AIDS Reviews 2004;6:208-17

Pharmacokinetics and Pharmacodynamics of Drug Interactions Involving HIV-1 Protease Inhibitors

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Abstract

Therapeutic agents used to inhibit the HIV-1 protease are integral to the effective suppression of HIV virus replication by use of synergistic combination therapy. This is inherently dependent on the achievement of effective plasma concentrations of the drug in its active form, and sustaining such levels for the duration of a dosing interval without exceeding thresholds of toxicity. The issues determining the absorption, biotransformation, distribution to and activity at the intended site, and elimination, are myriad and complex. Studies at molecular, cell, and tissue levels are useful for predicting the possible fate of these agents at in vivo, but the wide interindividual variability shown in whole-body pharmacokinetic studies is illustrative of the difficulty in making general statements rather than more guarded recommendations. This paper summarizes the current state of understanding of the major interactions between protease inhibitors themselves and other important commonly used agents in the management of HIV disease, based on data from clinical pharmacokinetic studies. **(AIDS Reviews 2004;6:208-17)**

Key words

Protease inhibitors. Pharmacokinetics. Pharmacodynamics. Drug-drug interactions.

Introduction

Antiretroviral (ARV) combination regimens are the treatment standard for HIV infection[1]. An HIV protease inhibitor (PI) is often included in treatment regimens that also include two or more nucleoside/nucleotide reverse transcriptase inhibitors (N/NtRTIs) or, less often, a non-NRTI (NNRTI) or enfuvirtide[1].

Seven PIs, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir (and more recently fosamprenavir), lopinavir (co-formulated with low dose ritonavir), and atazanavir, have already been approved and several others are in the late stages of clinical development.

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PIs bind to the active site of the HIV protease and prevent the enzyme from attaching to its substrate and cleaving HIV polyproteins into functional proteins. As a result, HIV cannot mature and noninfectious viruses are produced[2].

The available PIs are complex peptidomimetic compounds with poor aqueous solubility, low bioavailability and short plasma half-lives. The complexity of these agents not only contributes to their high cost, but also increases the potential for wide interindividual variability in drug exposure and unwanted drug interactions.

Pharmacokinetics and pharmacodynamics of drug interactions

Pharmacokinetics (PK) is the science describing what happens to drugs, both physically and chemically, after they are administered. PIs are rapidly absorbed, extensively metabolized – primarily via cytochrome P450 (CYP450) pathways – and mostly excreted in the feces in the form of metabolites[3]. When PIs reach their site of action, which is primarily within cells infected with HIV, they exert their pharmacologi-

Table 1. Processes involved in drug interactions

Pharmacokinetics	Pharmacodynamics
Absorption	***Non-receptor related***
Biotransformation	***Receptor related***
Enzyme induction	
Enzyme inhibition	
Distribution	
Excretion	
Renal	
Hepatic	

cal effect, and it is within this effect that the pharmacodynamic (PD) process is concerned. PD comprises not only the therapeutic effect, but also the development of adverse events (Table 1).

Drug interactions are an increasing challenge for providers treating HIV-infected individuals. Important drug interactions occur with the use of combinations of PIs, use of PIs along with N/NtRTIs or NNRTIs, and of PIs with many other therapeutic agents needed for the management of ARV side effects (e.g. lipid-lowering agents for the treatment of dyslipidemia) or for the cure of comorbidities (e.g. anti-tuberculosis agents)[4].

Drug interactions can reduce the efficacy of one or both interacting compounds and sometimes eliminate the clinical benefit. However, not all drug interactions are bad; interactivity may improve the therapeutic value of one agent. The discovery and widespread clinical use of low-dose ritonavir as a PK enhancer of other PIs, for example, has dramatically changed the management of HIV infection. Ritonavir exerts its effects through two mechanisms[5,6]: I) inhibition of CYP450 enzymes in the gut, which decreases first-pass metabolism and thereby increases total systemic absorption (e.g. lopinavir and saquinavir), or II) decreased hepatic metabolism, resulting in a prolonged terminal half-life (e.g. indinavir and amprenavir). As a result, the systemic exposure of the concomitant PI is increased, resulting in more potent activity against HIV. In addition, because greater exposure is achieved for prolonged periods of time, lower pill burdens with less frequent administration, often with the removal of food restrictions, are possible.

The study of drug interactions is a fundamental component of pharmacology. Careful clinical observations and scientific investigations (i.e. PK trials, laboratory tests) can detect unexpected interactions. However, despite the vast reservoir of knowledge, drug interactions are generally unpredictable and vary in magnitude from patient to patient, whose genetics, physiology, biochemistry, and metabolism, are to a certain extent unique.

PK drug interactions can occur at different levels: during absorption, distribution, metabolism, or excretion. Of all the processes that give rise to drug interactions, metabolism is by far the most frequent and important. However, several other mechanisms may be responsible for the occurrence of interactions and several are still unclear or unknown.

Moreover, the molecular mechanisms that underlie CYP450 activity are complex, with many different nuclear receptors playing a role. Recent evidence has demonstrated that PIs are ligands for the nuclear receptor pregnane X receptor (PXR), and induction of CYP3A4 genes by PIs may occur primarily through PXR activation[7]. Drug interactions may occur at this level, and further research is needed to understand the mechanisms behind this interactions and when these may become clinically relevant.

The main drug-metabolizing enzymes are CYP450 3A4, 2C9, 2C19, 2D6, 1A2, 2E1, 2B6, and 2A6. In both the liver and small intestine, CYP3A4 is the most abundant and active isozyme present. Frequently, drugs are metabolized by multiple cytochrome isozymes, but usually one isozyme predominates in their biotransformation. Drugs can be classified as CYP450 substrates, inhibitors, or inducers. However, some drugs, such as ritonavir and nelfinavir, may have properties of all three, depending on the specific combination impeding or increasing the biotransformation of other drugs that use the same isozyme for metabolism[4,8]. Of the PIs in clinical use, ritonavir is the most potent inhibitor of CYP3A4; indinavir, nelfinavir, and amprenavir are less potent by an order of magnitude, and saquinavir and lopinavir are the least potent[9].

The description of the interactions through the inhibition or induction of CYP isozymes is based on mean changes in the PK parameters. The organ-specific expression of the CYP450 isozymes across the population is large. Therefore, the usual dosing of these drugs can result in variable concentrations at steady state, with some subjects having high and potentially toxic levels, and others having low levels that are potentially inadequate to suppress the virus[9].

PD drug interactions arise from the specific action of drugs with their target structures. When two drugs are both directed to the same target they can compete with one another. This competition may either lead to the inhibition of drug activity or, in some circumstances,

result in a beneficial (i.e. synergistic) effect. To date, there is little information on in vivo PD interactions involving PIs. Whether administering two PIs at full doses, simultaneously, provides any benefit remains unclear. PIs compete for the same catalytic pocket on the HIV protease, as only one is present on one enzyme. Therefore, it is unlikely that administering more than one PI at full doses would enhance an anti-HIV pharmacological effect. However, in vitro studies have shown that combining different PIs may lead to the achievement of a synergistic anti-HIV activity[10], providing a rationale for the use of double-PI regimens in clinical practice.

Drug interactions involving multiple protease inhibitors

The interactions that occur with the simultaneous use of two PIs (in conjunction with low-dose ritonavir) have become more relevant as the need to combine members of this class in patients with established PI-resistant virus[11], intolerance to NNRTIs, or against virus with extensive NRTI and NNRTI resistance, but with retained susceptibility to PIs[12].

The potential for interaction among three PIs used in conjunction is high because of the different effects each may have on the CYP450 system – either induction or inhibition, in spite of the presence of ritonavir. PK studies are thus required to ensure that therapeutic drug plasma concentrations are being achieved.

Saquinavir/lopinavir/ritonavir

Recent trial data evaluating the use of lopinavir/ritonavir in combination with saquinavir have shown favorable PK profiles in ARV-experienced patients.

The PK interactions between these three drugs have been examined in a prospective, open-label, observational trial in which two groups of patients were studied. The first received lopinavir/ritonavir (400/100 mg twice daily) plus saquinavir soft gel (1000 mg twice daily) without a nucleoside backbone, and the second received saquinavir hard-gel/ritonavir (1000/100 mg twice daily) without lopinavir, but with two or three NRTIs. The median minimum and maximum concentrations (C_{min}, C_{max}) and area under the curve (AUC) of saquinavir demonstrated no significant difference between these two groups. Of note was the fact that ritonavir concentrations (C_{min} and C_{max}) as well as AUC were significantly lower in the saquinavir/lopinavir/ritonavir group than in the saquinavir/ritonavir group[13]. The concentrations measured in the former group indicate that this reduction in ritonavir concentrations was still able to boost both saquinavir and lopinavir. Lopinavir concentrations were also recently investigated by a similarly designed study and shown not to be altered by the presence of saquinavir[14]. Therefore, it would be suggested that one could utilize this combination without the need for dose adjustments.

However, the caveat exists that, within these data sets, a wide interindividual variability was observed in both saquinavir and lopinavir plasma concentrations. This indicates the need for therapeutic drug monitoring (TDM) for individual patient prescription in order to ensure the achievement and maintenance of adequate plasma concentrations.

In fact, when a group of highly treatment-experienced patients were stratified into virologic suppression outcomes (responders vs. nonresponders) higher concentrations of both saquinavir and lopinavir were found in the responders than in those who failed to achieve suppression of viral replication; this confirms the need to achieve high drug-exposure to suppress the replication of drug-resistant HIV strains[15].

Saquinavir/atazanavir/ritonavir

A PK study in 18 HIV-infected patients investigated the coadministration of saquinavir/ritonavir (1600/100 mg) with atazanavir given at a dose of 300 mg once daily[16]. A substantial increase in saquinavir exposure was demonstrated on the addition of atazanavir to the regime. Also notable was the 41% increase in total ritonavir exposure, and 34% increase in its C_{max}.

The mechanism by which the increases in saquinavir and ritonavir occurred with atazanavir coadministration remains unclear. The increase in saquinavir may be independent of the ritonavir dose[17], and is possibly a consequence of the presence of different boosters (ritonavir and atazanavir) impacting on different aspects of drug disposition.

Although saquinavir/ritonavir/atazanavir was well tolerated, an increase in indirect hyperbilirubinemia was common after the addition of atazanavir to the regime. A recent PK study has confirmed these findings, in investigating the coadministration of atazanavir 300 mg once daily and saquinavir/ritonavir 1000/100 mg twice daily[18]. The favorable PK of this combination suggests that these three PIs could be an attractive treatment option in ARV-experienced patients, although the optimum doses of this combination remain to be determined. A further study assessed the PK and tolerability of lower atazanavir doses (150 mg and 200 mg once daily) when

coadministered with saquinavir/ritonavir 1600/100 mg once daily[19]. Interestingly, saquinavir enhancement appeared to be independent of atazanavir dose, while the significant increase in ritonavir C_{max} was produced only by the 300 mg dose of atazanavir, and was not observed with lower atazanavir doses. The atazanavir concentrations achieved in the study were higher than those measured in historical controls for unboosted atazanavir (400 mg once daily), and atazanavir-related hyperbilirubinemia occurred less frequently with lower atazanavir doses. This supports the option of atazanavir dose reduction when atazanavir-related side effects occur[19,20].

In conclusion, in those clinical situations that indicate the use of dual-boosted PI regimens, a less substantial increase in drug concentrations may not adversely influence viral suppressive activity. However, excessive concentrations may lead to adverse drug events, resulting in decreased patient adherence or drug discontinuation. Thus, a careful assessment of patient complaints and changes in laboratory safety parameters is required, supplemented by the use of TDM where appropriate.

Saquinavir/fosamprenavir/ritonavir

Since amprenavir exhibits synergistic anti-HIV-1 activity with saquinavir in vitro[21-23] and the two agents have non-overlapping primary resistance patterns, there is a reasonable rationale for using fosamprenavir with saquinavir as part of a potent dual PI regimen.

To date, amprenavir exists as a soft-gel amprenavir formulation or as a hardened tablet containing the amprenavir prodrug fosamprenavir. Fosamprenavir is rapidly hydrolyzed to amprenavir by cellular phosphatases in the gut epithelium during drug absorption.

The addition of amprenavir to saquinavir/ritonavir has been shown to reduce both ritonavir and saquinavir exposure significantly, suggesting that the PK enhancement of saquinavir by low-dose ritonavir may not be able to compensate for the effects of CYP450 induction by amprenavir[24,25]. The optimal ritonavir dose to compensate for the effects of amprenavir on saquinavir exposure is yet to be determined.

The PK of saquinavir hard-gel/fosamprenavir 1000/700 mg twice daily, in combination with either 100 mg or 200 mg of ritonavir, has been investigated in 18 HIV-infected patients receiving saquinavir/ritonavir 1000/100 mg twice daily and two NRTIs[26]. On study day 1, patients had saquinavir steady-state PK evaluations while receiving saquinavir hard-gel/ritonavir alone, and then fosamprenavir 700 mg twice daily was added to the regimen for 11 days. On study day 12, following the PK assessment of saquinavir, fosamprenavir and ritonavir (day 11), the ritonavir dose was increased to 200 mg twice daily for an additional 11 days, and the PK of the combination was reassessed.

The coadministration of fosamprenavir with saquinavir/ritonavir resulted in a modest decrease in saquinavir concentrations (15% in AUC_{0-12}, 24% in trough concentration [C_{trough}] and 9% in C_{max}), but this was overcome by increasing the ritonavir dose to 200 mg twice daily. Notably, no significant alterations in amprenavir concentrations were observed with either 100 mg or 200 mg of ritonavir, while ritonavir exposure was significantly lower after the addition of fosamprenavir to the regimen (day 11). Both regimens were well tolerated, with adverse events limited to a small number of study participants who reported grade 1 or 2 nausea, fatigue, or diarrhea, after the addition of fosamprenavir to the saquinavir/ritonavir regimen. The PK data demonstrated are particularly reassuring for the use in patients without reverse transcriptase inhibitor treatment options, and suggest that the optimal dose combination for the three agents is saquinavir/ritonavir/fosamprenavir 1000/200/700 mg twice daily. The option of administering the lower 100 mg twice-daily dose of ritonavir remains, especially in conjunction with the use of TDM to ensure optimal drug plasma concentrations.

Fosamprenavir/lopinavir/ritonavir

A number of studies have demonstrated the occurrence of complex interactions between lopinavir, ritonavir and amprenavir. This combination has resulted in reduced plasma concentrations of both amprenavir and lopinavir to different extents[27,28].

Despite this, partial virologic inhibition and good immunologic efficacy have been observed in heavily pretreated HIV-infected subjects[29], particularly when higher doses of ritonavir are used as part of the regimen[30,31].

One study of 33 ARV-experienced patients showed a significant decrease in both amprenavir and lopinavir AUC_{0-12h} and C_{trough} following the administration of fosamprenavir in combination with lopinavir/ritonavir (administered at different dosages)[32]. A limited decrease in amprenavir and no change in lopinavir concentration was this time observed by increasing lopinavir and fosamprenavir doses, rather than increasing the ritonavir dose. Thus, further study is warranted to reach agreement on the optimal doses of these agents when combined. Moreover, it is noteworthy that ritonavir exposure was unexpectedly similar in all arms and did not reflect the alteration in amprenavir or lopinavir exposure.

An alternative strategy to attempt to overcome this complex interaction was investigated in healthy volunteers. The method used administered fosamprenavir and lopinavir/ritonavir, either with simultaneous dosing, or separated by 4 h or 12 h[33]. As expected, when lopinavir and fosamprenavir were administered simultaneously, both drug-plasma concentrations were lower than historical data. The 4-h and 12-h physical separation did not improve amprenavir exposure, despite the presence of higher ritonavir doses. However, the increased daily ritonavir dose did result in the achievement of adequate lopinavir PK parameters (when compared with historical data). More recently, however, reports that the combination of amprenavir or fosamprenavir/lopinavir/ritonavir may be effective in heavily treatment-experienced patients, providing TDM information, are available[34].

Lopinavir/ritonavir/nelfinavir

Lopinavir PK parameters have also been shown to be significantly decreased by the coadministration of nelfinavir in 13 healthy HIV-negative volunteers. Ritonavir was also decreased by the coadministration of nelfinavir. If the coadministration of lopinavir/ritonavir and nelfinavir is necessary, an increase in the dose of lopinavir/ritonavir to 533/133 mg twice daily is required to achieve adequate plasma concentrations.

Lopinavir/ritonavir/indinavir

The coadministration of standard doses of lopinavir/ritonavir (400/100 mg twice daily) and various doses of indinavir has been investigated in both HIV-infected and healthy volunteers by different authors[35-37]. Although the PK data on this combination are limited and contradictory, a recent study showed that lopinavir/ritonavir and indinavir have no negative drug-drug interactions. The addition of lopinavir/ritonavir to an indinavir-containing regimen (where low doses of ritonavir were already administered to enhance indinavir plasma concentrations) did not affect indinavir exposure at steady-state[37]. Therefore, dose adjustments of either drug are unnecessary. However, despite the remarkable virological response observed in subjects on this combination, 29% of patients had to stop treatment due to intolerance[37].

Atazanavir/fosamprenavir/ritonavir

This double-boosted PI regimen appears promising, although fosamprenavir and atazanavir share resistance profiles through changes at codon 50 (I50L for atazanavir and I50V for amprenavir). It is possible that the combination of these agents may limit the development of viral resistance; however, with the induction of CYP3A4 metabolism under the influence of fosamprenavir, significant interactions may occur, thus requiring dose adjustments. PK investigations of this combination are currently ongoing.

Tipranavir

This investigational PI has in vitro activity against multi-PI-resistant HIV-1[38]. It is clear from early studies that tipranavir must be coadministered with low-dose ritonavir in order to achieve clinically effective plasma concentrations. Interim results from a 24-week, open-label, safety and PK study of tipranavir/ritonavir (500/200 mg twice daily), alone or in combination with a second boosted PI (amprenavir, lopinavir, or saquinavir), in 315 highly treatment-experienced patients (≥ 3 PI mutations), were recently reported. Coadministration of tipranavir/ritonavir was associated with substantial reductions in the AUC of the other compounds: 70% reduction in saquinavir, 45% reduction in amprenavir, and 49% reduction in lopinavir. These results do not favor the possibility of coadministration of tipranavir with other PIs, even when boosted with ritonavir 200 mg twice daily[39].

Drug interactions between protease inhibitors and other antiretroviral drugs

Efavirenz

Metabolism induction by efavirenz may decrease PI exposure and therefore higher PI and/or ritonavir boosting dose may be necessary. In fact, the recommended dose of lopinavir/ritonavir with efavirenz is 533/133 mg twice daily (addition of one tablet)[40], and the dose of atazanavir/ritonavir is 400/100 mg once daily instead of 300/100, in particular if this drug is used in PI-experienced patients[41].

The dosage regimen of boosted twice-daily fosamprenavir/ritonavir (700/100 mg) does not require modification with efavirenz, while the addition of ritonavir 100 mg twice daily is recommended if fosamprenavir is used once daily[42].

Tenofovir

Tenofovir disoproxil fumarate is the oral prodrug of tenofovir. Clinically relevant drug interactions be-

tween tenofovir and PIs have been reported, most notably the reduction in concentrations of atazanavir (both with and without ritonavir boosting), by an unknown mechanism[41]. Although the concentrations of boosted atazanavir are higher than the unboosted atazanavir concentrations in the presence of tenofovir, it needs to be pointed out that they still remain lower than the boosted atazanavir concentrations in the absence of tenofovir (26% lower C_{min}). Whether this has an effect on atazanavir/ritonavir/tenofovir-containing regimens (leading to a reduction in drug potency) is unknown and needs to be evaluated, particularly in ARV-experienced patients.

Fosamprenavir exposure, when administered in the presence of ritonavir once or twice daily, seems not to be altered by tenofovir coadministration. This was shown by a sub-analysis of the CONTEXT study, which compared amprenavir C_{trough} in subjects with tenofovir (n = 45 and 60 on once-daily and twice-daily regimens, respectively) to subjects without tenofovir (n = 25 and 24 on once-daily and twice-daily regimens, respectively) as part of the ARV regimen[43]. There are no PK data available on the effect of fosamprenavir on tenofovir concentrations, although there were no reports of tenofovir renal disturbances in patients receiving tenofovir in the fosamprenavir CONTEXT study[43].

No change in lopinavir/ritonavir concentrations, but an increase in tenofovir plasma exposure (32%), has been observed when lopinavir/ritonavir and tenofovir are coadministered[44,45]. It is under debate if the increase of tenofovir concentrations is associated with increased tenofovir renal side effects.

Tenofovir is an acyclic nucleoside phosphate excreted by glomerular filtration and active tubular secretion, like cidofovir and adefovir. These have been shown to be substrates of different renal transporter proteins, such as human renal organic anion transporter 1 (hOAT1) and multi-drug resistance protein 2 (Mrp-2)[46].

Ritonavir is a potent inhibitor of Mrp-2-mediated transport[47] and may lead to an increase in tubular concentrations of tenofovir by reducing its efflux from the kidneys. Therefore, ritonavir use in patients on tenofovir could be an explanation of the tubular dysfunction described in several case reports following the introduction of tenofovir in routine clinical HIV care[48-52]. This hypothesis, however, has never been proven. Of note, all available case reports pertain to the increase of tenofovir plasma concentrations and tenofovir toxicity following the administration of lopinavir/ritonavir. Interestingly, unboosted atazanavir at the dose of 400 mg increased tenofovir AUC of 24% (90% CI: 21-28)[41]. This also suggests that tenofovir increase is not necessarily due to ritonavir.

Drug interactions between protease inhibitors and other drugs

Statins

Metabolic disturbances associated with HIV infection and ARV therapies are common. How best to treat these events is a pharmacological challenge because of the potential for clinically relevant drug-drug interactions associated with lipid-lowering agents (such as HMG-CoA reductase inhibitors, also known as statins) and ARV agents[53].

The primary route of metabolism for most statins is via oxidation utilizing the CYP3A4 pathway. Pravastatin, fluvastatin and rosuvastatin are exceptions since they follow different metabolic/elimination pathways. The lactone drugs, like lovastatin and simvastatin, which are administered as prodrugs, are avid substrates for CYP3A4 and as such are inhibited by CYP3A4 inhibitors, which include the PIs, and especially ritonavir[53].

Drug interaction studies have been performed with PIs and statins[54]. Coadministration of saquinavir/ritonavir in HIV-negative volunteers resulted in increased exposure to the active form of simvastatin by 3000%. Similarly, atorvastatin exposure increased by 343%, although the total atorvastatin activity (which includes the sum of atorvastatin and two of its active metabolites) increased by 79%. By contrast, pravastatin exposure declined by 50%. These data are of utmost clinical importance since all statins have the capacity for severe toxicity, including rhabdomyolysis and hepatic dysfunction.

Gastric acid-reducing drugs

Chemical factors can affect drug absorption by influencing the state of the drug in the gastrointestinal tract. The absorption of PIs is likely to be decreased in the absence of gastric acidity. Therefore, interactions between PIs and anti-acid drugs are theoretically possible.

This is important since a prevalence of 49.8% of nausea/anorexia/UGI symptoms has been reported by a large national cohort study[55], suggesting the frequent use of drugs able to control these symptoms, including anti-acidic drugs, such as H_2 antagonists, acid neutralizers and phosphate binders, proton pump inhibitors.

Available data suggest that there may be profound differences across PIs in terms of absorption depen-

dence on gastric pH and, therefore, in terms of the influence that anti-acid drugs may have on PI absorption.

Atazanavir[41] and indinavir[56] have been shown to exhibit significantly decreased absorption when given with anti-acid drugs. The AUC and C_{min} of atazanavir (400 mg qd) were reduced by 84 and 87% when administered with buffered didanosine (a didanosine formulation with cation chelating agents similar to Maalox). The deleterious effect of buffered drugs on atazanavir absorption may be counterbalanced by administering atazanavir two hours before or one hour after administration of these drugs, while for H_2-receptor antagonists (ranitidine) the two drugs should be administered separately as far as possible, e.g. 12 h.

Conversely, given the long pharmacological half-life of the proton pump inhibitors and irreversible inhibition of the proton pump, it is doubtful whether this interaction can be managed by separating atazanavir and the proton pump inhibitor doses, however, at present there are no PK data to support or reject this position.

Proton pump inhibitors interfere with drug intrinsic solubility, leading to a decrease in absorption with increasing pH. Combined administration of proton pump inhibitors and atazanavir is therefore not recommended[41].

Coadministration of high-dose ranitidine (300 mg), and Maalox with fosamprenavir has been shown to decrease amprenavir AUC by 30 and 18%, respectively, with no effect on the C_{min}, suggesting a lack of effect of the higher gastric pH on C_{trough} [57].

Recent data also showed that lopinavir/ritonavir-treated patients who received acid-reducing agents did not appear to have altered lopinavir plasma concentrations through 48 weeks of therapy, suggesting the absence of an alteration in lopinavir/ritonavir absorption with a less acidic gastric pH[58].

At last, a PK study investigating the impact of a single dose of Maalox on a single dose of tipranavir/ritonavir showed a 27% decrease in tipranavir total plasma exposure[59].

More, formal, multiple-dose PK studies are needed to confirm which PIs can be administered in presence of an altered gastric pH and how this may impact on plasma concentrations and therefore response. It has been argued that ritonavir boosting may not be capable of counterbalancing the effect of anti-acid drugs on PI bioavailability. Therefore, this should be thoroughly investigated.

Cannabinoids

The use of cannabinoids, such as smoked marijuana, in HIV-infected individuals is common for a variety of medical conditions, such as the management of wasting and appetite stimulation. This creates concerns regarding the combined use of PIs and cannabinoids; complex metabolic pathways characterize the latter. Interestingly, a PK study showed a limited decrease in nelfinavir and indinavir (administered unboosted) plasma exposure during marijuana intake[60]. The consequence of these changes is unknown, but with increasing use of boosted-PI regimens, such changes may not impact ARV drug efficacy.

Methadone

The PK interactions between methadone and various PIs have been studied: amprenavir[61], indinavir[62], lopinavir/ritonavir[63,64], nelfinavir[65,66] and boosted saquinavir[67,68] (Table 2). Whilst low-dose ritonavir (100 mg bd)[63] on its own and indinavir 800 mg td[62] appeared to have no significant effect on the PK of total (protein-bound and unbound) methadone, other PIs exhibited varying degrees of reduction of total methadone plasma levels. An interesting PK study of patients who were stable on methadone, before and 15 days after the administration of saquinavir/ritonavir, analyzed the stereoisomers of unbound methadone. Whilst a reduction in the AUC of S-methadone of 40% and R-methadone of 32% were observed, when the change in methadone AUC was expressed in terms of unbound methadone, it was no longer significant. Additionally, the patients exhibited no clinical evidence of methadone withdrawal.

The clinical recommendation for the management of these interactions is to be guided by clinical signs of opiate withdrawal, adjusting the dosage where necessary.

Rifamycins

The concurrent administration of rifamycins with PIs is often unavoidable in HIV clinical practice, and the significant PK interactions and the need for prolonged duration of therapy and prophylaxis in patients with mycobacterial coinfection, creates a major challenge.

Rifampin is well known to be a potent inducer of the CYP450 pathway and its use is therefore not recommended in combination with PIs[69].

Rifabutin decreases the dose of all PIs when given together, and thus all must be boosted with ritonavir in order to attain effective plasma levels. Ritonavir increases the levels of rifabutin and therefore the risk of rifabutin toxicity, most notably uveitis, leukopenia, and hepatotoxicity. Thus the dose of rifabutin is reduced to 150 mg daily, or less

Table 2. Summary of methadone – protease inhibitor interactions

Protease inhibitor	Effect of interaction on		Recommendation
	Methadone	Protease inhibitor	
Amprenavir	↓AUC of active methadone enantiomer	Delayed absoption of amprenavir	
Indinavir	No significant effect	AUC unchanged, but ↑C_{min} and ↓C_{max}	Combination appears safe
Lopinavir/ritonavir (Kaletra)	↓methadone AUC with Kaletra but not affected by low-dose ritonavir alone		
Nelfinavir	↓methadone PK parameters for both enantiomers, but not associated with withdrawal symptoms	Non-significant ↓in NFV 12 h C_{trough}	Adjust dose according to clinical signs of withdrawal
Saquinavir/ritonavir	↓total methadone, but change in unbound methadone not significant	Above 80% of study subjects had C_{min} of SQV > EC_{50}	

frequent dosing (three times or even twice weekly) in order to diminish total rifabutin exposure. Standard doses of the boosted PIs can thus be administered[69].

Herbal remedies

ARVs may interact with herbal treatments or supplements. While sometimes these interactions are beneficial, they may also be detrimental, causing either decreased effectiveness or increased toxicity of the antiretroviral drugs. As an example, St John's wort *(Hypericum perforatum),* a popular herb used to treat depression, was found to have an important interaction with the PI indinavir[70]. St John's wort is an inducer of the activity of CYP450 enzymes and therefore decreases indinavir plasma concentrations, leading to treatment failure. The same effect has been shown with drugs similarly metabolized, like cyclosporin, a medication used to prevent organ rejection after transplantation. St John's wort has been shown to decrease cyclosporin concentrations[71], which could potentially result in transplant rejection.

Similarly, garlic supplements, administered as commonly available garlic capsules, have been shown to decrease saquinavir plasma exposure by approximately 50%[72]. It is unclear if the administration of low-dose ritonavir would prevent the alteration in saquinavir plasma concentrations; however, caution in using garlic supplements during antiretroviral therapy is required.

In the absence of specific information on interactions between herbs and ARVs, it is important to understand the mechanisms responsible for these interactions in order to be able to predict them, when possible, or to manage them.

Unfortunately, there is little available research on herb-drug interactions. Many herbs have multiple ingredients and each may have a different effect, complicating the issue even more. Common herbals and foods that are known to interact with the CYP system and potentially alter the rate at which many drugs are metabolized are: grapefruit juice (inhibitor) and St. John's wort, cruciferous vegetables, red wine, cigarette smoke and charcoal grilled beef (all inducers). Of these, only grapefruit juice[73] and St. John's wort[70] have been specifically studied in combination with PIs.

Moreover, when drugs and herbs with similar beneficial effects, or similar toxic effects, are given together, PD interaction may take place. For example herbs that have sedative properties, such as kava, nettle and sage, may increase the sedative effects of some sleeping medications, while herbs that have antiplatelet activity, such as ginkgo biloba, ginger, ginseng, and garlic, may increase the risk of hemorrhage in patients taking drugs with antiplatelet activity[74].

Other commonly used medicinal plants which may potentially interact with PIs or other drugs administered to HIV-infected individuals for the management of comorbidities may be: betel nut, chili pepper *(capsicum)*, Dan-

shen, Devil's claw, dong quai, eleuthero or siberian ginseng, garlic, gingko, ginseng, guar gum, harela or bitter melon, liquorice, papaya, psyllium, tamarind, valerian, yohimbine, and several herbal mixtures[74]. Drug-herb interactions may put individuals at risk. Our knowledge to date is incomplete and further research is urgently warranted.

Conclusion

Despite the expanded knowledge on the role of the hepatic CYP450 isoenzyme system in drug interactions, drug interactions are often unpredictable. Several different mechanisms can be responsible for interactions involving PIs, and these are complex and generally unclear.

Consequently, TDM could be considered in this setting to confirm that adequate (not too low or too high and therefore subtherapeutic or toxic) plasma concentrations are being achieved.

There are numerous databases that list all specific drug interactions that have been observed in HIV clinical practice and that scientists believe may be likely. Some web sites that can be checked to obtain information on the most important drug interactions involving PIs are listed in table 3.

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