Darunavir (TMC114) is a new HIV protease inhibitor that has demonstrated substantial antiretroviral activity against wild-type HIV-1 virus and multidrug-resistant strains. Darunavir inhibits and is primarily metabolized by cytochrome P450 3A (CYP3A) isoenzymes and is co-administered with low-dose ritonavir (darunavir/r); ritonavir is an inhibitor of CYP3A isoenzymes and pharmacologically enhances darunavir, resulting in increased plasma concentrations and allowing for a lower daily dose. The $t_{1/2}$ (terminal elimination half-life) of darunavir is 15 h in the presence of ritonavir. An extensive darunavir/r drug–drug interaction programme has been undertaken, covering a wide range of therapeutic areas. Studies conducted in HIV-negative healthy volunteers and in HIV-infected patients show that the potential for interactions is well characterized and the interactions are manageable. For most drugs investigated, no dose adjustments of darunavir/r or the co-administered drug are required. This article reviews all the pharmacokinetic and drug–drug interaction studies conducted to date for darunavir/r, providing guidance on how to co-administer darunavir/r with many other antiretroviral or non-antiretroviral medications commonly used in HIV-infected individuals.

**Introduction**

The aim of antiretroviral therapy is to maximally and durably suppress levels of HIV-1 RNA, while restoring and preserving immunological function [1]. Failure to respond to treatment is often related to the development of viral drug resistance, occurring as a result of mutations in the viral genome. An understanding of resistance mechanisms is important for the design of new agents, particularly for the management of treatment-experienced patients who have usually failed to respond to multiple prior regimens and often developed mutations that confer resistance to most of the current antiretroviral drugs.

Darunavir (TMC114) is a new protease inhibitor (PI) that has been designed to have a high genetic barrier to the development of resistance [2]. Studies have demonstrated that darunavir has activity against wild-type HIV-1 virus and a wide range of PI-resistant viruses [2,3]. Co-administration of darunavir is with low-dose ritonavir (darunavir/r); the 600/100 mg twice daily dose has now been approved in many countries for treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one PI [4].

The efficacy and safety of darunavir/r in treatment-experienced patients have been demonstrated in the POWER 1, 2 (TMC114-C213, TMC114-C202) and 3 (TMC114-C215/C208) Phase IIb studies [5–7]. All patients in the POWER studies received treatment with an investigator-selected optimized background regimen plus either darunavir/r or (in POWER 1 and 2) an investigator-selected control PI. In a pooled analysis of the randomized, controlled, POWER 1 and 2 trials, treatment with darunavir/r 600/100 mg twice daily resulted in greater virological and immunological responses than treatment with control PIs (CPIs). At week 24, 45% of patients receiving darunavir/r 600/100 mg twice daily achieved undetectable viral load (HIV-1 RNA <50 copies/ml) compared with 12% of CPI patients. Furthermore, viral suppression was sustained to week 48, with the same proportion of darunavir/r patients achieving this undetectable level (compared with 11% of CPI patients at this time point) [8]. These results were corroborated by those from the larger POWER 3 analysis, which was performed on data from two non-randomized, open-label trials that were conducted to provide additional efficacy and safety data on darunavir/r in treatment-experienced patients; 40% of POWER 3 patients achieved HIV-1
RNA reductions to <50 copies/ml at week 24 [7]. In all three Phase Ib studies darunavir/r was generally safe and well tolerated [5–7].

This review summarizes the chemical and physical properties of darunavir, and discusses in detail the pharmacokinetic data from studies of darunavir/r that have been conducted as part of the extensive, ongoing clinical trial programme. Specifically, pharmacokinetic studies conducted in vitro, in animals, in HIV-negative healthy volunteers and HIV-infected patients are described, along with those from patients of different baseline subgroups, such as men and women, and patients with or without hepatitis B or C coinfection. In addition, given the need for HIV-infected patients to use other concomitant medications, it is important that any potential darunavir/r drug–drug interactions are identified and understood; thus, results from these studies are also discussed here.

Chemical and physical properties

Darunavir (molecular weight 593.73) is a peptidomimetic PI that contains a bis-tetrahydrofuranyl (bis-THF) moiety and sulfonamide isostere; the drug is administered as its ethanolate salt (Figure 1). Darunavir is structurally similar to another PI, amprenavir; however, whereas amprenavir has one THF ring, darunavir has two THF rings that are fused to each other. This bis-THF moiety reverses the stereochemistry at the bond that links it to the rest of the molecule and has a profound influence on the antiretroviral activity of darunavir; it allows additional interactions of darunavir with a key amino acid of the HIV protease, Asp29 [9,10]. As a result, darunavir binds with the HIV protease >100 times more tightly than amprenavir does [11]. High-resolution X-ray crystallography revealed the occurrence of at least six hydrogen bonds between darunavir and wild-type protease, with most of these interactions involving main-chain atoms at the bottom of the protease binding site [11]. Darunavir also fits closely within the substrate envelope; the protrusion of some atoms outside this envelope allows darunavir to form the network of hydrogen bonds. Together, these properties could help explain why resistance to darunavir develops more slowly than to other available PIs, such as nelfinavir, amprenavir and lopinavir [2].

Pharmacokinetics

Preclinical studies

The following section describes in detail the pharmacokinetic studies of darunavir conducted in vitro and in animals.

Absorption

Darunavir has an intermediate-to-high absorptive permeability in Caco-2 monolayers, indicating that darunavir would exhibit sufficient membrane permeability to obtain adequate intestinal absorption. The ratio of secretory/absorptive transport decreases with darunavir concentration, which is indicative of saturation of an active transport process (for example, P-glycoprotein [P-gp] or another efflux protein) (unpublished data). Inhibition of transepithelial permeation of P-gp substrates by darunavir could not be excluded, but findings from a study that assessed the potential interaction between darunavir/r and digoxin support P-gp inhibition with darunavir/r in the clinic [12].

Distribution

Darunavir is highly protein-bound. The binding of darunavir to human plasma protein (albumin and α1-acid glycoprotein [AAG]) was determined in vitro by equilibrium dialysis of plasma samples from healthy male volunteers using 14C-labelled darunavir. Darunavir was 95% bound to AAG and was also shown to be bound to albumin, but to a lesser extent than to AAG [13]. These findings are consistent with data obtained for almost all of the other available HIV-1 PIs [14].

Metabolism

Results from an in vitro study of human liver microsomes indicate that darunavir primarily undergoes oxidative metabolism [13] and is extensively metabolized by cytochrome P450 (CYP450) enzymes, mainly CYP3A [4]. This is consistent with the metabolic pathways of other available PIs [15]. At least three oxidative metabolites of darunavir have been identified in human liver microsomes. All these metabolites showed activity against wild-type virus, but their activity was at least 10-fold less than that of darunavir [4].
Clinical studies

Absorption and bioavailability: the effect of low-dose ritonavir
Darunavir is metabolized by and also inhibits CYP3A. However, in combination with ritonavir, a more potent inhibitor of CYP3A, there is a marked increase in darunavir plasma concentrations. In a study of HIV-negative, healthy volunteers, absolute bioavailability of darunavir (600 mg once daily) was increased to 82% in the presence of ritonavir (100 mg twice daily) compared with 37% when darunavir was administered alone [16]. This pharmacokinetic enhancement caused by ritonavir suggests that first-pass elimination of darunavir is almost completely inhibited. When the effect of elimination was taken into account, the overall increase in the AUClast (area under the plasma concentration–time curve) for darunavir was 14-fold when taken with ritonavir 100 mg twice daily versus administration alone (Figure 2). Darunavirr/ 600/100 mg twice daily was absorbed following oral administration with a time to maximum darunavir plasma concentration (Tmax) of approximately 2.5 to 4 h [4]. In a second, dose-escalation study, 32 HIV-negative, healthy volunteers received darunavir (200 mg once daily, 300 mg twice daily, 400 mg, 600 mg or 1,200 mg once daily) in the absence or presence of ritonavir (either 100 mg once daily, 100 mg twice daily or 200 mg once daily). The use of ritonavir at the higher dose of 200 mg twice daily with darunavir 600 mg once daily did not result in any relevant increase in plasma concentrations of darunavir compared with that of ritonavir 100 mg twice daily, indicating that maximum pharmacokinetic enhancement was achieved with the lower ritonavir dose [13]. Consequently, darunavir 600 mg should only be administered when combined with 100 mg of ritonavir [4].

Absorption and bioavailability: the effect of food
The presence of food in the stomach affects darunavir absorption and bioavailability. An open-label, randomized, two-panel, crossover study determined the effect of various meal types, or fasting, on darunavir bioavailability. When darunavir was given as a 400 mg single dose in the presence of low-dose ritonavir (100 mg) to HIV-negative, healthy volunteers immediately after intake of a standard meal, the plasma concentration of darunavir was increased by 30% compared with administration under fasted conditions (Figure 3) [17]. Furthermore, the plasma concentration–time profile for darunavir was comparable for the different types of meals assessed: standard breakfast, high-fat breakfast, nutritional protein-rich drink or croissant with coffee. It is, therefore, recommended that darunavir/r be given with food; however, there is no restriction on the type of food consumed, as this does not affect the plasma concentration–time profile for darunavir. These results are consistent with those reported for several other PIs where, compared with the fasted state, the AUC for nelfinavir, lopinavir and atazanavir in the presence of food was increased by 200–300%, 48–97% and 35%, respectively [18].

Distribution
The volume of distribution (Vd) was determined in a trial conducted in eight HIV-negative healthy volunteers; the mean Vd of darunavir alone was 88.1 l, while it was increased to 130 l in the presence of ritonavir 100 mg twice daily [4].

Metabolism and elimination
In a darunavir mass balance study, healthy volunteers received a single dose of darunavir (400 mg) radiolabelled with the isotope 14C and low-dose ritonavir (100 mg). After 48 h the metabolism of [14C]darunavir was found to be extensive when darunavir was administered alone, but was markedly reduced when co-administered with ritonavir; the proportion of unchanged drug eliminated was 8% (6.8% in faeces and 1.2% in urine) and 49% (41.2% in faeces and
7.7% in urine) in the absence and presence of ritonavir, respectively [4,13]. Results at 168 h after administration showed that $^{14}$C-darunavir or metabolites of $^{14}$C-darunavir were excreted mainly in the faeces (80%) and to a lesser extent in urine (14%) [4]. The $t_{1/2}$ (terminal elimination half-life) of darunavir when combined with ritonavir (1,200/100 mg once daily) in a dose-ranging study of healthy volunteers was found to be 15 h [4,13]. Following intravenous administration of darunavir (150 mg; single 1 h infusion) alone or darunavir in the presence of low-dose ritonavir (100 mg twice daily) in HIV-negative, healthy volunteers, the mean systemic clearance was 32.8 l/h and 5.9 l/h, respectively [16].

Effect of demographic characteristics on darunavir pharmacokinetics

**Gender**

Population pharmacokinetic analysis showed that HIV-infected female patients from the POWER 1 and 2 studies (n=68) had a slightly higher mean AUC$_{24h}$ for darunavir (16.8%) compared with that observed in males. However, this difference was not considered to be clinically relevant [4].

**Race**

There was no difference in the AUC$_{24h}$ for darunavir between people of different ethnic origins (Caucasian, Black, Hispanic, other) in a population pharmacokinetic analysis of HIV-infected patients from POWER 1 and 2 [4].

**Age**

Population pharmacokinetic analyses showed that there was no marked difference in the AUC$_{24h}$ for darunavir between the different age categories of 18–40, 40–50 and >50 years in HIV-infected patients from POWER 1 and 2, suggesting no dose modifications are required in older patients; however, there was a low number of patients aged >65 years in this analysis [4]. In general, caution should be exercised in the administration of darunavir/r to elderly patients, reflecting the greater frequency of reduced hepatic function and of concomitant disease or other drug therapy.

The pharmacokinetic profile of darunavir in combination with low-dose ritonavir has not been established in paediatric patients; this is currently under evaluation [4].

**Co-infection with hepatitis B or C virus**

Analysis of 24-week data from the POWER 1 study in 31 HIV-infected patients indicated that hepatitis B and/or C virus coinfection status had no apparent effect on the AUC$_{24h}$ for darunavir [4].

**Hepatic impairment**

As darunavir is primarily metabolized and eliminated by the liver, patients with hepatic impairment might be at risk of increased plasma concentrations of darunavir/r. The results of a multiple-dose study demonstrated that patients with mild or moderate hepatic impairment have an AUC for darunavir similar to that obtained for patients without hepatic impairment (unpublished data). Dose adjustments are not necessary in individuals with mild or moderate liver impairment, and usual clinical monitoring of these individuals receiving darunavir/r is considered adequate. This recommendation is consistent with recommendations for other PIs, as they are also metabolized by hepatic cytochrome CYP3A isoenzymes [18]. The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been studied.

**Renal impairment**

Moderate renal impairment is not expected to have a major effect on plasma concentration–time profiles for darunavir, as results from a mass balance study indicate that following darunavir/r administration only 7.7% of darunavir is recovered unchanged in urine [13]. A population pharmacokinetic analysis of 20 HIV-infected patients with mild/moderate impaired renal function (creatinine clearance 30–60 ml/min) showed that the AUC for darunavir was not significantly affected. There are no pharmacokinetic data available in HIV-infected patients with severe renal
impairment or end-stage renal disease. However, as the renal clearance of darunavir is limited (7.7% excreted unchanged in urine), a decrease in total body clearance is not expected in these patients. Given that darunavir and ritonavir are highly bound to plasma proteins, it is unlikely they will be removed by haemodialysis or peritoneal dialysis [4].

**Drug interaction studies**

The treatment of HIV-infected individuals with highly active antiretroviral therapy (HAART) requires long-term administration of combinations of multiple antiretroviral drugs [1]. In addition, these patients frequently need to co-administer other medications, such as those used to prevent or treat opportunistic infections, those to treat other concomitant illnesses or drugs to manage antiretroviral side effects. Given this unavoidable multidrug therapy, there is a potential for complex and difficult-to-predict drug interactions, some of which may be clinically significant [19]. As many of the drugs used by HIV-infected individuals have similar metabolic pathways, and also inhibit or induce enzymes used in these pathways, knowledge of drug interactions is essential. Although most pharmacokinetic interactions pose challenging clinical problems and therefore can be difficult to manage [15], not all drug–drug interactions are undesirable: the well-established pharmacokinetic enhancement effect of PIs by ritonavir illustrates how a drug–drug interaction can be beneficial. The potential for drug–drug interactions with darunavir/r has been investigated in numerous studies conducted in healthy volunteers and HIV-infected patients [20]. Results from these studies are described in the sections below and summarized in Table 1 [4,12,21–40].

Although many of the studies described below were conducted using lower doses of darunavir/r than those currently used in clinical practice, there has been extensive pharmacokinetic/pharmacodynamic (PK/PD) analysis of darunavir/r at doses of 400/100 mg once daily, 800/100 mg once daily, 400/100 mg twice daily and 600/100 mg twice daily in 468 POWER 1 and 2 treatment-experienced patients. These studies found that darunavir AUC and C_{Oh} (trough concentration) values increased less than dose proportionally [41]. The PK/PD studies supported the selection of darunavir/r 600/100 mg twice daily for the treatment of HIV-1 infected treatment-experienced patients. Where a lower dose was used in an interaction study it is possible that the magnitude of the interaction may be slightly different with the licensed dose, but currently there is no evidence to suggest any substantive difference and consequently we would predict similar results.

In all the drug interaction studies to date, both ritonavir and darunavir concentrations were measured and results are reported in each of the cited publications; however, no formal cross-study comparison of ritonavir concentrations have been made. It is worth noting that doses of ritonavir higher than 100 mg do not further increase darunavir concentrations [13] and, consequently, any increase in ritonavir concentrations due to the co-administered drug would not be expected to affect darunavir/r concentrations. Thus, it is predicted that any changes in darunavir concentrations represent a direct effect of the co-administered drug on darunavir disposition. Doses lower than 100 mg ritonavir have not been studied with darunavir and it therefore cannot be excluded that if the co-administered drug decreases ritonavir it might also affect darunavir pharmacokinetics.

**Drug interactions with antiretrovirals: PIs**

Both darunavir and ritonavir are inhibitors of and substrates for CYP3A [4] and, as all of the other currently available PIs act as substrates or inhibitors and/or inducers of the CYP3A isoenzymes [42], there is the potential that they will affect the plasma concentrations of each other when used in combination. In addition, PIs are substrates for, and modulators of, P-gp and other transport proteins; therefore, further drug–drug interactions are possible [43]. It is important to be able to predict drug interactions of darunavir/r with other PIs, as future therapies could potentially include double ritonavir-enhanced PI regimens. However, data from recent clinical trials have shown no benefit of double ritonavir-enhanced over single ritonavir-enhanced PIs and in vitro studies have also shown varying types of interaction [44,45]. Several studies have examined darunavir/r drug interactions with PIs in healthy volunteers and HIV-infected patients; those in the former provide an insight into the possibility of interactions among HIV-infected individuals.

**Atazanavir**

The potential interaction between atazanavir/r (300/100 mg once daily) and darunavir/r (400/100 mg twice daily) has been evaluated in HIV-negative, healthy individuals [21]. The AUC for darunavir was not affected when co-administered with atazanavir, and vice versa. Thus, dosage adjustments of either drug in patients receiving darunavir/r and atazanavir are not considered necessary. In contrast, it might be necessary to make alterations to the drug dosage or timing of administration for other ritonavir-enhanced PIs when used in combination with atazanavir.
Table 1. Summary of drug interaction studies of darunavir with low-dose ritonavir (darunavir/r)

<table>
<thead>
<tr>
<th>Co-administered drug</th>
<th>Dose/schedule</th>
<th>Number of individuals</th>
<th>AUC, LSM (90% CI)*</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir [21]</td>
<td>300 mg qd (+ritonavir 100 mg qd in combination)</td>
<td>13</td>
<td>↔ 1.08 (0.94–1.24) ↔ 1.03 (0.94–1.12)</td>
<td>No clinically relevant interaction</td>
</tr>
<tr>
<td>Indinavir [22]</td>
<td>800 mg bid</td>
<td>9</td>
<td>↑ 1.23 (1.06–1.42) ↑ 1.24 (1.09–1.42)</td>
<td>Indinavir dose reduction from 800 to 600 mg bid in case of intolerance</td>
</tr>
<tr>
<td>Lopinavir [23]</td>
<td>400 mg bid (+ritonavir 100 mg bid) 1,200/100 or 600/100 mg bid</td>
<td>29</td>
<td>↔ 1.09 (0.86–1.37) ↓ 0.62 (0.53–0.73)</td>
<td>Combination not recommended</td>
</tr>
<tr>
<td>Saquinavir [24]</td>
<td>1,000 mg bid (+ritonavir 100 mg bid in combination)</td>
<td>14</td>
<td>↔ 0.94 (0.76–1.17) ↓ 0.74 (0.63–0.86)</td>
<td>Combination not recommended</td>
</tr>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir [4,25]</td>
<td>300 mg qd</td>
<td>12</td>
<td>↑ 1.22 (1.10–1.35) ↑ 1.21 (0.95–1.54)</td>
<td>No clinically relevant interaction anticipated but monitor renal function</td>
</tr>
<tr>
<td>Didanosine [26]</td>
<td>400 mg qd</td>
<td>17</td>
<td>↔ 0.91 (0.75–1.10) ↔ 1.01 (0.95–1.07)</td>
<td>No clinically relevant interaction</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz [27]</td>
<td>600 mg qd</td>
<td>12</td>
<td>↑ 1.21 (1.08–1.36) ↓ 0.87 (0.75–1.01)</td>
<td>No clinically relevant interaction anticipated but monitor for CNS toxicity</td>
</tr>
<tr>
<td>Etravirine [29]</td>
<td>100 mg bid</td>
<td>32</td>
<td>↓ 0.63 (0.54–0.73) ↔ 1.06 (1.00–1.13)</td>
<td>No clinically relevant interaction anticipated</td>
</tr>
<tr>
<td>Nevirapine [28]</td>
<td>200 mg bid</td>
<td>8</td>
<td>↑ 1.27 (1.12–1.44) ↑ 1.24 (0.97–1.57)</td>
<td>No clinically relevant interaction anticipated</td>
</tr>
<tr>
<td><strong>Fusion inhibitor</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Enfuvirtide [30]</td>
<td>90 mg (1 ml) bid (subcutaneous injection) 600/100 mg bid</td>
<td>292</td>
<td>ND ND</td>
<td>No clinically relevant interaction</td>
</tr>
<tr>
<td><strong>Integrase inhibitor</strong></td>
<td></td>
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</tr>
<tr>
<td>Elvitegravir [31]</td>
<td>125 mg qd (+ritonavir 100 mg qd in combination) 600/100 mg bid</td>
<td>20</td>
<td>↔ 111* (99.1–122) ↔ 88.7* (82.3–95.6)</td>
<td>No clinically relevant interaction</td>
</tr>
<tr>
<td><strong>HMG-CoA reductase inhibitors</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Atorvastatin [32]</td>
<td>40 mg qd alone and 10 mg qd in combination 300/100 mg bid</td>
<td>15</td>
<td>↑ Marked increase a 0.85 b (0.76–0.97) ND</td>
<td>Atorvastatin starting dose 10 mg qd titrated to clinical response</td>
</tr>
<tr>
<td>Pravastatin [33]</td>
<td>40 mg qd</td>
<td>14</td>
<td>↑ 1.81 (1.23–2.66) ND</td>
<td>Start at lowest dose and titrate to clinical response</td>
</tr>
<tr>
<td><strong>Gastric pH modifiers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole [34]</td>
<td>20 mg qd</td>
<td>16</td>
<td>ND ND</td>
<td>No clinically relevant interaction</td>
</tr>
</tbody>
</table>
### Table 1. continued.

<table>
<thead>
<tr>
<th>Co-administered drug [reference]</th>
<th>Dose/schedule</th>
<th>Number of individuals</th>
<th>AUC, LSM (90% CI)*</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine [34]</td>
<td>150 mg bid</td>
<td>400/100 mg bid</td>
<td>ND</td>
<td>↔</td>
</tr>
<tr>
<td>Narcotic analgesic</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>R-methadone [35]</td>
<td>55–150 mg qd</td>
<td>600/100 mg bid</td>
<td>↓ 0.84† (0.78–0.91)</td>
<td>ND</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
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</tr>
<tr>
<td>Ethinyl estradiol [36]</td>
<td>35 μg (with 1 mg norethindrone)</td>
<td>600/100 mg bid</td>
<td>↓ 0.56 (0.50–0.63)</td>
<td>ND</td>
</tr>
<tr>
<td>Norethindrone [36]</td>
<td>1 mg (with 35 μg ethinyl estradiol)</td>
<td>600/100 mg bid</td>
<td>↓ 0.86 (0.75–0.98)</td>
<td>ND</td>
</tr>
<tr>
<td>PDE-5 inhibitors</td>
<td></td>
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</tr>
<tr>
<td>Sildenafil [37]</td>
<td>100 mg qd alone and 25 mg qd in combination</td>
<td>400/100 mg bid</td>
<td>↑Marked increase 0.97‡ (0.86–1.09)</td>
<td>ND</td>
</tr>
<tr>
<td>Mood-disorder drugs</td>
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<tr>
<td>Paroxetine [38]</td>
<td>20 mg qd</td>
<td>400/100 mg bid</td>
<td>↓ 0.61 (0.56–0.66)</td>
<td>↔</td>
</tr>
<tr>
<td>Sertraline [38]</td>
<td>50 mg qd</td>
<td>400/100 mg bid</td>
<td>↓ 0.51 (0.46–0.58)</td>
<td>↔</td>
</tr>
<tr>
<td>Anti-infective and antifungal agents</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Clarithromycin [39]</td>
<td>500 mg bid</td>
<td>400/100 mg bid</td>
<td>↑ 1.57 (1.35–1.84)</td>
<td>↔</td>
</tr>
<tr>
<td>Ketoconazole [40]</td>
<td>200 mg bid</td>
<td>400/100 mg bid</td>
<td>↑ 3.12 (2.65–3.68)</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Digoxin [12]</td>
<td>0.4 mg qd</td>
<td>600/100 mg bid</td>
<td>↑ 1.35 (1.00–1.82)</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Based on least squares mean (LSM) ratio of area under the plasma concentration–time curve (AUC) values. †HIV-1-infected patients. ‡Determined by geometric mean ratio. The mean AUC for atorvastatin at 40 mg alone was similar to that of 10 mg when combined with darunavir/r (R)-isomer. The mean AUC for atorvastatin at 40 mg alone was similar to that of 25 mg when combined with darunavir/r, bid, twice daily; CI, confidence interval; CNS, central nervous system; ND, not determined; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; qd, once daily. ↔, no change; ↑, increase; ↓, decrease.
**Indinavir**

The co-administration of indinavir (800 mg twice daily) and darunavir/r (400/100 mg twice daily) was investigated in HIV-negative healthy volunteers [22]. The mean AUC for darunavir and indinavir was increased by 24% and 23%, respectively, when these drugs were combined. These increases are deemed not to be clinically significant, and both can be co-administered without dose adjustments. Dose reductions of indinavir from 800/100 mg twice daily to 600/100 mg twice daily may be warranted, however, if the known indinavir side effect of gastrointestinal intolerance occurs [46]. This result is consistent with those from studies of the combined use of indinavir and currently available ritonavir-enhanced PIs.

**Lopinavir**

Lopinavir/r (400/100 mg twice daily) was administered in combination with darunavir/r (1,200/100 mg or 600/100 mg twice daily) in a study in HIV-infected patients [23]. Despite a twofold increase in darunavir dose, from 600 mg to 1,200 mg twice daily, mean values of AUC$_{12h}$, C$_{max}$ (maximum plasma concentration), C$_{trough}$ (trough plasma concentration) and C$_{min}$ (minimum plasma concentration) for darunavir were considerably reduced (by ~40% for AUC$_{12h}$ compared with 600 mg twice daily) by co-administration of lopinavir/r 400/100 mg twice daily. In contrast, lopinavir AUC$_{12h}$, C$_{max}$, C$_{max}$ and C$_{0h}$ were unaltered or slightly increased when lopinavir/r 400/100 mg twice daily was co-administered with darunavir/r 1,200/100 mg twice daily. Given the substantial reduction in pharmacokinetic parameters for darunavir, co-administration of darunavir/r and lopinavir/r is not recommended. The combined use of other ritonavir-enhanced PIs and lopinavir/r requires close monitoring, altering of drug dosage or timing of administration.

**Saquinavir**

The potential interaction of saquinavir/r with darunavir/r has been studied in healthy volunteers [24]. Although the mean AUC$_{12h}$ for saquinavir (1,000/100 mg twice daily) was not affected by concomitant darunavir/r use, the mean AUC for darunavir (darunavir/r 400/100 mg twice daily) was reduced by 26% and the C$_{min}$ of darunavir was reduced by 42% when co-administered in the presence of saquinavir/r. As reductions in plasma concentrations of darunavir in the presence of saquinavir/r were considered to be of clinical relevance in treatment-experienced patients, use of this combination is currently not recommended. The use of saquinavir/r with other ritonavir-enhanced PIs is permitted; however, close monitoring and alterations to the drug dosage or timing of administration may be required.

**Tipranavir**

No formal study on the interaction of darunavir/r and tipranavir has been conducted. However, as tipranavir markedly affects the AUC for other PIs, possibly through multiple mechanisms, it is likely to have an unfavourable interaction with darunavir/r and use of the combination is not recommended [47].

**Drug interactions with antiretrovirals: NNRTIs**

Efavirenz, nevirapine and etravirine are all non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are substrates for and inducers of CYP3A4 and, consequently, combined use with darunavir/r could reduce darunavir concentrations.

**Efavirenz**

Darunavir/r (300/100 mg twice daily) and efavirenz (600 mg once daily) were co-administered in a study involving 12 HIV-negative, healthy volunteers [27]. The mean AUC for efavirenz was increased by 21% in the presence of darunavir/r. Conversely, the AUC for darunavir was decreased by 13% when given with
efavirenz. These changes are unlikely to be of clinical significance, however, until additional data are available, combinations of darunavir/r and efavirenz should be used with caution. This result is consistent with those from studies of the use of efavirenz co-administered with other currently available ritonavir-enhanced PIs. The combination of efavirenz and darunavir/r is currently being evaluated further in patients who have efavirenz in their optimized background regimen in a Phase III clinical trial, TITAN.

Etravirine (TMC125)

The pharmacokinetic interaction of the investigational NNRTI, etravirine (100 and 200 mg twice daily) and darunavir/r (600/100 mg twice daily) was investigated in a study of 32 healthy volunteers [29]. With darunavir/r co-administration, the mean AUC12h for etravirine given as 100 mg twice daily was decreased by 37%; Cmax and Cmin were decreased by 32% and 49%, respectively. For etravirine 200 mg twice daily co-administered with darunavir/r, the mean AUC12h, Cmax and Cmin of etravirine were 80%, 81% and 67% greater, respectively, than etravirine 100 mg given alone twice daily. Darunavir pharmacokinetics were unchanged except a 15% increase in mean AUC12h was observed when darunavir/r was given with etravirine 200 mg twice daily. The magnitude of this interaction is comparable to etravirine interactions with other ritonavir-enhanced PIs observed in Phase IIb trials in HIV-1-infected patients. Darunavir/r can be co-administered with etravirine without dose adjustments.

Nevirapine

The two-way pharmacokinetic interaction between darunavir/r (400/100 mg twice daily) and nevirapine (200 mg twice daily) was investigated in HIV-infected patients who were on stable nevirapine therapy and taking ≥ 2 NRTIs [28]. Co-administration of nevirapine with darunavir/r caused a 24% increase in the mean AUC for darunavir compared with historical data for darunavir/r alone, and the mean AUC for nevirapine was increased by 27% when combined with darunavir/r. These mean AUC changes for nevirapine and darunavir are unlikely to be of clinical significance, and darunavir/r and nevirapine may be co-administered with no dose adjustment. This finding is contrary to those from other studies on the use of ritonavir-enhanced PIs with nevirapine, where altering the drug dosage or timing of administration may be required.

Drug interactions with antiretrovirals: entry inhibitors

Efavirenz is an antiretroviral drug from the fourth and newest licensed class of drugs available for HIV treatment, the entry inhibitors. Given the additional efficacy benefits observed when enfuvirtide is co-administered with an antiretroviral regimen compared with an antiretroviral drug alone [52], it is likely that enfuvirtide will be combined with darunavir/r in the treatment of HIV-infected highly treatment-experienced patients. Enfuvirtide is not metabolized by CYP450 enzymes, hence no drug–drug interaction would be expected when it is co-administered with darunavir/r or other agents that are metabolized by the CYP450 enzyme system. A possible pharmacokinetic interaction was investigated by population pharmacokinetic analysis in 292 treatment-experienced, HIV-infected patients from the POWER 3 analysis [30]. The mean AUC for darunavir was unaffected when darunavir/r (600/100 mg twice daily) was combined with enfuvirtide; therefore, no dose adjustment is needed. With the exception of tipranavir (which is given with 200 mg of ritonavir and where monitoring, altering of drug dosage or timing of administration may be required), the same findings were reported with the use of other ritonavir-enhanced PIs and enfuvirtide.

Drug interactions with other drugs commonly used in HIV-infected patients

Patients with HIV receiving darunavir/r are likely to receive drugs for other co-morbidities, especially given their vulnerability to opportunistic infections, thus it is important to investigate how such drugs interact with darunavir/r and to determine if therapeutic drug levels are compromised.

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors are drugs used to lower cholesterol. A study of the interaction between darunavir/r (300/100 mg twice daily) and the HMG-CoA reductase inhibitor atorvastatin (10 mg or 40 mg once daily) in healthy volunteers indicated that low-dose atorvastatin plus darunavir/r gives an atorvastatin AUC that is 15% lower than atorvastatin 40 mg once daily alone [32]. As atorvastatin metabolism is CYP3A4-mediated, this result is expected and is presumably driven by the ritonavir component of darunavir/r. When these drugs are combined, the
The oral synthetic opioid methadone is given as a racemic mixture of \((R)-\) and \((S)\)-isomers, although only the former is the active isomer. As ritonavir is a known inducer of the metabolism of methadone, a decrease in the AUC for methadone is expected when methadone and darunavir\(r\) are combined [53]. The effect of darunavir\(r\) (600/100 mg twice daily) on the pharmacokinetics of methadone was investigated in 16 HIV-negative opioid-dependent volunteers, receiving once daily methadone maintenance therapy at a stable individualized dose of 55–200 mg [35]. The mean AUC for \((R)\)-methadone was decreased by 16% when combined with darunavir\(r\), as compared with \((R)\)-methadone alone. No methadone dose adjustment was required in this study. Therefore, no prior dose adjustment of methadone is required when methadone and darunavir\(r\) are combined; however, patients should be monitored for opiate abstinence syndrome [54]. The observations and recommendations in this study are consistent with those for use of methadone with other ritonavir-enhanced PIs.

**Oral contraceptives/oestrogens**

The possibility of contraceptive failure is a general concern for HIV-infected women being treated with HAART who are also receiving oestrogen and progestin (a synthetic progestogen). The effect of darunavir\(r\) (600/100 mg twice daily) on the pharmacokinetics of the combined oral contraceptive, ethinyl estradiol/norethindrone (0.035/1 mg once daily) was investigated in 19 HIV-negative healthy volunteers [36]. The mean AUC for ethinyl estradiol was decreased by 44% when combined with darunavir\(r\) compared with ethinyl estradiol alone. Thus, it is recommended that alternative or additional contraceptive measures are used when darunavir\(r\) and the above oral contraceptives are combined. Ethinyl estradiol is metabolized by CYP3A and glucuronoyl transferase; hence, this finding is consistent with other drugs (such as PIs) that affect these enzymes and lead to loss of ethinyl estradiol effectiveness [55,56].

**Phosphodiesterase type-5 inhibitors**

Sildenafil is a phosphodiesterase type-5 (PDE-5) inhibitor used for the treatment of erectile dysfunction. It is converted to its primary metabolite, N-desmethyl-sildenafil, primarily by the isoenzyme CYP3A4. As ritonavir is a potent inhibitor of this isoenzyme, combined use of darunavir\(r\) and sildenafil may reduce the metabolism of sildenafil and could cause an increase in concentration. Indeed, when these three drugs were taken concomitantly by 16 HIV-negative healthy male volunteers, the mean AUC for sildenafil was increased by fourfold compared with sildenafil alone [37]. Thus, when co-administered with darunavir\(r\), the recommended dose of sildenafil is 25 mg over a 48-h period (instead of 100 mg). These findings are consistent with those found with other PIs [57] and can be used to provide dosing recommendations for other PDE-5 inhibitors that are also CYP3A substrates (vardenafil [2.5 mg once daily in 72 h] and tadalafil [10 mg once daily in 72 h] when co-administered with darunavir\(r\)).
HIV-negative healthy volunteers [38]. The mean AUC for sertraline and paroxetine was reduced by 49% and 39%, respectively, when co-administered in the presence of darunavir/r, without affecting the AUC for darunavir. If clinically indicated, sertraline or paroxetine can be co-administered with darunavir/r. Although previous studies failed to show a correlation between SSRI concentrations and mood-disorder response [59,60], clinical monitoring and, if needed, dose titration of the SSRI is recommended. These findings are similar to those found for fosamprenavir/r.

**Anti-infectives and antifungals**

Clarithromycin and ketoconazole are frequently prescribed for prophylaxis and the treatment of bacterial and fungal infections, respectively, which are common opportunistic infections in HIV-infected patients. Both drugs inhibit CYP3A4 and, therefore, are associated with a number of drug interactions.

A study of the interaction between darunavir/r (400/100 mg twice daily) and clarithromycin (500 mg twice daily) in HIV-negative healthy volunteers indicates that there is a 57% increase in the AUC for clarithromycin [39]. Conversely, the AUC for darunavir was decreased by 13% when given with clarithromycin. Plasma concentrations of the active metabolite, 14-hydroxy-clarithromycin, were reduced to undetectable levels when clarithromycin was combined with darunavir/r, probably due to the inhibition of CYP3A by darunavir. No dose adjustments are necessary for patients with normal renal function; however, patients with renal impairment should have their dose adjusted to that recommended for patients taking clarithromycin alone [61]. The dose of clarithromycin should be reduced by 50% for patients with creatinine clearance of 30–60 ml/min, and by 75% for patients with creatinine clearance of <30 ml/min [61]. This finding is generally similar to those in studies of other ritonavir-enhanced PIs and ketoconazole.

When ketoconazole (200 mg twice daily) and darunavir/r (400/100 mg twice daily) were co-administered in HIV-negative healthy volunteers, the mean AUC for ketoconazole was increased by 212% compared with administration of ketoconazole alone; the mean AUC for darunavir was increased by 42% versus darunavir/r alone [40]. The increase in darunavir AUC was not considered to be clinically relevant; nonetheless, given the changes in the AUC for ketoconazole, the maximum daily dose of ketoconazole should be 200 mg when these drugs are combined. This recommendation is similar to that for other ritonavir-enhanced PIs and ketoconazole.

**Cardiac glycosides**

The two-way pharmacokinetic interaction between darunavir/r (600/100 mg twice daily) and the cardiac glycoside digoxin (0.4 mg once daily) was investigated in HIV-negative healthy volunteers [12]. When these two drugs were combined the mean AUC for digoxin was increased by 77%, with substantial interindividual variability. As a consequence of this interaction, it is recommended that the lowest possible dose of digoxin should initially be used, with careful titration of dose and monitoring of digoxin concentrations.

**Other commonly prescribed medications**

As described above, darunavir and ritonavir are both inhibitors of the CYP3A subfamily. Therefore, co-administration of darunavir/r with drugs metabolized primarily by CYP3A may increase plasma concentrations of such drugs, thus increasing and/or prolonging their therapeutic effect and adverse events. Consequently, drugs highly dependent on CYP3A for clearance are contraindicated for use with darunavir/r; these include the antihistamines astemizole and terfenadine, the ergot derivatives dihydroergotamine, ergonovine, ergotamine and methylergonovine, certain gastrointestinal motility agents, for example, cisapride, certain neuroleptics, pimozide, and the sedative/hypnotics midazolam and triazolam [4].

As darunavir and ritonavir are both metabolized by CYP3A, co-administration of darunavir/r with drugs that induce CYP3A could increase clearance of darunavir and ritonavir, and decrease their plasma concentrations and therapeutic effect. Therefore, several drugs should not be co-administered with darunavir/r: the anticonvulsants carbamazepine, phenobarbital and phenytoin; rifampin and St. John’s Wort. In addition, we consider that systemic dexamethasone should be started at the lowest possible dose, as it induces CYP3A and can thereby potentially decrease darunavir plasma concentrations [4].

**Conclusions**

Darunavir is a new PI that represents a substantial advancement in the treatment of treatment-experienced HIV-infected patients. The pharmacokinetics of darunavir/r have been extensively studied in numerous Phase I studies as part of the clinical development programme of darunavir. In addition, the potential for interactions of darunavir/r with other drugs are well characterized and results from the studies outlined in this article can be used as guidance for the use of darunavir/r with other agents.

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