals.edu/drugs-supplements/drug-interaction/	A "generalist" database
https://www.rxlist.com/drug-interaction-checker.htm	A "generalist" database
https://stahlonline.cambridge.org/drug_interaction.jsf?page=drugDetails	A "generalist" database that particularly focuses on drugs acts on the central nervous system

classification of severity. Nevertheless, there is no doubt that they are useful in distinguishing the most clinically relevant interactions, providing that they are used correctly.

As can be seen from the above, it is difficult to transfer the importance of interactions to everyday clinical practice, which makes it increasingly necessary to collect and divulge information concerning expected interactions, differentiate those that are clinically relevant from those that are not, and adopt a more rational approach to both antiretroviral and other pharmacological treatments.

The GAP outpatient clinic

The GAP outpatient clinic of Luigi Sacco Hospital's Department of Infectious Diseases in Milan was opened in September 2016 with the aim of serving HIV-positive patients undergoing multiple drug treatments. These include patients receiving chronic treatment for infectious and other diseases, patients with chronic renal and/or hepatic diseases, elderly patients aged > 60 years, patients whose clinical conditions predispose them to inadequate dosing (obesity, pregnancy, etc.), "special" populations (patients of different ethnicities, menopausal women, etc.), patients taking supplements or natural products, and patients with liver disease being treated with the new antiviral agents. The clinic is run with the collaboration of a specialist in infectious diseases and a clinical pharmacologist and has the purpose of verifying the appropriateness of the different drug combinations and doses that the patients are prescribed. The clinical principal activities are summarized in Box 1. When considered

Box 1. Activities of the GAP outpatient clinic

- The detailed collection of anamnestic, clinical, therapeutic, and *ad hoc* laboratory data relating to individual patients taking antiretroviral and other drugs, phytotherapeutic agents, supplements, etc., to verify whether there are potential pharmacological interactions between treatments.
- When appropriate, prescription of the pharmacokinetic tests offered by the hospital's pharmacological service to quantify any identified interactions.
- Verification of known/potential interactions on the basis of drug metabolism and scientific evidence.
- Verification of the real clinical relevance of the interactions by carefully evaluating the current and previous clinical conditions of each patient, and the possible risks/benefits of his/her current treatments.
- Written report to each patient's general practitioner and attending specialist

Table 2. TDM service available in our center

Antiretrovirals	Anti-infectives	Antiepileptics	Psychotropics	Others
Tenofovir	Teicoplanin	Lamotrigine	Citalopram	Quinidine
Efavirenz	Levofloxacin	Etosuccimide	Escitalopram	Theophylline
Etravirine	Rifampicin	Zonisamide	Quetiapine	Acetaminophen
Nevirapine	Linezolid	Rufinamide	Paroxetine	Ibuprofen
Rilpivirine	Ciprofloxacin	levetiracetam	Aripiprazole	Lithium
Amprenavir	Vancomycin	Topiramate	Olanzapine	Dabigatran
Atazanavir	Amikacin	Felbamate	Risperidone	Rivaroxaban
Darunavir	Gentamicin	Oxcarbazepine	Haloperidol	Apixaban
Indinavir	Trimethoprim	Perampanel	Clozapine	Dabigatran
Lopinavir	Meropenem	Lacosamide	Paliperidone	Cyclosporine
Saquinavir	Piperacillin	Valproate	Fluoxetine	Tacrolimus
Tipranavir	Voriconazole	Carbamazepine	Duloxetine	Mycophenolate
Dolutegravir	Posaconazole	Phenobarbital	Fluphenazine	Sirolimus
Elvitegravir	Isavuconazole	Phenytoin	Clomipramine	Everolimus
Raltegravir	Itraconazole	Primidone	Venlafaxine	
Maraviroc	Caspofungin		Ziprasidone	
			Sertraline	

TDM: Therapeutic drug monitoring

appropriate, the GAP outpatient clinic can take advantage from the availability of a therapeutic drug monitoring (TDM) service setup in our hospital in 2009. Beside the quantification of pharmacokinetic-based DDIs, TDM is a useful tool for the management of HIV-infected patients in selected clinical conditions, such as: (a) monitor short-term compliance, (b) improve antiretroviral tolerability with dosage reduction (as in the case of atazanavir, efavirenz or tenofovir toxicity); (c) improve treatment efficacy (i.e., resistant patients), and (d) optimize drug dosages in pregnancy, infancy, obese, and patients with renal or liver insufficiency. A detailed list of the TDM available in our clinic is given in table 2.

The experience of the gap clinic

The following paragraphs describe some of the real-life scenarios encountered during the first 2 years of the GAP clinic. They also describe and consider the clinical relevance of interactions that may be encountered by any specialist in infectious diseases managing HIV-positive outpatients who are taking other medications (in the widest sense of the term) in addition to their antiretroviral drugs.

Expected and unexpected clinically relevant interactions

Weight-reducing products

The prevalence of obesity (body mass index > 30 kg/m^2) among HIV-infected subjects in the USA is approaching parity among the general population and is particularly high among women and minorities[23-25]. The only FDA-approved drugs for the long-term treatment of obesity are currently orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide[26].

Table 3. Clinical characteristics of the four patients experiencing virological failure while taking weight-reducing drugs

Sex, age	Antiretroviral therapy	Interacting agent	First trough concentration	Second trough concentration
Female, 43 years	ATV/r 300/100 mg TDF/FTC 245/200 mg	Orlistat 60 mg thrice daily	ATV: 50 ng/mL	ATV: 195 ng/mL
Female, 39 years	EFV 600 mg TDF/FTC 245/200 mg	Orlistat 60 mg thrice daily	EFV: <150 ng/mL	EFV: 3795 ng/mL
Female, 40 years	ATV/r 300/100 mg TDF/FTC 245/200 mg	Sinetrol 450 mg twice daily	ATV: 85 ng/mL	ATV: 719 ng/mL
Male, 44 years	DRV/c 800/150 mg TAF/FTC 10/200 mg	Gunabasic 7 g daily Lepidium 6.5 g daily	Not available	Not available

ATV: atazanavir, r: ritonavir, TDF: tenofovir difumarate, FTC: emtricitabine, EFV: efavirenz, DRV: darunavir, c: cobicistat, TAF: tenofovir alafenamide

The GAP database includes four patients concomitantly receiving stable antiretroviral treatment and weight-reducing drugs who experienced virological failure due to DDIs[27,28], and all of them had a long-term history of optimal adherence to their antiretroviral treatment leading to the control of HIV (Table 3). Two patients (one treated with atazanavir plus tenofovir/emtricitabine and the other with efavirenz) autonomously decided to buy over-the-counter (OTC) orlistat to lose body weight. In both cases, TDM revealed suboptimal drug concentrations during orlistat therapy in comparison with afterward. The third patient (treated atazanavir plus tenofovir/emtricitabine) had recently started a naringin-containing supplement, a complementary and alternative medicine (CAM) claimed to be a fat-burning accelerator; in this case, TDM revealed suboptimal drug concentrations during concomitant naringin treatment that increased thereafter. The fourth patient autonomously bought two CAMs on the internet a few weeks before a visit to the clinic: Gunabasic, a taraxacum-containing dietary supplement claimed to be a draining agent, and Lipidyum, a dietary supplement of phytosterols (mainly psyllium) that is recommended as a non-pharmacological treatment for constipation, hypercholesterolemia, and overweight. He was enrolled in a clinical trial assessing the efficacy of a once-daily fixed-dose formulation of tenofovir alafenamide, emtricitabine, darunavir and cobicistat, and no TDM data were available. Remarkably, HIV viral load assessed a few weeks after the discontinuation of the weight-reducing agents returned to < 37 copies/mL in all cases.

The first two events were attributed to orlistat, a potent selective inhibitor of pancreatic and gastric lipases, that has been reported to inhibit the intestinal absorption of dietary fats and highly lipophilic drugs such as efavirenz or atazanavir[29], thus reducing their bioavailability and consequently limiting their efficacy[30]. The third event was attributed to naringin, a flavanone-7-O-glycoside, that inhibits the activity of carrier proteins (p-glycoprotein and organic anion transporting polypeptide) and ultimately impairs drug absorption[31]. The fourth event may have been related to psyllium, a soluble fiber from the husks of *Plantago ovata* that increases stool weight, promotes defecation, and has been reported to decrease calcium absorption[32].

Weight-reducing drugs should, therefore, be used cautiously in HIV-infected patients treated with lipophilic antiretroviral drugs due to the risk of virological failure[27,28,33]. This is, particularly, important as orlistat and natural products such as naringin and psyllium are available OTC and could, therefore, escape medical control. More generally, this observation underlines the clinical relevance of interactions between lipophilic antiretroviral drugs and weight-reducing products, and it is to be hoped that drug regulatory agencies will introduce more restrictive rules to govern their use.

Expected but not clinically relevant interactions

Alpha1-blockers

Alpha1-blockers are considered first-line drugs for the treatment of benign prostatic hyperplasia[34]. Although their coadministration with boosted protease inhibitors (PIs) has not yet been formally studied, it is contraindicated because the inhibitory effect of ritonavir or cobicistat on the metabolism of alpha1-blockers

ultimately leads to increased alpha1-blocker exposure and the development of severe hypotension[35-37]. This is particularly important in the case of alfuzosin, whose clearance is highly dependent on CYP3A, and high plasma concentrations are associated with serious and/or life-threatening events[35]. Similar warnings have been issued for tamsulosin (mainly metabolized by CYP3A and, to a lesser extent, by cytochrome 2D6) and silodosin (mainly metabolized by CYP3A and, to a lesser extent, by uridine diphosphate glucuronosyltransferase)[36,37].

The database of the GAP clinic showed that almost 5% of the patients had been treated with boosted PIs and alpha1-blockers for at least 6 months. The clinical relevance of this interaction was verified by evaluating the arterial pressure (AP) readings recorded in the patients' records after the beginning of their combined treatments, which showed that none of them had experienced any episodes of hypotension[38]. Surprisingly, most of them were also being treated with a median of one (range 1-2) antihypertensive drug.

The discrepancy between the predicted DDI and clinical outcomes may be related to the wide therapeutic index of alpha-1 blockers and/or the lack of any clear correlations between their plasma concentrations and hemodynamic effects[39-41] even though their pharmacokinetic characteristics are well known. It should be underlined that as nearly 20% of the patients treated with boosted PIs were also taking non-nucleoside analog reverse-transcriptase inhibitors (NNRTIs); it can be alternatively hypothesized that the reason for the less pronounced effect on AP observed in these patients is that the NNRTIs may have neutralized the inhibitory effect of the boosted PIs on the metabolism of the alpha-1 blockers by inducing CYP3A4 activity.

The fact that 86% of the patients were receiving antihypertensive treatment can be interpreted in two opposite ways: it can be considered further proof that the concomitant administration of an alpha-1 blocker and a boosted PI does not cause hypotension or it can be argued that the potential episodes of hypotension in these patients may have been masked or attenuated by the presence of essential hypertension. Although the findings of this study obviously cannot resolve this dilemma, they do seem to refute the clinical relevance of the expected interactions between boosted PIs and alfuzosin, the metabolism of which is almost exclusively dependent on CYP3A[32]. A similar tendency has also been observed in the case of silodosin and tamsulosin,however, this interaction is more predictable given the higher alpha-1 receptor selectivity of these agents associated with less hemodynamic effects, their availability at different dosages, and their less dependence on CYP3A metabolism[36,37]. For these reasons, tamsulosin or silodosin may be more suitable than alfuzosin for treating benign prostatic hyperplasia in patients receiving boosted PIs[37].

Finally, as many drug interactions are managed by adjusting the dose of the drug involved when an alpha1-blocker is added to an antiretroviral regimen including a boosted PI, it is important to start it at a low dose to minimize the risk of interactions.

Calcium antagonists

Calcium channel blockers (CCBs) are widely used and effective antihypertensive drugs[42] that are mainly metabolized by CYP3A isoenzymes, whose activity is significantly inhibited by ritonavir or cobicistat; their use with boosted antiretroviral regimens should, therefore, be carefully monitored due to the risk that high plasma CCB concentrations may lead to hypotension and/or a prolonged PR interval[42]. However, the coadministration of boosted antiretroviral drugs and CCBs has only been investigated in pharmacokinetic studies of healthy volunteers and described in a few case reports[43-45], which explains why the Liverpool University website that evaluates drug interactions in HIV-infected patients rates the quality of the evidence concerning this DDI "low," although it does conservatively suggest that combinations of boosters and CCBs should be administered extremely cautiously[9].

About 7% of the 620 GAP clinic patients were being treated with calcium antagonists, equally divided between those treated with ritonavir or cobicistat and those treated with unboosted antiretroviral regimens. The clinical relevance of the interactions was evaluated by verifying the AP values and ECG traces in the patients' medical records. There were no between-group differences in the daily dose of the CCBs nor in the median or lowest systolic and diastolic AP recorded. None of the patients manifested any episodes of hypotension or a prolonged PR interval[46], even though most of them were also taking other antihypertensive drugs (a median of one, range 1-2).

Once again, the discrepancy between the expected interaction and clinical outcomes was due to the broad therapeutic index of the CCB, the possibility of adjusting its dose on the basis of easily assessable indicators (AP measurements), and/or the absence of plasma CBB concentrations associated with toxic electrophysiological or hemodynamic effects[47]. The results of this

small study seem to discount the clinical relevance of the expected interaction which, in any case, can be easily managed in clinical practice by periodically monitoring AP values and ECG traces and so it is probably unnecessary to discontinue the administration of CCBs or adjust the antiretroviral regimen.

Dolutegravir and metformin

As mentioned above, dolutegravir inhibits the activity of OCT2 in proximal tubular cells, thus reducing metformin excretion and ultimately increasing the metformin area under the curve and C_{max} by, respectively, 79-145% and 66-111%[6]. In accordance with these findings, the Liverpool University website and the drug monograph recommend that the dose of metformin should not exceed 1000 mg/day in HIV-infected patients receiving dolutegravir-based antiretroviral treatment[15].

To verify the clinical relevance of this DDI in a real-life setting, we retrospectively analyzed all of the HIV-infected patients in the GAP database who had been diagnosed as having type II diabetes, had been treated with metformin for at least 12 months, and had been switched to dolutegravir-based treatment for at least 6 months[48]. There were no significant differences in mean fasting blood glucose concentrations or glycated hemoglobin (HbA1c) levels before and after the switch; metformin was well tolerated when administered with or without dolutegravir; and none of the patients had experienced any episodes of hypoglycemia or lactic acidosis after the switch.

This further example of how highly significant pharmacokinetic-based DDIs do not affect clinical outcomes was not unexpected as a recent systematic review has concluded that there is a considerable variability in reportedly therapeutic plasma metformin concentrations (the proposed values range from 0.13 to 90 mg/L), with threshold values for metformin intoxication of up to 270 mg/L[49]. This seems to suggest that, after excluding obvious risk factors for inadequate drug exposure (such as renal dysfunction), plasma metformin levels fall within the “therapeutic range” in most patients, including those treated with dolutegravir. Furthermore, a population pharmacokinetic analysis found no correlation between metformin and lactate concentrations or HbA1c levels, thus suggesting that there is no correlation between metformin pharmacokinetics and its therapeutic or toxic effects[50].

The fear of interactions (misinterpreted interactions)

Antipsychotic drugs and antidepressants

Many HIV-infected patients have psychiatric disorders such as major depression, schizophrenia, and psychoses and are subjected to substance and/or alcohol abuse[51,52]. Furthermore, all of these conditions are associated with a wide range of negative clinical outcomes, including viral load rebound, declining CD4+ cell counts, reduced adherence to antiretroviral treatment, risk behaviors that increase the transmission of HIV infection, and mortality[53,54]. Psychotropic medications are frequently used by HIV-infected patients receiving medical care[55], but a recent review has clearly shown that there is only limited evidence concerning their effectiveness and safety in such patients, especially in the case of antipsychotic drugs[56]. There is certainly a risk of addictive side effects and a risk of potential DDIs with antiretroviral treatment[55] because most psychotropic drugs are metabolised by CYP3A or induced by NNRTIs[55-57], and some may inhibit the activity of cytochrome enzymes and induce DDIs when simultaneously administered with antiretroviral medications[58,59]. This creates a complex scenario that may lead to inadequate psychotropic or antiretroviral drug doses and consequently suboptimal clinical responses.

The GAP database included 82 patients receiving antiretroviral treatment together with at least one psychotropic drug , thus allowing a real-life assessment of the exposure of HIV-infected patients to antiretroviral and antidepressant or antipsychotic drug concentrations[60,61]. These patients had at least one recorded TDM of antiretrovirals and psychotropic plasma trough concentrations as well as optimal adherence to therapies. The distribution of plasma antidepressant and antipsychotic trough levels according to each reference range was firstly assessed in HIV-infected patients and then compared with that of a control group of HIV-negative patients undergoing TDM of psychotropic drugs in the same period. The results showed that trough concentrations of nearly all of the antiretroviral drugs fell within or close to their therapeutic ranges in everyday clinical practice; the only exception was raltegravir, but this was of limited clinical relevance given its highly variable intra- and inter-individual pharmacokinetics, especially trough concentrations[62].

About 55% of the samples had trough psychotropic drug levels below the minimum effective concentrations,

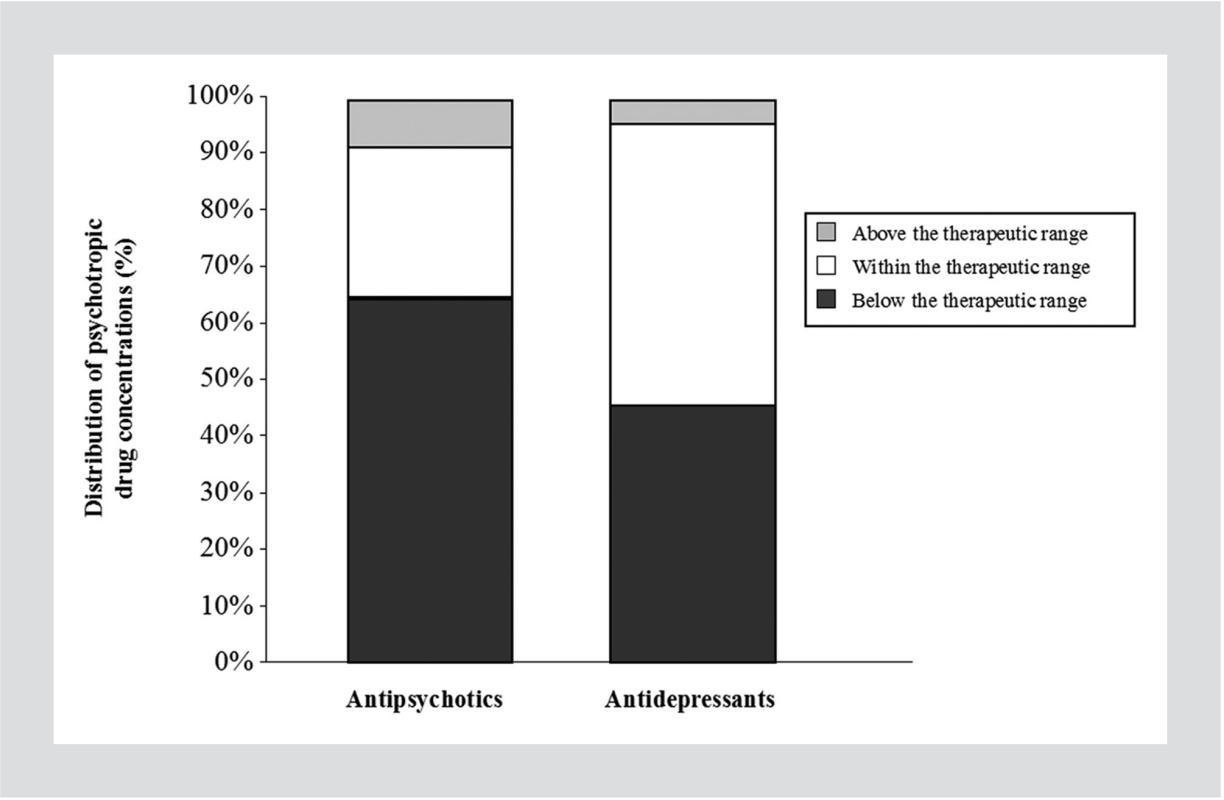

Figure 1. *Trough antipsychotic drug and antidepressant concentrations below, within, or above the therapeutic reference ranges in HIV-infected patients.*

and only 6% had levels that exceeded the upper threshold of their therapeutic ranges. This trend was confirmed when the data were stratified by psychotropic drug class: antidepressant and antipsychotic drug levels were below their minimum effective concentrations in, respectively, 55% and 64% of the samples and above the upper threshold of the therapeutic range in, respectively, 5% and 9% (Fig. 1). To exclude the possibility that our observations were biased by the fact that the concentrations of these drugs may be low in outpatients regardless of HIV serostatus, we looked at the plasma concentrations of drugs measured also in HIV-negative patients and found that only 26% of the trough psychotropic levels measured among these patients were below the minimum effective threshold concentrations[60].

One possible explanation is that psychiatrists may be reluctant to prescribe full doses of psychotropic drugs in the case of HIV-infected patients due to the risk that DDIs may lead to virological failure; furthermore, specialists in infectious diseases (who are very familiar with antiretroviral DDIs) may be equally cautious about changing the psychotropic doses prescribed by psychiatrists. The result is a vicious circle that may lead to HIV-infected patients with inadequately treated psychiatric diseases.

This view is indirectly supported by a recently published cross-sectional analysis that clearly identified substantial failings in the pharmacological treatment of HIV-infected patients with depression, the adjustment of antidepressant doses, and the occurrence of remissions requiring dose optimisation[63]. Similarly, the selection of inappropriate psychotropic doses may also explain the comparable effectiveness of dual and single-action antidepressants recently reported by Mills et al.,[64] which suggests that intensifying antidepressant treatment in HIV-infected patients does not lead to any additional benefit.

Conclusions

Over the 2 years since the opening of our GAP outpatient clinic, we have evaluated various types of DDI, and this has contributed to clearing some of the interactions that were theoretically suspected of having a considerable clinical impact but subsequently proved not to be clinically relevant. These were mainly pharmacokinetic interactions involving drugs characterized

by a broad therapeutic index that did not show any correlation between their systemic concentrations and their pharmacological and/or toxicological activity, such as CCBs and metformin. We have also identified some previously unreported DDIs that are clinically relevant it is important to underline the fact that, as these involved OTC drugs or supplements, they represent a highly critical grey area insofar as patients (and sometimes their physicians) tend to underestimate the clinical relevance of such products. Finally, we have documented the fact that a mistaken interpretation or excessive fear of DDIs can lead to the underdosing of concomitant drugs (as in the paradigmatic case of antipsychotic drugs and antidepressants), which may negatively affect the management of HIV-infected patients with psychiatric disorders.

On the basis of what is said above, identifying personalized therapeutic regimens for each individual patient by means of currently available web-based tools and taking advantage of the possibility of measuring the plasma levels of antiretroviral agents and many concomitantly administered drugs by TDM services are likely to reduce the incidence of the adverse events associated with both antiretroviral and other treatments by maintaining or possibly improving the response to both. This is important not only for the health of individual patients but, more generally, can also contribute to containing public health-care costs by favoring the rationalization of the treatments of individual patients with HIV infection.

Conflicts of interest

None

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