The management of HIV-1 protease inhibitor pharmacokinetic interactions

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The HIV-1 protease inhibitors (PIs) are widely used in combination antiretroviral therapy for the management of HIV-1 infection. Certain characteristics of the PIs, in particular their metabolism being mainly via the cytochrome P450 isoenzyme group and their gastric absorption being pH dependent, make them prone to clinically significant drug interactions with other antiretrovirals, concomitant medication and complementary treatments. Owing to the nature of the disease, individuals with HIV are frequently prescribed complex treatment regimens (both for the management of intolerance, toxicity and viral resistance to antiretroviral therapy, and in the management of co-morbid states) that may interact with PI therapy. For many of these potential interactions, few data are available. This review will focus on the current use of PIs, highlighting some important management issues encountered with common pharmacokinetic interactions seen in clinical practice.

Keywords: drug–drug interactions, antiretroviral, HIV therapy

Introduction

The introduction of HIV-1 protease inhibitors (PI) has been associated with a dramatic reduction in AIDS-related morbidity and mortality.1 However, the use of PIs is constrained by several factors including high pill burden, intolerable side-effects, difficulties with long-term adherence, development of drug-resistant viral species and pharmacokinetic interactions with other prescribed and non-prescribed medication.

All the currently available PIs are metabolized mainly by the cytochrome P450 (CYP450), in particular the CYP3A4 isoenzyme group. With the concurrent administration of a CYP3A4 inhibitor, commonly ritonavir, plasma exposure of these agents is increased. The use of low-dose ritonavir with a PI at therapeutic doses allows the achievement of a pharmacokinetic benefit that leads to higher drug plasma exposure, creating a higher genetic barrier to resistance (boosting). Boosting of PIs has become common practice and is recommended in treatment guidelines.2

Despite this favourable pharmacokinetic interaction used to boost PI plasma exposure, several PI pharmacokinetic interactions are less favourable and pose challenging clinical problems. One such problem involves the co-administration of agents also metabolized by the CYP3A4 isoenzyme, some of which are commonly used in the treatment of HIV infection (e.g. the antituberculous agents and lipid lowering agents). Another common interaction exists with agents that may affect PI gastric absorption. Gastric absorption for some of the PIs is pH dependent, and will be altered by agents that decrease gastric acidity.

For some of these potential interactions, formal pharmacokinetic studies are available, helping to guide physicians in determining optimal treatment choices. However, a large number of potential pharmacokinetic interactions exist (some of these predictable and some unpredictable), with few formal data available. This review will focus on the use of boosted PIs in clinical practice and highlight our knowledge to date on how to manage some common interactions.

Boosted PIs

Boosted single PIs

Boosted single PI therapy in combination with a nucleoside backbone compared with non-boosted PI regimens has shown superiority for both surrogate marker endpoints and a reduced rate of development of PI-associated resistance mutations.3 One disadvantage of this approach is a possible risk of greater lipid abnormalities, particularly raised fasting triglycerides.

Several boosted single PI therapies are currently licensed for use, with differing pill burdens, toxicity profiles, dosing frequencies and efficacy data in treatment-experienced and naive individuals. Currently, boosted atazanavir is the only PI licensed for once daily administration in Europe. New formulations of saquinavir and lopinavir are in development, with studies underway to assessing once daily therapy for both of these agents.

Boosted double PIs

As experience accumulated with the use of boosted single PI therapy, the concept of boosted double PI therapy emerged.
Initially, this was as a salvage regimen in individuals with resistant virus, making use of both the high drug concentrations achieved and the preservation of susceptibility to one PI often seen in strains resistant to other agents in this class. Recently, this approach has also been proposed as a novel way to avoid cross class toxicity. The use of antiretroviral regimens containing agents from only the PI class will avoid the potential mitochondrial toxicity associated with the reverse-transcriptase inhibitors.

The use of boosted double PI regimens is not without problems, as complex pharmacokinetic interactions, sometimes quite unexpected, can be involved when combining these agents. Some combinations must be avoided, such as the use of tipranavir/ritonavir with other PIs, which has been shown to significantly reduce plasma concentrations of saquinavir, amprenavir and lopinavir.5

Initial studies of lopinavir/ritonavir when combined with fosamprenavir showed substantially lower amprenavir levels than in patients dosed with fosamprenavir/ritonavir alone.6 This is partially but not completely overcome by increasing the fosamprenavir dose from 700 mg twice daily to 1400 mg twice daily, but was not overcome by increasing the dose of ritonavir, suggesting there is a complex bidirectional interaction with this combination.5

The combination of saquinavir with lopinavir/ritonavir seems to be free from the above problems7 and efficacy studies are underway, with encouraging results.

Another interesting interaction observed is with the boosted double PI combination of atazanavir/saquinavir/ritonavir. Saquinavir levels are enhanced in this regimen further than when dosed with fosamprenavir/ritonavir alone, suggesting a role for this as a once daily regimen.6 Further studies assessing this combination as once daily antiretroviral therapy are underway. Finally, saquinavir/fosamprenavir/ritonavir has been studied and the use of 200 mg of ritonavir advised,4 while no formal pharmacokinetic data are yet available on the combinations containing atazanavir plus either lopinavir/ritonavir or fosamprenavir/ritonavir.

### Interactions with commonly used concomitant medication

#### Drugs used for dyspepsia

The bioavailability of some PIs is pH dependent, absorption being greater with a lower pH. Medications such as antacids that increase gastric pH may reduce absorption, thereby leading to lower plasma PI concentrations and the potential development of virological failure. Many antacids, H2-receptor antagonists and proton pump inhibitors are available over-the-counter and are widely used by HIV-infected subjects.

Some formal pharmacokinetic studies have been performed to assess the use of drugs used for dyspepsia with PIs. In one study enrolling HIV-1-infected subjects, no significant change in unboosted saquinavir exposure with concomitant cimetidine use was observed.7 Further studies are planned to assess boosted saquinavir exposure with omeprazole use in healthy volunteers.

Studies assessing atazanavir and indinavir exposure have shown significant interactions. In healthy volunteers, boosted indinavir exposure was reduced by almost half when administered with either 20 or 40 mg of omeprazole,8 and a recent report has described a 79% reduction in boosted atazanavir exposure when administered with 40 mg omeprazole.9 Moreover, cohort data for atazanavir exist in clinical practice describing no significant changes in boosted atazanavir exposure in HIV-positive individuals on antiretrovirals exposed to over-the-counter drugs used for dyspepsia, including the use of omeprazole 20 mg daily.10 However, data obtained from cohort studies cannot rule out any interactions, but may sometimes be useful in screening for drug–drug interactions.

Fosamprenavir exposure has also been investigated during co-administration with ranitidine (unboosted, single dose)11 and esomeprazole 20 mg once daily (both boosted and unboosted, at steady-state)12 and, interestingly, while the first study showed a 30% decrease in amprenavir total plasma exposure, the second study showed no effect of the esomeprazole on amprenavir levels, suggesting that it is safe to co-administer fosamprenavir and antacid drugs.12

Finally, one cohort has described no change in boosted lopinavir exposure with the concomitant administration of omeprazole in HIV-1-infected individuals.13

Until further formal pharmacokinetic studies are available, PIs with known interactions should not be prescribed with drugs used for dyspepsia, especially when these are characterized by a prolonged effect (e.g. proton pump inhibitors). On the other hand, in the case of buffered drugs that alter gastric acidity or H2-receptor antagonists, the two drugs should be administered as far apart as possible (i.e. 12 h).

#### Antituberculous drugs

HIV infection is a major risk factor for the development of tuberculosis (TB) and significant interactions occur between the two pathogens, as HIV infection may accelerate the natural progression of TB by diminishing cell-mediated immune response and host immune reactions to TB may enhance HIV replication. Therefore, patients co-infected with HIV and TB often need to be treated for both diseases to improve their clinical outcome.

However, there is a high potential for clinically relevant negative drug interactions between PIs and the rifamycins currently used in HIV-infected subjects to treat TB.14 First, unexpected severe hepatotoxicity has been observed in healthy volunteers following the administration of multiple doses of rifampicin and saquinavir/ritonavir.15

Furthermore, rifamycins tend to decrease PI plasma concentrations principally through the induction of CYP450 (specifically the isoenzyme 3A4) mediated metabolism in the intestinal wall and liver,15 resulting in therapeutic failure and the potential development of viral resistance. The available rifamycins differ in potency as CYP3A4 inducers, with rifampicin being the most potent and rifabutin the least potent inducer.16 As such, rifabutin can be safely used with most PIs (Table 1). Rifabutin, however, is also a substrate for CYP3A4; thus PIs may lead to an increase in rifabutin (and its active metabolite) exposure, potentially resulting in toxic adverse events.

In some instances, interactions between PIs and rifamycins may be managed by appropriate dose adjustments (Table 1). For example, to adequately adjust for the interaction between ritonavir boosted PIs and rifabutin, the latter should be decreased to 150 mg daily or 300 mg three times per week.2

Guidelines for the treatment of HIV infection suggest that alternative antiretroviral therapy (ART) be considered for patients requiring treatment for both HIV and Mycobacterium tuberculosis, specifically the option of replacing the PI with a non-nucleoside reverse-transcriptase inhibitor.2 This is of particular importance in limited resource countries, in which rifabutin may not be available.
However, this strategy is not always applicable, especially in the management of those patients who are intolerant to reverse transcriptase inhibitors or who are infected by viruses resistant to these ARV classes.

### Statins

Metabolic disturbances associated with HIV infection and PI therapy are common and the potential for significant drug interactions associated with lipid lowering agents, such as HMG-CoA reductase inhibitors (also known as statins), and PIs is high.17

The primary route of metabolism for most statins is via oxidation by CYP3A4. Pravastatin, fluvastatin and rosuvastatin are exceptions, since they follow different metabolic pathways. Lactone drugs (e.g. lovastatin and simvastatin) should not be co-administered with PIs, as they are avid substrates for CYP3A4 and as such their metabolism is significantly inhibited by CYP3A4 inhibitors, which include the PIs and especially ritonavir.17

Drug interaction studies have been performed with PIs and statins.18 Co-administration of saquinavir/ritonavir to 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%, resulting in the need for atorvastatin dose adjustments. In contrast, pravastatin exposure declined by 50%. These data are of extreme clinical importance, since all statins have the capacity for severe toxicity, including rhabdomyolysis and hepatic dysfunction.

### Oral contraceptives

Physicians should be cautious when prescribing oral contraceptives to patients receiving PIs because of the variations in effect on ethinyl oestradiol levels. The limited data regarding the interaction between oral contraceptives and PIs make it difficult to provide sound clinical recommendations.

One published study found that ethinyl oestradiol area under the time concentration curve (AUC) was reduced by 41% in healthy female volunteers during concomitant ritonavir.19 Similar results have been reported with nelfinavir and lopinavir/ritonavir.20 Therefore, women receiving these drugs should use alternate forms of birth control. In contrast, data for indinavir demonstrate an increase in the AUC for both ethinyl oestradiol and norethindrone.20

### Table 1. Recommendations for co-administering PIs with rifampicin and rifabutin

<table>
<thead>
<tr>
<th>PI</th>
<th>Rifampicin</th>
<th>Rifabutin</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Atazanavir</td>
<td>↓ atazanavir $C_{\text{min}}$ by 93% (300/100), 80% (300/200), 60% (400/200)</td>
<td>↑ rifabutin AUC (205%)</td>
<td>(i) Avoid co-administration with rifampicin</td>
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<td></td>
<td></td>
<td></td>
<td>(ii) Reduce rifabutin dose&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Fosamprenavir</td>
<td>↓ amprenavir AUC by 82%</td>
<td>↑ rifabutin AUC (193%)</td>
<td>(i) Avoid co-administration with rifampicin</td>
</tr>
<tr>
<td>(amprenavir)</td>
<td></td>
<td></td>
<td>(ii) Reduce rifabutin dose&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or <em>if boosted</em></td>
</tr>
<tr>
<td>Indinavir</td>
<td>↓ indinavir AUC by 89% (unboosted)/87% (boosted)</td>
<td>↑ indinavir AUC by 32%, compensated by low-dose ritonavir; ↑ rifabutin AUC (204%)</td>
<td>(i) Avoid co-administration with rifampicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(ii) Reduce rifabutin dose&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Lopinavir/ritonavir</td>
<td>↓ lopinavir AUC by 75%; increased doses to 400/400 or 800/200 bid compensate decrease</td>
<td>↑ rifabutin AUC (303%)</td>
<td>(i) Increased toxicity during co-administration of rifampicin and increased dose of lopinavir/ritonavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(ii) Reduce rifabutin dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>↓ nelfinavir AUC by 82%</td>
<td>↑ nelfinavir AUC by 32%; ↑ rifabutin AUC (207%)</td>
<td>(i) Avoid co-administration with rifampicin</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>↓ saquinavir AUC by 84%; induction partly compensate by saquinavir/ritonavir 400/400 mg bid</td>
<td>↑ saquinavir AUC by 43%; compensated by addition of low-dose ritonavir</td>
<td>(i) Hepatotoxicity during co-administration of rifampicin and saquinavir/ritonavir</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>(ii) Reduce rifabutin dose&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tipranavir (boosted: 200 mg ritonavir bid)</td>
<td>↑ tipranavir levels by 80%</td>
<td>↔ tipranavir; ↑ rifabutin AUC (190%), $C_{\text{max}}$ (70%), and $C_{\text{min}}$ (114%); greater effect on active metabolite&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(i) Avoid co-administration with rifampicin</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(ii) Reduce rifabutin dose&lt;sup&gt;a&lt;/sup&gt;</td>
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AUC, area under the curve; $C_{\text{max}}$ and $C_{\text{min}}$, maximum and minimum concentrations; ↑, increase; ↓, decrease; ↔, no change; bid, twice daily; TDM, therapeutic drug monitoring.

<sup>a</sup>150 mg every other day or 150 mg three times per week.

<sup>b</sup>150 mg every other day or 300 mg three times per week.

<sup>c</sup>25-O-desacetyl-rifabutin.
Ketoconazole and other azole antifungal drugs inhibit CYP450 metabolism and P-glycoprotein (an efflux drug transporter) function, and therefore result in an increase in PI plasma exposure. This effect is limited for fluconazole, which is currently the best option for use with PIs.

Drug interactions between PIs and antiepileptic medications may be complex. The presence of ritonavir as part of the ARV combination may increase the plasma concentrations of carbamazepine, but decrease lamotrigine and valproic acid20 through the different effects (inhibition and induction, respectively) exerted on different CYP450 isoenzymes responsible for the metabolism of these agents. The effect of PIs (especially when boosted by ritonavir) on phenytoin plasma concentrations can be unpredictable, with either higher or lower concentrations occurring.20

Moreover, antiepileptic medications may alter PI plasma exposure, resulting in either increased and toxic or decreased plasma levels. The clinical significance of these interactions is unknown and therapeutic drug monitoring of both antiepileptic and ARV agents should be performed when used in combinations.

Methadone is metabolized primarily by CYP3A4. Therefore, CYP enzyme inducers can abbreviate the duration of methadone’s effects by lowering plasma methadone levels and possibly precipitate an abstinence (withdrawal) syndrome. Conversely, CYP enzyme inhibitors may slow methadone metabolism, extend the duration of its effects and possibly cause methadone-related toxicity (e.g. over-sedation and/or respiratory depression). Interestingly, a 53% and 40% decrease in total methadone plasma exposure and a 13% and 14% in the active methadone enantiomer (R-enantiomer) was observed in the presence of lopinavir/ritonavir, nelfinavir, saquinavir/ritonavir and amprenavir, respectively. However, none of the subjects studied experienced symptoms of opioid withdrawal, or requested a change in methadone dosing during co-administration of the PI and methadone.20 However, withdrawal symptoms have been observed clinically in patients stabilized on methadone who have commenced PI-containing regimens.

Finally, substances of abuse, specifically recreational drugs, including ethanol, marijuana, methamphetamine, ecstasy and heroin, may compromise efficacy by promoting drug interactions and non-adherence.20

Although considered natural, many herbal therapies may interact with prescribed medications causing either potentially dangerous adverse events or reduced drug efficacy. Drug interactions are known to occur when PIs are used concurrently with herbal remedies such as St John’s Wort, garlic supplements and Echinacea.20 Therefore, when combining herbal therapies with antiretrovirals, extreme caution is required.

Conclusions

Knowledge on the pharmacological aspects of PIs is a powerful tool for improving and maintaining patient quality of life when multiple medications are prescribed. Management of the drug interactions that accompany the use of PIs is challenging and requires great attention to detail. Moreover, the several new drugs under development will expand the risk for adverse drug interactions; therefore, careful clinical monitoring and pharmacokinetic studies are needed to investigate the occurrence of such events.

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Leading article


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