Special article – Part 2

Therapeutic drug monitoring and drug–drug interactions involving antiretroviral drugs

Marta Boffito1,2*, Edward Acosta3, David Burger4, Courtney V Fletcher5, Charles Flexner6, Rodolphe Garaffo7, Giorgio Gatti8, Michael Kurowski9, Carlo Federico Perno10, Gilles Peytavin11, Mario Regazzi12 and David Back13

1Chelsea and Westminster Hospital, London, UK
2University of Turin, Department of Infectious Diseases, Turin, Italy
3Division of Clinical Pharmacology, University of Alabama at Birmingham, Birmingham, AL, USA
4Department of Clinical Pharmacy & Nijmegen University Centre for Infectious Diseases, University Medical Centre, Nijmegen, The Netherlands
5Department of Clinical Pharmacy, University of Colorado Health Sciences Center, Denver, CO, USA
6The Johns Hopkins University, School of Medicine, Division of Clinical Pharmacology, Baltimore, MD, USA
7Unité de Pharmacocinetique Clinique, Pasteur University Hospital, Nice, France
8Vertex Pharmaceuticals (Europe) Ltd, Genoa, Italy and University of Genoa, c/o San Martino Hospital, Genoa, Italy
9Therapia GmbH, Berlin, Germany
10University of Rome Tor Vergata, Rome, Italy
11Département de Pharmacocinétique Clinique, Hôpital Bichat-Ci Bernard, Paris, France
12Service of Clinical Pharmacology, IRCCS Policlinico S Matteo, Pavia, Italy
13Department of Pharmacology, University of Liverpool, Liverpool, UK

*Corresponding author: Tel: +44 20 8846 6507; Fax: +44 20 8746 5628; E-mail: marta.boffito@chelwest.nhs.uk

The consensus of current international guidelines for the treatment of HIV infection is that data on therapeutic drug monitoring (TDM) of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) provide a framework for the implementation of TDM in certain defined scenarios in clinical practice. However, the utility of TDM is considered to be on an individual basis until more data are obtained from large clinical trials showing the benefit of TDM.

In April 2004, a panel of experts met for the second time in Rome, Italy. This was following the inaugural meeting in Perugia, Italy, in October 2000, which resulted in the manuscript published in AIDS 2002, 16(Suppl 1):S5–S37. The objectives of this second meeting were to review and update the numerous questions surrounding TDM of antiretroviral drugs and discuss the clinical utility, current concerns and future prospects of drug concentration monitoring in the care of HIV-1-infected individuals. A major focus of the meeting was to discuss and critically analyse recent and precedent clinical drug–drug interaction data to provide a clear framework of the pharmacological basis of how one drug may impact the disposition of another.

This report, which has been updated to include material published or presented at international conferences up to the end of December 2004, reviews recent pivotal pharmacokinetic interaction data and provides advice to clinical care providers on how some drug–drug interactions may be prevented, avoided or managed, and, when data are available, on what dose adjustments and interventions should be performed.

Antiretroviral drug–drug interactions: recent advances

Clinically relevant antiretroviral (ARV) drug–drug interactions may occur among ARV drugs belonging to the same or to different classes or between ARV drugs and drugs received by HIV-positive patients for the treatment of co-existing medical conditions, the treatment and prevention of opportunistic infections, for supportive care or for the limitation of adverse events caused by ARV agents [1].

Despite the Food and Drug Administration and European Medicine Agency requiring a set number of
interaction studies before drug approval, drug–drug interactions involving ARV medications are frequently not recognized until after Phase 4 drug development. This is largely due to the speed at which new antiretroviral drugs are introduced into clinical care, usually through expanded access programmes and clinical trials for treatment-experienced subjects with limited treatment options who are on salvage regimens. As a result, the use of new ARVs often exceeds our knowledge of how these agents may be best used and how they may interact with other drugs.

It is worth noting that despite the well-known mechanisms behind drug interactions involving non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) (metabolism by cytochrome P450 isoenzymes in the gastrointestinal tract and liver), other potential mechanisms involving such interactions are emerging (for example transporters and gastric pH-dependent absorption).

Nucleoside/nucleotide reverse transcriptase inhibitors

Currently, there is no indication for monitoring plasma concentrations of NRTIs, since these compounds are converted to their active forms intracellularly and plasma levels may not be a good indicator of the triphosphate concentrations present within the cell. However, the recently licensed nucleotide (Nt) RTI tenofovir has shown a drug–drug interaction with ddI [2]. This led to the measurement of ddi and tenofovir plasma concentrations in HIV-infected subjects and the observation of a wide interindividual variability in exposure [3]. However, if this is to be included in patient clinical care a greater understanding of the relationship between plasma concentrations, intracellular concentrations and drug activity/toxicity is needed.

Tenofovir and other antiretroviral drugs

Tenofovir disoproxil fumarate (DF) is the oral prodrgug of tenofovir. Clinically relevant drug interactions between tenofovir and PIs have been reported, most notably the reduction in concentrations of atazanavir (ATZ) (both with and without ritonavir (RTV) boosting), by an unknown mechanism [4]. Although the concentrations of boosted ATZ are higher than the unboosted ATZ concentrations in the presence of tenofovir, it is important to note that they still remain lower than the boosted ATZ concentrations in the absence of tenofovir (26% lower C\text{min}) [9]. Whether this has an effect on ATZ/RTV/tenofovir-containing regimens (leading to a reduction in drug potency) is unknown and needs to be evaluated, particularly in ARV-experienced patients.

Although recent analysis of plasma samples for routine TDM of ATZ (administered in presence or absence of low-dose RTV) did not show important differences when comparing subjects on tenofovir DF versus subjects on a different NRTI-backbone [5], these data are not from a well-designed study and many uncontrolled factors (concomitant drug intake, dietary restriction and HIV-HCV co-infection) may have contributed to inflate variability and mask the interaction previously revealed by well-controlled studies.

Fosamprenavir (fAPV) exposure, when administered in the presence of RTV once or twice daily, seems not to be altered by tenofovir DF co-administration. This was shown by a sub-analysis of the CONTEXT study which compared amprenavir (APV) C\text{trough} in subjects with tenofovir DF (n=45 and 60 on once daily and twice daily regimens, respectively) with subjects without tenofovir DF (n=25 and 24 on once daily and twice daily regimens, respectively) as part of the ARV regimen [6].

No change in lopinavir (LPV)/RTV concentrations but an increase in tenofovir plasma exposure (32%) has been observed when LPV/RTV and tenofovir DF are co-administered [7,8]. It is under debate if the increase of tenofovir concentration is associated with increased tenofovir renal side effects and the mechanism of this interaction is unknown. Patients receiving LPV/RTV and tenofovir may have to be monitored closely for tenofovir-associated 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 and multi-drug resistance protein 2 (MRP-2) [9].

RTV is a potent inhibitor of MRP-2-mediated transport [10] and may lead to an increase in tubular concentrations of tenofovir by reducing its efflux from the kidneys. Therefore, RTV 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 [11–15]. 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 LPV/RTV. Interestingly, unboosted ATZ at the dose of 400 mg increased tenofovir area under the curve (AUC) by 24% [90% confidence intervals (CI): 21–28] [4]. This also suggests that tenofovir increase is not necessarily due to RTV.

There are no pharmacokinetic (PK) data available on the effect of fAPV on tenofovir concentrations, although there were no reports of an increased incidence of renal abnormalities in patients receiving tenofovir and fAPV during the CONTEXT study period [6].
Double-boosted PI regimens

Drug–drug interactions among PIs are becoming important since utilizing two PIs at therapeutic exposures with a booster (so-called ‘double-boosted PI therapy’) is now being increasingly considered. These regimens are most commonly used in patients with established PI resistance but may also be used in individuals intolerant to NRTIs or against virus with extensive NRTI and NNRTI resistance but retained PI susceptibility. Choice of which PIs to combine is influenced by knowledge of differences in viral susceptibility between drugs and the results of resistance testing. Broadly, extensive cross-resistance is observed between RTV, LPV and indinavir (IDV), the other PIs each having some uniqueness to their initial resistance profiles [16]. Drug–drug PK interactions between approved PIs may be unpredictable. The PKs of different combinations of PIs have been studied and are summarized in Table 1. Whether or not additivity and synergy exist between PIs leading to the requirements of lower concentrations to produce the same effect is still unknown. This would further complicate the little available information on drug plasma concentration thresholds. An important concern with double-boosted PI therapy could be the risk of increased toxicity, especially dyslipidaemia, which can occur on such regimens. A role of TDM in this context is suggested. The efficacy of SQV/ATZ 1200/400 mg once daily (plus two NRTIs) has shown favourable PK profiles [17–19] and encouraging results among ARV-experienced patients [20–24].

A PK study in 18 HIV positive patients has investigated the co-administration of SQV/RTV 1600/100 mg and ATZ 300 mg once daily and demonstrated that the addition of ATZ to the regimen substantially increased SQV exposure [25]. Interestingly, the addition of ATZ to the once daily SQV/RTV regimen also influenced the pharmacokinetics of RTV. The mechanism by which SQV exposure was increased during ATZ co-administration is unclear. This effect may be independent of RTV dose and be a consequence of different boosters (RTV and ATZ) impacting different aspects of drug disposition.

Although SQV/RTV/ATZ was well tolerated, the increase in indirect hyperbilirubinaemia was common after the addition of ATZ to the regimen. These findings were recently confirmed by a PK study which investigated the co-administration of ATZ 300 mg once daily and SQV/RTV 1000/100 mg twice daily [26].

The PK interaction between ATZ and SQV (without RTV) has also been evaluated both in healthy volunteers and HIV-infected subjects [27–29]. Although SQV exposure is increased in the presence of ATZ, a regimen of SQV/ATZ 1200/400 mg was insufficient to achieve SQV plasma concentrations above the suggested SQV therapeutic trough concentration of 100 ng/ml [27,28].

It is not surprising that 1200 mg of SQV administered once daily resulted in low SQV plasma concentrations, since dosages of 1600 mg once daily are administered in combination with RTV, a much stronger inhibitor of CYP3A4. These PK findings were reflected in the results of a study investigating the efficacy of SQV/ATZ 1200/400 mg once daily (plus two NRTIs), which was associated with poor therapeutic responses [29].

ATZ/fAPV (with low-dose RTV) is a potential combination which requires further investigation. The few PK data available to date on ATZ/APV (in the absence of low-dose RTV) seem to show lower concentrations of ATZ (compared with historical controls) in the presence of APV [30], while APV levels have been shown to be increased by the concomitant administration of ATZ in heavily pre-treated subjects [31]. Recently, the combination of ATZ 150 or 200 mg twice daily and fAPV/RTV 700/100 mg twice daily showed the achievement of adequate concentrations for both drugs [32]. The different resistance profiles of the two drugs, including mutations at the same protease amino acid (I50), but incompatible with each other (leucine, L, for ATZ and valine, V, for APV) makes this an attractive combination that deserves further study.

APV exhibits synergistic anti-HIV activity with SQV in vitro [33] and the two agents have non-overlapping primary resistance patterns. APV exists in two different forms, a soft-gel APV formulation and a hardened tablet containing the APV pro-drug fAPV [34]. fAPV is rapidly hydrolysed to APV by cellular phosphatases in the gut epithelium during drug absorption.

APV not only undergoes CYP450-based metabolism in the gastrointestinal tract and liver, but has been shown to inhibit and induce other CYP isoforms.

### Table 1. Summary of interactions between double-boosted protease inhibitors (PIs)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Summary of interactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r + APV or fAPV</td>
<td>LPV ↓ APV [39–49]†</td>
</tr>
<tr>
<td>LPV/r + SQV</td>
<td>LPV ↔ SQV ↔[17–24]</td>
</tr>
<tr>
<td>LPV/r + NFV</td>
<td>LPV ↓ NFV ↔ [51]</td>
</tr>
<tr>
<td>LPV/r + IDV</td>
<td>LPV ↔ IDV ↔[52–54]†</td>
</tr>
<tr>
<td>ATZ + RTV + SQV</td>
<td>ATZ ↔ SQV ↑[25,26]</td>
</tr>
<tr>
<td>SQV + RTV + APV</td>
<td>SQV ↓ APV ↔ [37]</td>
</tr>
<tr>
<td>fAPV + RTV + SQV</td>
<td>APV ↔ SQV ↔[38]†</td>
</tr>
<tr>
<td>TPV + SQV or APV or LPV</td>
<td>SQV, APV, LPV ↓ [57]</td>
</tr>
</tbody>
</table>

*Compared with single-boosted regimens (in some cases, historical data).

†Small studies with variable findings. ‡If RTV dosed 200 mg twice daily. SQV moderately ↓ if RTV dosed 100 mg twice daily; APV, amprenavir; ATZ, atazanavir; fAPV, fosamprenavir; IDV, indinavir; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPV, tipranavir.
For this reason, the combination of SQV/APV has been found to reduce SQV exposure, even in the presence of RTV [33,37]. The drug interaction between fAPV and SQV has been recently investigated to establish the optimal RTV dose able to compensate for the effects of fAPV on SQV PK.

It was observed that the co-administration of fAPV 700 mg twice daily with SQV/RTV 1000/100 mg twice daily resulted in a non-statistically significant decrease in SQV PK parameters (by 14, 24 and 9% for SQV AUC\(_{0-12h}\), C\(_{\text{trough}}\) and C\(_{\text{max}}\), respectively). This was more than compensated for by the addition of a further 100 mg RTV twice daily (total RTV dose: 200 mg twice daily) [38], suggesting an optimal dose combination for the three agents SQV/RTV/fAPV of 1000/200/700 mg twice daily. However, the possibility of administering lower doses of RTV (100 mg twice daily) remains an option, especially when TDM is available to ensure optimal drug plasma concentrations.

A complex interaction is observed when APV is combined with LPV/RTV. Evidence, from both HIV-infected patients and healthy volunteers, suggests that in addition to decreased LPV/RTV concentrations following induction of CYP450 by APV, LPV also seem to cause a decrease in APV concentrations, albeit to a lesser extent [39–46].

Despite this, a median viral load decrease of 2.5 log\(_{10}\) copies/ml was observed at week 26 in subjects on RTV 200 mg twice daily compared with a viral load decrease of 1.4 log\(_{10}\) copies/ml for those on RTV 100 mg twice daily, suggesting that the addition of further RTV to the regimen was able to compensate for APV induction [47]. Moreover, a prospective study investigating the efficacy of APV plus LPV/RTV (and NRTIs) in HIV subjects previously failing three classes of drugs showed a partial virological inhibition and good immunological efficacy, despite lower than historical APV and LPV C\(_{\text{max}}\) and C\(_{\text{trough}}\) values being measured [39]. The pharmacokinetics of the combination of fAPV and LPV/RTV has also been investigated by different authors [48,49].

A strategy to overcome this complex drug–drug interaction has been investigated in healthy volunteers. The study investigated the administration of fAPV and LPV/RTV either together or separated by 4 or 12 h. This strategy did not improve APV exposure, despite the addition of further RTV. However, the increased RTV daily dose led to the achievement of adequate (compared with historical data) LPV PK parameters.

Another study [49] investigating different dosing strategies in healthy volunteers identified the combination of fAPV 1400 mg twice daily plus LPV/RTV 533/133 mg twice daily as the one resulting in acceptable concentrations of both APV and LPV: concentrations of LPV were similar to LPV/RTV 400/100 mg twice daily alone and concentrations of APV were higher that those reported for fAPV 1400 mg twice daily alone, but lower than those reported for fAPV/RTV 700/100 mg twice daily alone.

The incidence of side effects in this study was, however, unacceptably high, and therefore no dose recommendation can be provided. Therefore, fAPV and LPV/RTV should be administered with extreme caution and only to patients who do not have alternative treatment options. TDM may be useful in selecting the patients who may benefit from this combination. In fact, due to the high interindividual variability in concentrations, a percentage of patients, at the upper bound of the variability range, might achieve inhibitory concentrations [50].

LPV PK parameters have also been shown to be significantly decreased by the co-administration of nelfinavir in 13 healthy HIV-negative volunteers [51], leading to a reduction of the median inhibitory quotient from 105 to 76. RTV was also decreased by the co-administration of nelfinavir. If the co-administration of LPV/RTV and nelfinavir is necessary, the LPV/RTV dosage would therefore need to be increased to 533/133 mg twice daily in order to achieve adequate plasma concentrations. The PKs of the co-administration of LPV/RTV and IDV have been investigated by different authors in both HIV-positive and -negative subjects who have been administered LPV/RTV at standard doses (400/100 mg twice daily) and IDV at different dosages [52–54].

Although PK data on this combination are limited and conflicting, a recent study showed that LPV/RTV and IDV have no negative drug–drug interactions [54]. The addition of LPV/RTV to an IDV-containing regimen (where low doses of RTV were already administered to enhance IDV plasma concentrations) did not affect IDV exposure at steady-state. However, RTV plasma concentrations were significantly lower under these conditions, suggesting that a lower exposure to RTV is sufficient to ensure therapeutic plasma concentrations of both LPV and IDV. Therefore, dose adjustments of either drug are unnecessary [55]. However, despite the remarkable virological response observed in subjects on this combination, 29% of patients had to stop treatment due to intolerance.

Tipranavir is an investigational PI that has \textit{in vitro} activity against multi-PI-resistant HIV-1 [56]. It has been well established that tipranavir must be co-administered with RTV in order to achieve clinically effective plasma concentrations. Interim results from a 24-week, open-label, safety and PK study of tipranavir/RTV (500/200 mg twice daily) alone or in combination with a second boosted PI (APV, LPV or SQV) in 315 highly treatment-experienced patients (≥3 PI mutations) were recently reported. Co-administration of
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tipranavir/RTV was associated with substantial reductions in the AUC of the other PIs: 70% reduction in SQV, 45% reduction in APV, and 49% reduction in LPV. These results cast doubt on the ability to co-administer tipranavir with other PIs, even when boosted with 200 mg of RTV twice daily [57].

PI and statins
Metabolic disturbances associated with HIV infection and ARV therapy 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 [58].

The primary route of metabolism for most statins is via oxidation utilizing the cytochrome P450 3A4 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 pro-drugs, are avid substrates for CYP3A4 and as such are inhibited by CYP3A4 inhibitors, which include the PIs and especially RTV [58].

Drug interaction studies have been performed with PIs and statins [59]. Co-administration of SQV/RTV 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%. 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.

Drug–drug interactions involving efavirenz (EFV)
Metabolism induction by EFV may decrease PI exposure and therefore higher PI and/or RTV boosting dose may be necessary. In fact, the recommended dose of LPV/RTV with EFV is 533/133 mg twice daily (addition of one tablet) [60], and the dose of ATZ/RTV is 400/100 mg once daily instead of 300/100 mg, in particular if this drug is used in PI-experienced patients [4].

The dosage regimen of boosted twice daily fAPV/RTV (700/100 mg) does not require modification with EFV, while the addition of 100 mg twice daily of RTV is recommended if fAPV is used once daily [61].

The effect of EFV on the PK of pravastatin, atorvastatin and simvastatin in HIV-negative volunteers has also been studied and appeared to be safe [62]. From a PK perspective, EFV is a potent inducer of simvastatin metabolism (leading to a 60% decrease in its plasma concentrations) and a less potent, but still significant, inducer of atorvastatin metabolism (35% decrease in exposure). Non-steady-state exposure of EFV did not change, this needs to be confirmed by steady-state data. Higher doses should be considered for simvastatin when co-administered with EFV. The AIDS Clinical Trials Group guidelines for the evaluation and management of dyslipidaemia in HIV-infected adults on ARV treatment are now available [63].

It has been reported that EFV and nevirapine induce the metabolism of methadone extensively [64–66] and that tailoring the appropriate methadone coverage in EFV recipients can be problematic for the first few weeks of therapy [67]. This has been recently confirmed in presence of the NRTI abacavir (also responsible for an accelerated methadone clearance), where the marked reduction in methadone concentrations was compensated for by a methadone dose increase of approximately 30% up to 60 weeks following ARV initiation [66].

PIs and 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 antacid drugs are theoretically possible (Table 2).

This is important since a prevalence of 49.8% of nausea/anorexia/upper gastrointestinal symptoms has been reported by a large national cohort study [68], and confirmed by a recent report investigating gastrointestinal acidity in HIV-infected subjects [69]. This suggests the frequent use of drugs able to control these symptoms, including antacidic drugs [H2 antagonists, acid neutralizers and phosphate binders, proton pump inhibitors (PPIs)]). Available data suggest that there may be profound differences across PIs in terms of absorption dependence on gastric pH and, therefore, in terms of the influence that anti-acidic drugs may have on PI absorption.

ATZ [4] and IDV [70] have been shown to exhibit significantly decreased absorption when given with antacid drugs. The AUC and Cmin of ATZ (400 mg once daily) was reduced by 84% and 87%, respectively, when administered with buffered ddl (a ddl formulation with cation chelating agents similar to Maalox) while the AUC of fAPV (1400 mg twice daily) was reduced by only 18%, with no significant effect on Cmin by concomitant administration of Maalox. The deleterious effect of buffered drugs on ATZ absorption may be counterbalanced by administering ATZ 2 h before or 1 h after administration of these drugs, while for H2 receptor antagonists (ranitidine) the two drugs should be administered as far apart as possible, ideally
12 h apart. Conversely, given the prolonged effect of the PPIs and major decrease in ATZ concentrations with these drugs, this interaction cannot be managed by separating ATZ and the PPI doses.

In fact, a recent warning issued by the manufacturing company [71] revealed that steady-state ATZ Cmin and AUC were 78% and 76% lower, respectively, when ATZ was administered at the standard dose of 300/100 mg once daily in association with 40 mg of omeprazole. Addition of 100 mg of ATZ or 8 ounces of cola were unable to compensate the effect of omeprazole on ATZ absorption.

Table 2. Effect of gastric pH modifiers on PI pharmacokinetics

<table>
<thead>
<tr>
<th>PI</th>
<th>Antacids (Maalox)</th>
<th>H2-blockers (ranitidine)</th>
<th>PPI (omeprazole)</th>
<th>Buffered ddl</th>
<th>Probability of interaction with gastric pH modifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQV (not reported)</td>
<td>Cmin↑ [76]</td>
<td>Cmin↓55% AUC↓ 46.2% [70]</td>
<td>AUC↓ 84% [75]</td>
<td>Clinical significance not likely</td>
<td></td>
</tr>
<tr>
<td>IDV (800 mg single dose)</td>
<td>Ctrough ↔ [74]</td>
<td>Ctrough ↔ [74]</td>
<td>Ctrough ↔ [74]</td>
<td>Retrospective study: formal PK study required</td>
<td></td>
</tr>
<tr>
<td>LPV/r (400/100 mg twice daily; 800/200 mg once daily)</td>
<td>Cmin ↑14% [76]</td>
<td>Cmin ↔ [72]</td>
<td>AUC ↓ 18% [72]</td>
<td>Clinical significance not likely</td>
<td></td>
</tr>
<tr>
<td>fAPV (1400 mg single dose)</td>
<td>AUC ↓ 30% [72]</td>
<td>AUC ↓ 46.2% [70]</td>
<td>Cmin ↓ 84% AUC ↓ 87% [4]</td>
<td>Clinically significant</td>
<td></td>
</tr>
<tr>
<td>ATZ (400 mg single dose)</td>
<td>Cmin ↓ 78% AUC ↓ 76% [71]</td>
<td>Cmin ↓ 29% AUC ↓ 27% [73]</td>
<td>Clinical significance to be confirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATZ/r (300/100 mg once daily)</td>
<td>Cmin ↓ 78% AUC ↓ 76% [71]</td>
<td>Cmin ↓ 29% AUC ↓ 27% [73]</td>
<td>Clinical significance to be confirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tipranavir/r (500/200 mg single dose)</td>
<td>Cmin ↑14% [76]</td>
<td>Cmin ↔ [72]</td>
<td>AUC ↓ 30% [72]</td>
<td>Clinical significance not likely</td>
<td></td>
</tr>
</tbody>
</table>

*No information is available regarding which PK parameter is increased. SQV, saquinavir; IDV, indinavir; LPV/r, lopinavir/ritonavir; fAPV, fosamprenavir; ATZ, atazanavir; ATZ/r, atazanavir/ritonavir; TPV/r, tipranavir/ritonavir. AUC, area under the curve; Cmin, minimum concentrations; Ctrough, trough concentrations; ddl, didanosine; PI, protease inhibitor; PK, pharmacokinetic, PPI proton pump inhibitor.

Although the panel agreed that randomized, prospective, controlled trials remain a high priority to evaluate the benefit of TDM of ARV agents, they recognised that plasma concentration monitoring may be beneficial in particular clinical scenarios where drug concentrations are difficult to predict. One such scenario is the management of drug–drug interactions.

Despite an ever-expanding knowledge base on the role of CYP450 isoenzymes and transporter proteins in drug interactions, it is nevertheless important to be aware that drug interactions are often unpredictable. Several different mechanisms can be responsible for interactions involving PIs, and these are complex and often unclear.

Intensive PK trials and laboratory based studies focussing on the molecular, cellular and tissue level, all have a role in seeking to explain and predict the interactions in vivo. This is particularly true for the investigational ARVs which will become available in the near future and are likely to be involved in clinically important, often adverse, drug interactions.

Acknowledgements

The authors would like to acknowledge the unrestricted support of Vertex Pharmaceuticals (Cambridge, MA, USA) for the realization of this project and Dr Akil Jackson, from Chelsea and Westminster Hospital (London, UK), for his careful review of the manuscript and his advice.
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