Pharmacokinetics and pharmacodynamics of boosted once-daily darunavir

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The ability to dose antiretroviral agents once daily simplifies the often complex therapeutic regimens required for the successful treatment of HIV infection. Thus, once-daily dosing can lead to improved patient adherence to medication and, consequently, sustained virological suppression and reduction in the risk of emergence of drug resistance. Several trials have evaluated once-daily darunavir/ritonavir in combination with other antiretrovirals (ARTEMIS and ODIN trials) or as monotherapy (MONET, MONO1 and PROTEA trials) in HIV-1-infected adults. Data from ARTEMIS and ODIN demonstrate non-inferiority of once-daily darunavir/ritonavir against a comparator and, together with pharmacokinetic data, have established the suitability of once-daily darunavir/ritonavir for treatment-naive and treatment-experienced patients with no darunavir resistance-associated mutations. The findings of ARTEMIS and ODIN have led to recent updates to treatment guidelines, whereby once-daily darunavir/ritonavir, given with other antiretrovirals, is now a preferred treatment option for antiretroviral-naive adult patients and a simplified treatment option for antiretroviral-experienced adults who have no darunavir resistance-associated mutations. Once-daily dosing with darunavir/ritonavir is an option for treatment-naive and for treatment-experienced paediatric patients with no darunavir resistance-associated mutations based on the findings of the DIONE trial and ARIEL substudy. This article reviews the pharmacokinetics, efficacy, safety and tolerability of once-daily boosted darunavir. The feasibility of darunavir/ritonavir monotherapy as a treatment approach for some patients is also discussed. Finally, data on a fixed-dose combination of 800/150 mg of darunavir/cobicistat once daily are presented, showing comparable darunavir bioavailability to that obtained with 800/100 mg of darunavir/ritonavir once daily.

Keywords: antiretroviral, HIV protease inhibitors, pharmacology

Introduction

Darunavir is an HIV protease inhibitor (PI) with in vitro activity against wild-type and PI-resistant HIV isolates.1–3 Once-daily darunavir is approved for use in combination with low-dose ritonavir (darunavir/ritonavir) and other antiretrovirals for HIV-1-infected, treatment-naive adults and adolescents at a dose of 800/100 mg. It is also approved in children using a weight-based dose as well as for treatment–experienced patients who have no darunavir resistance-associated mutations (RAMs). Darunavir/ritonavir at 600/100 mg twice daily is approved for use in treatment–experienced adults with darunavir RAMs and in children aged ≥3 years using a weight-based dose. Darunavir when boosted with low-dose ritonavir has a relatively long elimination half-life,4 indicating its potential suitability for once-daily dosing in the treatment of HIV-infected patients. In addition to simplifying the regimen, once-daily dosing is preferred to twice-daily dosing of darunavir/ritonavir as it halves the required daily dose of ritonavir (from 200 to 100 mg), thereby reducing the risk and/or severity of ritonavir-associated side effects such as gastrointestinal and lipid disorders.5 During the clinical development of darunavir/ritonavir, both once-daily and twice-daily dosing schedules have been evaluated in a range of patient populations with HIV-1 infection.

This review considers the pharmacokinetic and pharmacodynamic characteristics of darunavir/ritonavir in HIV-1-infected patients that support once-daily darunavir/ritonavir dosing and also explores the potential of cobicistat as an alternative pharmacoenhancer to ritonavir.

Pharmacokinetic characteristics supporting once-daily dosing of ritonavir-boosted darunavir

Absorption, distribution, metabolism and excretion of darunavir

Orally administered darunavir is rapidly absorbed, reaching peak plasma concentrations within 2.5–4 h. The absorption of...
darunavir appears to involve an active transport process and darunavir has been shown to be a substrate of P-glycoprotein. At clinically relevant darunavir plasma concentrations, mean plasma protein binding was 95% in HIV-1-negative healthy male volunteers. Darunavir is mostly bound to α1-acid glycoprotein and, to a lesser extent, to albumin.

Initial data demonstrate penetration of darunavir into the CNS, although once-daily darunavir/ritonavir dosing led to lower darunavir CSF concentrations than twice-daily dosing. Darunavir is predominantly unbound in the CSF (93.5%) and unbound concentrations have been shown to exceed the median IC90 for wild-type HIV by a median of 20.6-fold in 16 patients who were treated with 600/100 mg of darunavir/ritonavir twice daily.

Darunavir is extensively and almost exclusively metabolized by cytochrome P450 (CYP) 3A. Metabolism studies performed in vitro in human liver microsomes showed that darunavir is metabolized into three primary metabolites (M19 (by carboxamide hydrolysis), M23 (by aliphatic hydroxylation) and M29 (by aromatic hydroxylation)) and three minor metabolites (M27 and M28 (by alicyclic hydroxylation) and M6 (by a different pathway)). While metabolism primarily occurs in the liver, some CYP3A metabolism also occurs in the intestine.

**Impact of low-dose ritonavir on darunavir bioavailability**

As for other HIV PIs that are CYP3A substrates, administration with low-dose ritonavir as a pharmacokinetic enhancer leads to clinically significant increases in the plasma concentrations of darunavir. Ritonavir has a potent inhibitory effect on CYP3A, reducing the metabolism of HIV PIs such as darunavir with consequent increase in systemic exposure. Ritonavir is also an inhibitor of P-glycoprotein. The metabolism of darunavir in the presence (boosted) or absence (unboosted) of low-dose ritonavir was studied in HIV-1-negative healthy male volunteers (n = 8) following a single oral dose of 400 mg of 14C-labelled darunavir. The mean blood-to-plasma concentration ratio of total radioactivity ranged from 0.68 to 0.74 in volunteers with boosted darunavir and from 0.59 to 0.70 in volunteers with unboosted darunavir, showing that the radioactivity in blood was mainly distributed to plasma. In volunteers receiving unboosted darunavir, the level of radioactivity had fallen below the lower limit of detection in blood samples obtained 4 h after dosing, while in volunteers receiving boosted darunavir it remained detectable in samples taken after 24 h.

By reducing the metabolism of the parent drug, coadministration with ritonavir results in an ~11-fold increase in its exposure. Based on the exposure ratio for the parent drug and total radioactivity, the parent drug accounted for ~37% and 68% of the total radioactivity in the plasma of individuals receiving unboosted and boosted darunavir, respectively. Furthermore, 49% of the darunavir dose was excreted unchanged in volunteers receiving boosted drug, while in volunteers receiving unboosted darunavir the parent drug accounted for only 8% of the dose. These results indicate a marked reduction in the metabolism of darunavir when administered together with ritonavir, with consequent increase in oral bioavailability.

Increased darunavir bioavailability in the presence of ritonavir has been confirmed in two Phase I studies in HIV-negative healthy volunteers, which evaluated the plasma concentration–time profiles of darunavir given orally or intravenously with or without coadministration of ritonavir. In the first study (TMC114-C114), the mean ± SD systemic clearance of unboosted and boosted darunavir was 32.8 ± 7.0 and 5.9 ± 2.1 L/h, respectively. In the presence of ritonavir, the oral bioavailability of darunavir was increased >2-fold, from 37% to 82%. This indicated that first-pass elimination of darunavir was almost completely inhibited in the presence of ritonavir. Together with the 5-fold inhibition of the systemic clearance of darunavir, the net result was an ~14-fold increase in systemic exposure when 600 mg of darunavir was given orally in combination with 100 mg of ritonavir twice daily. In the second study (TMC114-C112), administration of 200 mg of ritonavir once daily compared with 100 mg of ritonavir twice daily increased the exposure to ritonavir, but this did not lead to increased exposure to darunavir. For both dosing regimens of darunavir/ritonavir (600/200 mg once daily and 300/100 mg twice daily), exposure to darunavir was generally comparable. Based on these findings, a coadministered ritonavir dose of 100 mg was selected for pharmacokinetic enhancement of darunavir. Lower doses of ritonavir (i.e. 20 and 50 mg) compared with 100 mg were evaluated in a subsequent study (TMC114-C181, NCT00744887). Results from this study suggest that 50 mg of ritonavir provides comparable darunavir exposure [i.e. area under the plasma concentration–time curve over 24 h (AUC24)] but lower minimum plasma concentration (Cmin) and C0 values (32% and 25%, respectively); 20 mg of ritonavir was insufficient to boost darunavir to the same magnitude as 100 mg of ritonavir.

Two randomized Phase I dose-ranging trials have evaluated the pharmacokinetics of various dosing regimens of darunavir in HIV-1-negative healthy volunteers. One was a placebo-controlled, double-blind trial of unboosted darunavir given at doses of 400 mg twice daily, 800 mg twice daily, 800 mg three times daily and 1200 mg three times daily. In the second, open-label trial, darunavir/ritonavir was given at once-daily doses of 200/100, 400/100, 600/200 or 1200/200 mg or a twice-daily dose of 300/100 mg. In both of these trials, darunavir was administered as a PEG400-containing oral solution that was eventually abandoned during the development programme. In this formulation, darunavir was rapidly absorbed, with a time to maximum plasma concentration (Cmax) within 3 h for both boosted and unboosted darunavir. For unboosted darunavir, the median Cmin, Cmax and AUC24 at day 14 ranged from 18 ng/mL, 2040 μg/mL and 7020 ng-h/mL for the lowest dosage to 142 ng/mL, 8040 μg/mL and 48600 ng-h/mL, respectively, for the highest dosage. In the ritonavir-boosted trial, the median Cmin, Cmax and AUC24 at day 14 ranged from 358 ng/mL, 1420 μg/mL and 16400 ng-h/mL for the lowest dosage to 1010 ng/mL, 5240 μg/mL and 54 100 ng-h/mL, respectively, for the highest dosage. With once-daily regimens of darunavir/ritonavir, the Cmax of darunavir apparently increased linearly with increasing darunavir dose, while the Cmin increased less than dose proportionally.

The time taken for darunavir plasma concentrations to fall below the pre-specified protein binding-adjusted EC50 value of 55 ng/mL for wild-type HIV-1 has been evaluated in a Phase I, open-label, parallel-group trial (TMC114-C137). In this trial, five groups of HIV-negative healthy volunteers were treated for 7 days with darunavir/ritonavir according to the following treatment regimens: once-daily doses of 400/100 mg, 800/100 mg or 1200/100 mg; or twice-daily doses of 400/100 or 800/100 mg. Steady-state plasma pharmacokinetic profiles of
Table 1. Comparison of pharmacokinetics of 800 mg of darunavir when coadministered with 150 mg of cobicistat or 100 mg of ritonavir.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cobicistat (geometric mean and 90% CI)</th>
<th>Ritonavir (geometric mean and 90% CI)</th>
<th>Geometric mean ratio (%) [mean (CV%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{24} (ng·h/mL)</td>
<td>81.100 (31.0)</td>
<td>80.000 (34.0)</td>
<td>102 (97.4–106)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>7740 (21.8)</td>
<td>7460 (20.3)</td>
<td>103 (100–106)</td>
</tr>
<tr>
<td>C_{24} (ng/mL)</td>
<td>1330 (66.8)</td>
<td>1870 (83.3)</td>
<td>69.4 (59.0–81.7)</td>
</tr>
<tr>
<td>C_{0} (ng/mL)</td>
<td>2400 (50.7)</td>
<td>2480 (34.3)</td>
<td>89.4 (80.4–99.4)</td>
</tr>
</tbody>
</table>

CV, coefficient of variation.

darunavir were determined for up to 120 h post-final dose on day 7. The mean pre-dose plasma concentration (C_{0}) for all treatment groups exceeded 55 ng/mL and remained above this value for ≥48 h after the last dose while ritonavir dosing was continued (Figure S1, available as Supplementary data at JAC Online). These results indicate that darunavir/ritonavir at a once-daily dosing frequency may maintain sufficient darunavir plasma concentrations for adequate wild-type viral suppression. Further studies in HIV-infected patients have shown that intracellular concentrations of darunavir are comparable to, or higher than, those in plasma, with an intracellular-to-plasma concentration ratio ranging from 1.32 to 5.6.

Impact of cobicistat on darunavir bioavailability
Cobicistat (GS-9350) is a selective and potent inhibitor of CYP3A with no antiviral activity. A Phase I study showed that cobicistat exposure increased more than proportionally with increasing dosage and time possibly from auto-induction. Cobicistat exhibited a short plasma half-life of 2–8 h at all the dose levels studied (50, 100, 200 and 300 mg multiple dosing). The study also showed potent inhibition of the CYP3A probe substrate midazolam apparent clearance (95% reduction), with 200 mg of cobicistat once daily giving a similar effect to 100 mg of ritonavir once daily.

Initial pharmacokinetic data have demonstrated comparable bioavailability of darunavir (AUC_{24}, C_{max} and C_{0}) between 800/150 mg of darunavir/cobicistat once daily when dosed as single agents compared with 800/100 mg of darunavir/ritonavir once daily (Table 1). A fixed-dose combination of 800/150 mg of darunavir/cobicistat tablets is being developed. Two candidate tablet formulations of 800/150 mg of darunavir/cobicistat have been tested relative to 800/100 mg of darunavir/ritonavir. Both candidate formulations were comparable to 800/100 mg of darunavir/ritonavir in terms of darunavir C_{max} and AUC_{24}. Least-squares mean ratios were between 0.97 and 1.00 and all 90% CIs were within 80.00%–125.00%. Darunavir C_{0} and C_{max} were modestly (26%–35%) lower when boosted with cobicistat relative to ritonavir. One of the two candidate fixed-dose combination tablets was chosen for further development. This formulation has been shown to be bioequivalent to the coadministered single agents.

Effect of food intake on darunavir bioavailability
Food intake is known to influence the bioavailability of darunavir. In HIV-1-negative healthy volunteers, a single dose of 400 mg of darunavir was coadministered with 100 mg of ritonavir twice daily (from 2 days before until 2 days after darunavir) following one of four different types of meal (standard breakfast, high-fat breakfast, protein-rich nutritional drink or croissant with coffee) or under fasted conditions. Darunavir/ritonavir administered in the fasting state resulted in ~30% lower plasma concentrations of darunavir compared with administration after a standard meal. These findings may reflect the effect of reduced ritonavir bioavailability in the fasted state compared with administration after a meal, which has been shown in a second study. Exposure to darunavir and ritonavir were not, however, affected by the type of food. A food effect has also been observed for darunavir/ritonavir. Darunavir with cobicistat or ritonavir should therefore be taken with food, but the type of food does not affect exposure.

Drug interactions
Boosted darunavir is prescribed together with other antiretrovirals and often with other medications. Hence, the potential for interactions with other drugs has been studied in both HIV-1-negative volunteers and HIV-1-infected patients.

In addition to CYP2D6 and CYP3A inhibition by darunavir/ritonavir, a Phase I study using a cocktail of CYP probes demonstrated induction effects on CYP2C9 and CYP2C19 activities, which was attributed to the coadministration of ritonavir. Thus, coadministration of darunavir/ritonavir with any medications that are primarily metabolized by CYP3A or CYP2D6 could result in increased plasma concentrations of these drugs. Similarly, since darunavir and ritonavir are metabolized by CYP3A, their plasma levels may be affected if coadministered with medications that either induce or inhibit CYP3A activity. Other potential sources of drug interactions include effects of darunavir on transport proteins. Thus, darunavir is both a substrate for and a modulator of P-glycoprotein. In addition, darunavir and other HIV PIs (including ritonavir) have been shown to have some inhibitory action on the organic anion transporting polypeptides, OATP1B1 and OATP1B3.

Potential interactions between darunavir/ritonavir and antiretrovirals or non-antiretrovirals have been extensively examined. The darunavir/ritonavir doses used in these studies were sometimes lower than the approved doses. Nonetheless, darunavir AUC and C_{0} increase less than dose proportionally with increasing dosage and analyses (using data for 800/100 or 400/100 mg once daily and 400/100 or 600/100 mg twice daily) predict that higher doses would have yielded substantively similar results. The drug interaction studies have been comprehensively reviewed by Back et al. The main conclusions are summarized below, together with data from studies published subsequent to the review by Back et al.

Drug interactions with other antiretrovirals
Based on the clinical pharmacology, darunavir/ritonavir can be used without dose adjustment with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs; e.g. abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate (DF) and zidovudine), atazanavir, enfuvirtide, etravirine, nevirapine, raltegravir and rilpivirine. However, the combination of darunavir and efavirenz should be used with caution. While no dose adjustment is required with rilpivirine, concomitant use with darunavir/ritonavir does increase rilpivirine plasma concentrations of darunavir and efavirenz should be used with caution. However, the combination of darunavir and efavirenz should be used with caution.
concentrations, with the AUC$_{24}$ being 2.3-fold higher following coadministration with 800/100 mg of darunavir/ritonavir once daily. No dose adjustment is recommended for rilpivirine, however.\(^{35}\) Similarly, no dose adjustment is necessary when darunavir/ritonavir and tenofovir DF are coadministered, although monitoring of renal function may be advised because of slight increases in plasma concentrations of both drugs.\(^{79}\) Coadministration of darunavir/ritonavir with either saquinavir or lopinavir/ritonavir is not recommended and indinavir dose adjustment may be warranted.\(^{24,40\text{–}42}\) Coadministration of darunavir/cobicistat with other HIV PIs is not recommended as the interactions have not been evaluated.

A recent pharmacokinetic study of darunavir/ritonavir with or without concomitant raltegravir in 53 HIV-1-infected patients (treatment naive and treatment experienced) showed that $C_{\text{min}}$ of darunavir and ritonavir were not significantly different between patients who received raltegravir and those who did not.\(^{36}\) However, coadministration of raltegravir was associated with a 40% reduction in the darunavir $C_{\text{max}}$ and estimated AUC$_{24}$. This interaction was independent of the dosage of darunavir and was not due to any effect of raltegravir on ritonavir pharmacokinetics. The mechanism by which raltegravir may decrease darunavir plasma concentrations is not known. In a separate Phase IIb study (ACTG A5262, NCT00830804) evaluating a nucleoside-sparing regimen of darunavir/ritonavir (800/100 mg once daily) plus raltegravir (400 mg twice daily), darunavir $C_{\text{rough}}$ values remained within the range previously reported for 800/100 mg of darunavir/ritonavir once daily in the absence of raltegravir.\(^{39}\) Furthermore, darunavir and raltegravir average $C_{\text{rough}}$ values were not significantly different for patients with or without virological failure.

The interaction between darunavir/ritonavir and elvitegravir was evaluated in 33 healthy volunteers participating in a three-way crossover interaction study. The treatments administered included 125/100 mg of elvitegravir/ritonavir once daily alone, 600/100 mg of darunavir/ritonavir twice daily and 600/100 mg of darunavir/ritonavir twice daily with 125 mg of elvitegravir once daily. No clinically relevant interaction was noted between the three compounds.\(^{41}\) The interaction between elvitegravir/cobicistat (with emtricitabine/tenofovir DF) and darunavir has not been investigated and is not recommended as no dosing information is available. Dolutegravir is primarily metabolized by glucuronidation (UGT1A1) with CYP3A having a minor role. The drug–drug interaction between darunavir/ritonavir and dolutegravir was investigated in an open-label, repeat-dose, two-period, two-sequence crossover study in healthy volunteers. The dolutegravir AUC$_{24}$, $C_{\text{max}}$ and $C_{\text{min}}$ decreased 22%, 11% and 38%, respectively. The decrease in dolutegravir is not considered to be clinically relevant.\(^{44}\) Etravirine can significantly decrease dolutegravir exposure; however, the addition of darunavir/ritonavir to dolutegravir and etravirine can abrogate the interaction (dolutegravir AUC$_{24}$, $C_{\text{max}}$ and $C_{\text{min}}$ were decreased 25%, 12% and 37%, respectively).\(^{45}\)

The C-C chemokine receptor type 5 (CCR5) antagonist maraviroc is primarily metabolized by CYP3A. Coadministration of 600/100 mg of darunavir/ritonavir twice daily with 150 mg of maraviroc twice daily in healthy volunteers resulted in a 4-fold increase in maraviroc exposure.\(^{46}\) Maraviroc at 150 or 300 mg once daily coadministered with darunavir/ritonavir at 800/100 mg once daily in HIV-1-infected patients resulted in higher maraviroc $C_{\text{min}}$ at a dose of 300 mg once daily compared with 150 mg once daily or maraviroc at 300 mg twice daily dosed with NRTIs.\(^{57}\) The implication of higher $C_{\text{min}}$ for maraviroc when used together with darunavir/ritonavir is unclear. Maraviroc at 150 mg once daily coadministered with 800/100 mg of darunavir/ritonavir once daily versus 800/100 mg of darunavir/ritonavir once daily with emtricitabine and tenofovir DF was planned to be evaluated in a Phase III study (MODERN; A4001095, NCT01345630), which was terminated prematurely because of the inferior efficacy of the maraviroc arm as compared with the comparator arm.

Cenicriviroc is an investigational CCR5 antagonist. Coadministration of 800/100 mg of darunavir/ritonavir once daily with 50 mg of cenicriviroc once daily resulted in a ~2-fold increase in cenicriviroc $C_{\text{max}}$, a 4-fold increase in $C_{\text{min}}$, and a 3-fold increase in AUC$_{24}$ with no effect on darunavir pharmacokinetics.\(^{58}\)

### Drug interactions with non-antiretrovirals

Subsequent to the Back et al.\(^{24}\) review, some further studies have been published on potential interactions of darunavir with non-antiretrovirals. These studies suggest that dose adjustment or monitoring of one or both agents is required if darunavir/ritonavir is used with artemether/lumefantrine (antimalarial), carbamazepine (anticonvulsant), buprenorphine/naloxone (narcotic analgesic), rifabutin (anti-infective) or rosuvastatin (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor).\(^{69\text{–}73}\) One study suggests that darunavir/ritonavir can be used without dosage adjustment with the inhaled corticosteroid beclomethasone.\(^{74}\) Coadministration of darunavir/ritonavir is not recommended with the hepatitis C virus PI boceprevir, simeprevir or telaprevir. When coadministered with these agents, darunavir exposure is decreased as well as exposure to boceprevir or telaprevir. The mechanism for this interaction is unknown.\(^{55\text{–}56}\) In contrast, faldaprevir and simeprevir exposure is increased 1.3- and 2.6-fold, respectively, when coadministered with 600/100 mg of darunavir/ritonavir twice daily in healthy volunteers.\(^{57,58}\) When coadministered with darunavir/ritonavir, the recommended dose of faldaprevir is 120 mg once daily, whereas it is not recommended to coadminister simeprevir as no dose has been established. No interaction is observed between darunavir/ritonavir and sofosbuvir.\(^{59}\)

### Effect of intrinsic and extrinsic factors on the pharmacokinetics of darunavir

The effect of intrinsic and extrinsic factors on darunavir pharmacokinetic parameters has been evaluated in several Phase III/I/IIIb trials. In the ARTEMIS trial in treatment-naive patients, exposure to darunavir following a once-daily dose of 800/100 mg of darunavir/ritonavir was not influenced by age or hepatitis B/C coinfection status and sex or race showed no clinically relevant effects.\(^{60}\) Similar results were observed in treatment-experienced patients in the TITAN trial, which used twice-daily darunavir/ritonavir dosing, and in the ODIN trial, which compared once-daily with twice-daily darunavir/ritonavir in treatment-experienced patients with no darunavir RAMs. In both TITAN and ODIN, exposure to darunavir (AUC$_{24}$ and $C_{\text{0}}$) was not affected by hepatitis coinfection status, age or body weight. There were also no clinically

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relevant differences by sex, race or region. The GRACE study of twice-daily darunavir/ritonavir at 600/100 mg plus an optimized background regimen enrolled 429 HIV-1-infected, treatment-experienced adults, including women (67%), black patients (62%), Hispanic patients (22%) and white patients (15%). Overall, values for both the darunavir plasma AUC12 and the Cmin were comparable between women and men and between black, Hispanic and white patients. Subgroup analyses were also performed for etravirine use, tenofovir DF use, hepatitis B virus coinfection, age group and weight. None of these factors showed any clinically meaningful effects on darunavir AUC12 or Cmin values.

The similar findings of the ARTEMIS, TITAN, ODIN and GRACE trials demonstrate that there are no clinically meaningful differences in the pharmacokinetics of darunavir/ritonavir for different patient subgroups, regardless of whether darunavir is dosed once daily or twice daily.

Safety and tolerability profile of once-daily darunavir/ritonavir and darunavir/cobicistat

The safety and tolerability profile of once-daily darunavir/ritonavir has been studied in several trials, the largest of which is the Phase III ARTEMIS study. Over the 192 weeks of the trial, a more favourable gastrointestinal and lipid profile was observed with darunavir/ritonavir (800/100 mg once daily) than with the lopinavir/ritonavir comparator (800/200 mg total daily dose). The incidence of grade 2–4 treatment–related diarrhoea was higher for lopinavir/ritonavir than for darunavir/ritonavir (P = 0.003). Elevations in triglycerides and total cholesterol were less frequent in the darunavir/ritonavir group than in the lopinavir/ritonavir group (P < 0.0001 for both). No adverse events (AEs) occurred at a significantly higher incidence in the darunavir/ritonavir arm than in the lopinavir/ritonavir arm. Rash (all causes) occurred in 2.6% of darunavir/ritonavir patients versus 1.4% for lopinavir/ritonavir (P = 0.295). Other trials evaluating once-daily darunavir/ritonavir have provided similar safety and tolerability findings.

As with any ritonavir–boosted PI, a proportion of the AEs observed will be attributable to ritonavir. Hence, once-daily darunavir/ritonavir dosing may result in a more favourable tolerability profile than twice-daily dosing due to the lower total daily ritonavir dose (100 mg rather than 200 mg). This effect has been observed in the 48 week ODIN trial in treatment–experienced patients with no darunavir RAMs. In the ODIN trial, grade 2–4 triglycerides occurred at approximately half the incidence for 800/100 mg of darunavir/ritonavir once daily than for 600/100 mg of darunavir/ritonavir twice daily (P < 0.05). The lower total daily dose of ritonavir with the once-daily regimen may at least partly explain this finding. Similarly, the incidence of diarrhoea was numerically lower in the once-daily arm (9.9% versus 15.2% for twice daily).

In the ARTEMIS trial, the lower incidence and severity of gastrointestinal and lipid AEs with darunavir/ritonavir compared with lopinavir/ritonavir may have been partly due to the 100 mg dose of ritonavir, which is half of the required amount for lopinavir/ritonavir treatment.

One of the driving forces behind looking for new pharmacoenhancers is the hope of less gastrointestinal and lipid problems than those associated with ritonavir. Initial results for cobicistat suggest that it may have a similar safety and tolerability profile to ritonavir, based on 48 week Phase III data comparing cobicistat with ritonavir, when combined with atazanavir, emtricitabine and tenofovir DF. The trial is, however, ongoing to evaluate longer-term safety and tolerability.

Pharmacokinetics and pharmacodynamics of once-daily darunavir/ritonavir combination therapy in adult antiretroviral-naive patients

ARTEMIS trial (TMC114–C211, NCT00258557)

The demonstrated efficacy and safety of darunavir/ritonavir in treatment–experienced patients in the Phase IIb trial programme (see below) prompted the study of its potential use in treatment–naive HIV-1-infected adult patients. The randomized, open-label, multicentre, Phase III ARTEMIS trial compared the efficacy, safety and tolerability, resistance characteristics and pharmacokinetics of darunavir/ritonavir at a dose of 800/100 mg once daily versus a total daily dose of 800/200 mg of lopinavir/ritonavir (once daily or twice daily depending on local regulatory approval and investigator/patient preference) in 689 treatment–naive patients. Patients also received a fixed background regimen of tenofovir DF and emtricitabine.

In the 48 week primary analysis, the proportions of patients achieving viral load <50 copies/mL were 84% in the darunavir/ritonavir group and 78% in the lopinavir/ritonavir group [intent–to–treat (ITT) and per–protocol, time–to–loss of virological response (TLOVR)], thereby demonstrating non–inferiority of darunavir/ritonavir versus lopinavir/ritonavir (P < 0.001). In the 96 week analysis, a higher proportion of patients in the darunavir/ritonavir group (79%) than in the lopinavir/ritonavir group (71%) had viral load <50 copies/mL, confirming non–inferiority (estimated difference: 8%; 95% CI 2%–15%; P < 0.001; per protocol) and superiority (P = 0.012; ITT) in virological response of darunavir/ritonavir to lopinavir/ritonavir. In patients with high baseline HIV-1 viral load (>100000 copies/mL; n = 237), virological response rates were higher with darunavir/ritonavir than with lopinavir/ritonavir (76% versus 63%, respectively; P = 0.023 at week 96). In patients with baseline viral load <100000 copies/mL, response rates were not significantly different between the darunavir/ritonavir (81%) and lopinavir/ritonavir (75%) arms. A post hoc subgroup analysis assessing once–daily or twice–daily dosing of lopinavir/ritonavir revealed a higher rate of virological response with once–daily darunavir/ritonavir (79%) than with twice–daily lopinavir/ritonavir (72%; P = 0.038; ITT–TLOVR). The response rate was even lower in those receiving once–daily lopinavir/ritonavir (69%). Median increases from baseline in CD4 cell count at week 96 were 171 and 188 cells/mm3 for darunavir/ritonavir and lopinavir/ritonavir, respectively (P = 0.57; non–completer = failure analysis). Self–assessed adherence affected virological response rates in the lopinavir/ritonavir arm but not in the darunavir/ritonavir arm. In patients characterized as suboptimally adherent (<95% average adherence), the response rate was higher in the darunavir/ritonavir arm compared with in the lopinavir/ritonavir arm (76% versus 53%, respectively; P = 0.0001). In adherent patients (>95% average adherence), the response rates were similar between the treatment arms (82% and 78%, respectively). Virological failure was lower in the darunavir/ritonavir arm than in the lopinavir/ritonavir arm (12% versus 17%, respectively; P = 0.0437; TLOVR non–virological failure censored analysis).
In the 192 week analysis, 69% of patients in the darunavir/ritonavir group versus 57% of patients in the lopinavir/ritonavir group had viral load 50 copies/mL (P = 0.001 for darunavir/ritonavir non-inferiority; P = 0.002 for darunavir/ritonavir superiority). The pharmacokinetics of darunavir were evaluated at weeks 4, 24 and 48 in a substudy of ARTEMIS. Darunavir pharmacokinetic parameters are presented in Table 2 and the mean plasma concentration–time profiles are presented in Figure 1. The relationship between darunavir pharmacokinetics and efficacy and safety following treatment with 800/100 mg of darunavir/ritonavir once daily was explored using sparse sampling data from 335 darunavir/ritonavir-treated patients (blood samples taken at 4, 8, 24 and 48 weeks). A population pharmacokinetic model for darunavir was developed based on data in HIV-infected patients and healthy volunteers and this was then applied to the sparse samples to derive empirical Bayesian estimates of darunavir exposure at steady-state. Overall median darunavir AUC(0→24) and C₀ were 87854 ng·h/mL and 2041 ng/mL, respectively (Figure 2a). No relationships were observed between the darunavir C₀ and AUC(0→24) values and change in viral load from baseline or the proportion of patients achieving viral load 50 copies/mL. The relationship between darunavir pharmacokinetics and efficacy was further explored using a univariate generalized additive model (GAM) and ARTEMIS week 48 data. The analysis confirmed that there was no relationship between darunavir C₀ and either the observed virological response or the response predicted by the GAM.

### Table 2. Darunavir pharmacokinetics in the Phase III ARTEMIS trial in treatment-naive patients (Sekar et al. and V. Sekar, T. N. Kakuda and R. M. W. Hoetelmans, unpublished results)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>week 4</th>
<th>week 24</th>
<th>week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9a</td>
<td>13b</td>
<td>10</td>
</tr>
<tr>
<td>C₀ (ng/mL), mean ± SD</td>
<td>1826 ± 1003</td>
<td>1786 ± 838.0</td>
<td>2133 ± 1220</td>
</tr>
<tr>
<td>C₂₄ (ng/mL), mean ± SD</td>
<td>1440 ± 513.9</td>
<td>1644 ± 726.9</td>
<td>1447 ± 705.7</td>
</tr>
<tr>
<td>Cₘ₈ (ng/mL), mean ± SD</td>
<td>1189 ± 409.6</td>
<td>1419 ± 671.0</td>
<td>1352 ± 687.8</td>
</tr>
<tr>
<td>Tₘ₈ (h), median (range)</td>
<td>3.00 (1.00–4.10)</td>
<td>3.00 (0.92–4.02)</td>
<td>3.50 (0.80–6.00)</td>
</tr>
<tr>
<td>AUC₂₄ (ng·h/mL), mean ± SD</td>
<td>64230 ± 18210</td>
<td>66950 ± 18610</td>
<td>75620 ± 26440</td>
</tr>
<tr>
<td>AUC₂₄ (ng·h/mL), median (range)</td>
<td>69350 (33010–88350)</td>
<td>63490 (38210–108100)</td>
<td>76850 (29180–117300)</td>
</tr>
<tr>
<td>Cₚₛₛ,av (ng/mL), mean ± SD</td>
<td>16.84 ± 7.229</td>
<td>19.25 ± 9.593</td>
<td>15.03 ± 6.359</td>
</tr>
<tr>
<td>Fluctuation index (%), mean ± SD</td>
<td>166.6 ± 48.69</td>
<td>160.9 ± 39.39</td>
<td>185.3 ± 60.84</td>
</tr>
</tbody>
</table>

f₁₂, functional elimination half-life; Cₚₛₛ,av, average steady-state plasma concentration.

a n = 8 for f₁₂.
b n = 11 for f₁₂.
c Accurate determination not possible for all patients.

![Figure 1](image-url) Darunavir plasma concentration–time profiles in the ARTEMIS trial. Values are means ± SD. qd, once daily.
Lower values within the observed darunavir $C_0$ range did not correlate with lower predicted virological response. Thus, a 50% reduction in darunavir $C_0$ resulted in a predicted mean virological response rate of 93.9%, which was similar to the overall mean predicted virological response rate of 92.8%. The study therefore showed that 800/100 mg of darunavir/ritonavir achieves the required drug exposure in treatment-naive patients.

**Pharmacokinetic study of once-daily etravirine with or without darunavir/ritonavir in antiretroviral-naive patients (NCT00534352)**

In a Phase IIa trial, the combination of once-daily darunavir/ritonavir (800/100 mg once daily) and etravirine (400 mg once daily), given with tenofovir DF/emtricitabine, in antiretroviral-naive adults yielded $C_{\text{min}}$ levels for both darunavir and etravirine that were well above the protein binding-adjusted EC$_{50}$ for wild-type HIV.

**Nucleoside-sparing regimen with once-daily darunavir/ritonavir combined with maraviroc in antiretroviral-naive patients**

In a single-arm, open-label, 96 week study, 24 treatment-naive, R5-tropic patients received a dual once-daily regimen of 800/100 mg of darunavir/ritonavir and 150 mg of maraviroc. At week 96, 90% of patients maintained virological suppression (confirmed viral load $\leq$50 copies/mL; modified ITT). Maraviroc, but not darunavir, pharmacokinetics were determined and trough plasma concentrations were not predictive of virological response.
Pharmacokinetics and pharmacodynamics of once-daily darunavir/ritonavir combination therapy in adult antiretroviral-experienced patients

**POWER 1 (TMC114-C213) and 2 (TMC114-C202)**

The two Phase IIb trials (POWER 1 and POWER 2) based on a similar design were conducted to determine the optimum dosage, efficacy and safety of darunavir/ritonavir in highly treatment-experienced HIV-1-infected patients. The trials consisted of a 24 week dose-finding phase followed by longer-term follow-up (over 144 weeks) of efficacy and safety using the selected dosage. In both trials, patients with viral load >1000 copies/mL and one or more primary PI mutations were randomized to receive darunavir/ritonavir at 400/100 mg once daily, 800/100 mg once daily, 400/100 mg twice daily or 600/100 mg twice daily or investigator-selected control PIs. Patients in all groups also received optimized background therapy consisting of NRTIs with optional enfuvirtide, based on genotypic resistance and treatment history. The 24 week analyses from the POWER 1 and 2 trials demonstrated that 600/100 mg of darunavir/ritonavir twice daily with an optimized background regimen over 24 weeks was the most effective dosing regimen in treatment-experienced HIV-1-infected patients with virus carrying multiple PI RAMs. This dosing regimen was thus selected for the open phase of both trials (week 24 onwards) and all patients were transferred to this dose.

In the pooled analysis of POWER 1 and 2, a subgroup of patients with no darunavir RAMs were found to achieve comparable virological response rates for both once-daily and twice-daily darunavir/ritonavir dosing at week 24. Overall, 67% of patients taking once-daily darunavir/ritonavir (800/100 mg) and 62% taking twice-daily darunavir/ritonavir (600/100 mg) achieved a viral load <50 copies/mL at week 24; both showed superiority to control PIs (11%; P < 0.0001). Additionally, statistical comparisons showed no significant differences between the once-daily and twice-daily groups for changes in CD4 cell count. This analysis indicated the potential benefit of once-daily darunavir/ritonavir at 800/100 mg in treatment-experienced patients with no darunavir RAMs and formed part of the rationale for the ODIN trial.

Pharmacokinetic/pharmacodynamic relationships in POWER 1 and 2 were assessed at week 24 for darunavir/ritonavir using analysis of covariance models. There was no apparent relationship between darunavir pharmacokinetic parameters and safety measures. While there was a relationship between pharmacokinetic parameters and virological response, this was strongly influenced by the baseline fold change in the 50% effective concentration (EC50) of darunavir (i.e. in inhibiting viral activity in vitro) and was only observed at an FC between 4 and 40.

**ODIN trial (TMC114-C229, NCT00524368)**

The results of the subanalysis described above from the POWER 1 and 2 trials led to further evaluation of the potential benefits of once-daily darunavir/ritonavir dosing in a larger population of 590 treatment-experienced patients with no darunavir RAMs. ODIN was a randomized, open-label, 48 week Phase IIIb trial designed to compare the efficacy, safety and tolerability of once-daily darunavir/ritonavir at 800/100 mg against twice-daily darunavir/ritonavir at 600/100 mg in this patient population. Patients also received an investigator-selected optimized background regimen (at least two NRTIs). Baseline characteristics were well balanced across treatment arms. The mean baseline viral load was 4.16 log10 copies/mL and the median cell count was 228 cells/mm3. Overall, 46% of patients entering the trial were PI naive, 28% had previously used at least two PIs, 57% had previously used at least three NRTIs and 88% of patients had used at least one non-nucleoside reverse transcriptase inhibitor (NNRTI).

In the primary week 48 analysis, the proportion of patients achieving viral load <50 copies/mL (ITT-TLOVR) was 72% for darunavir/ritonavir once daily and 71% for darunavir/ritonavir twice daily. Non-inferiority of once-daily compared with twice-daily darunavir/ritonavir was established (difference in response rate 1%; 95% CI −6% to 9%; P = 0.001). Stratification according to baseline viral load ≤50 000 or >50 000 copies/mL showed consistency of virological responses across once-daily and twice-daily darunavir/ritonavir treatments. Median increases in CD4 cell count from baseline to week 48 were also similar across treatment arms, at 100 and 94 cells/mm3 for once-daily and twice-daily darunavir/ritonavir, respectively (ITT, last-observation-carried-forward analysis). Self-reported adherence (>95% adherence) was slightly higher for patients taking once-daily darunavir/ritonavir (63%) compared with twice-daily darunavir/ritonavir (56%) in weeks 4–48 (P = 0.0931, Fisher’s exact test). For adherence measured by pill count, 58% of once-daily and 54% of twice-daily patients were considered adherent (>95% adherence). The once-daily and twice-daily arms showed comparable virological failure rates (viral load >50 copies/mL), with 22% and 18% of patients, respectively (P = 0.2599). The development of resistance was uncommon among patients who experienced virological failure.

Pharmacokinetic data were available for 280 once-daily and 278 twice-daily patients from whom plasma samples had been taken at 4, 8, 24 and 48 weeks for determining the darunavir plasma concentrations. The comparable efficacy of once-daily darunavir/ritonavir at 800/100 mg against twice-daily darunavir/ritonavir at 600/100 mg in this patient population. Patients also received an investigator-selected optimized background regimen (at least two NRTIs). Baseline characteristics were well balanced across treatment arms. The mean baseline viral load was 4.16 log10 copies/mL and the median cell count was 228 cells/mm3. Overall, 46% of patients entering the trial were PI naive, 28% had previously used at least two PIs, 57% had previously used at least three NRTIs and 88% of patients had used at least one non-nucleoside reverse transcriptase inhibitor (NNRTI).

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Pharmacokinetic data were available for 280 once-daily and 278 twice-daily patients from whom plasma samples had been taken at 4, 8, 24 and 48 weeks for determining the darunavir C0 and AUC24, (calculated as AUC12 × 2 for twice daily) using a two-compartment model with first-order absorption. The median (range) darunavir C0 was 1896 (184–7881) ng/mL for once-daily and 3197 (250–11865) ng/mL for twice-daily darunavir/ritonavir dosing (Figure 2b). The median (range) AUC24 values were 87788 (45456–236920) ng·h/mL and 109401 (48934–323820) ng·h/mL for once-daily and twice-daily darunavir/ritonavir dosing, respectively (Figure 2b). AUC24 and C0 showed no clinically significant effect on viral load at week 48. Furthermore, univariate GAM analysis at week 48 confirmed that there was no clear relationship between darunavir C0 values of up to 3000 ng/mL and observed virological response in patients receiving once-daily darunavir/ritonavir. There was, however, an inverse relationship between darunavir C0 and the predicted virological response at C0 values >3000 ng/mL. This finding is counterintuitive with no obvious explanation, although it should be noted that the variability in the estimates was greater for the higher darunavir plasma concentrations. The comparable efficacy of once-daily (800/100 mg) and twice-daily (600/100 mg) darunavir/ritonavir dosing, despite the somewhat lower AUC24 and C0 values with once-daily dosing, confirmed that adequate darunavir exposure was achieved with the once-daily regimen in the study population. There were no clinically relevant relationships between darunavir pharmacokinetics and efficacy or safety at week 48.
The findings of the ODIN trial therefore support the use of the 800/100 mg of darunavir/ritonavir once-daily treatment schedule in treatment-experienced, HIV-1-infected adults with no darunavir RAMs.

**RADAR study**

An open-label, non-comparative study has provided data to suggest that treatment-experienced patients who have stable virological suppression (HIV-1 RNA <50 copies/mL) can be switched from twice-daily to once-daily darunavir/ritonavir, even when genotypic testing for darunavir RAMs is not feasible.60 Viral suppression was maintained in 92% of patients at week 24, with similar results at week 48 (ITT, missing=failure analysis). Pharmacokinetic evaluation in 11 patients at week 4 showed high darunavir AUC (61,380 ng·h/mL) and median trough (1340 ng/mL) concentrations.60

**Pharmacokinetics and pharmacodynamics of once-daily darunavir/ritonavir monotherapy in adult patients**

Ritonavir-boosted PI monotherapy represents an attractive switch approach for some patients who are virologically suppressed on HAART. Potential benefits include a lower risk of toxicity, lower costs and treatment simplification, which may lead to improved long-term adherence. Against this is primarily the concern about long-term efficacy.81 A meta-analysis suggests that switching from HAART to boosted PI monotherapy has been associated with a somewhat lower probability of maintaining viral suppression. However, reintroduction of NRTIs in virologically failing patients is generally successful in regaining suppression.82 Some factors make boosted PI monotherapy a more viable option for virologically suppressed patients, such as absence of chronic hepatitis B, no history of treatment failure on PIs, ability to tolerate low-dose ritonavir and demonstrated good adherence.81 Trials evaluating boosted PI monotherapy are ongoing, as further long-term efficacy and tolerability data will be needed before this approach can be recommended as a routine treatment option.

**MONET trial (NCT00458302)**

The MONET trial was designed to evaluate whether darunavir/ritonavir monotherapy showed non-inferior efficacy compared with darunavir/ritonavir as part of triple therapy with two NRTIs in patients with stable virological suppression.65,83 The trial was a 144 week, randomized, controlled, open-label, multicentre Phase IIIb trial that recruited 256 patients with viral load <50 copies/mL on a stable triple antiretroviral regimen at screening, with no history of virological failure and no experience of darunavir treatment or with intensified treatment. Therefore, in the ‘switch included’ analysis, non-inferiority was shown. There were no patients who developed phenotypic resistance to darunavir during the trial, although one patient per arm showed at least one genotypic PI mutation.

**MONOI-ANRS 136 study**

MONOI was a prospective, open-label, non-inferiority, randomized, 96 week trial of darunavir/ritonavir monotherapy.86 The study included an initial 8 week phase in which 600/100 mg of darunavir/ritonavir twice daily replaced the existing third agent (PI, NNRTI or NRTI). Patients whose viral load remained <50 copies/mL after 4 weeks and who had no severe AE or drug-related toxicity were then randomly assigned 1:1 to either continue the darunavir/ritonavir-based triple-drug regimen or to stop the two NRTIs (darunavir/ritonavir monotherapy). After week 48, patients were transferred to the 800/100 mg once-daily dose of darunavir/ritonavir. Of the randomized patients, 211 reached the 96 week follow-up. At week 96, in the ITT analysis, 88% (95% CI 81%–94%) of patients in the darunavir/ritonavir monotherapy arm and 84% (95% CI 75%–90%) of patients in the darunavir/ritonavir triple-drug regimen achieved a viral load <50 copies/mL with no statistical difference between the
two groups. The study concluded that darunavir/ritonavir monotherapy is efficacious in maintaining virological suppression in HIV-1-infected patients and may be considered as a (tailored) treatment option for patients on triple-drug therapy who have been virologically suppressed for a substantial period of time.86

**PROTEA study (TMC114IFD3003, NCT01448707)**

A third darunavir/ritonavir monotherapy trial is ongoing.87 The Phase IIIb PROTEA study is evaluating the efficacy, safety and tolerability of darunavir/ritonavir monotherapy versus darunavir/ritonavir-based triple combination therapy (800/100 mg of darunavir/ritonavir once daily plus two NRTIs) in ~260 long-term virologically suppressed HIV-1-infected patients. In addition to the primary objective of non-inferiority at 48 weeks, the study will also assess changes in neurocognitive function over 96 weeks of treatment and potential correlation with plasma and CSF viral load.

**Pharmacokinetics and pharmacodynamics of once-daily darunavir/ritonavir combination therapy in HIV-infected pregnant women**

The US Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission currently recommends that twice-daily dosing of darunavir should be used for pregnant women because of low trough levels with once-daily dosing.88 However, a recent small study (n = 8) found that total darunavir concentrations remained well above the IC50 for wild-type HIV during the third trimester following 800/100 mg of darunavir/ritonavir once daily plus tenofovir DF and emtricitabine. This study found that the total darunavir AUC24 was 32% lower and Ctrough, 46% lower in the third trimester compared with post-partum; unbound darunavir was 24% lower than post-partum for both values.89

An ongoing Phase III, non-randomized study is further evaluating the pharmacokinetics and pharmacodynamics of darunavir/ritonavir during the second and third trimesters of gestation in HIV-1-infected women who are receiving darunavir/ritonavir either once daily or twice daily.90 Findings from the once-daily part of the trial are not yet available. However, data on twice-daily dosing with 600/100 mg of ritonavir/darunavir (n = 14) showed that, consistent with other PIs, lower darunavir exposures were observed during pregnancy compared with post-partum, with 17%–24% reductions in the total darunavir AUC12 compared with post-partum concentrations.90 Nonetheless, there was no clinically relevant change in unbound darunavir during pregnancy, which suggests that when 600/100 mg of darunavir/ritonavir twice daily is used in pregnant women, no dose adjustment is required.

**ARIEL trial (TMC114-TiDP29-C228, NCT00919854)**

Once-daily darunavir/ritonavir dosing in treatment-experienced paediatric patients has been explored in a substudy of the ARIEL trial.92 ARIEL recruited HIV-infected, treatment-experienced children aged 3 to <6 years and weighing 10 to <20 kg. Participants with confirmed viral suppression at week 32 were given the option of entering into a pharmacokinetic substudy, in which the twice-daily 20/3 mg/kg darunavir/ritonavir-based regimen was replaced with once-daily darunavir/ritonavir (40/7 mg/kg if patients weighed <15 kg or 600/100 mg if ≥15 kg) for 2 weeks after which they resumed their twice-daily 20/3 mg/kg darunavir/ritonavir dosing regimen. The substudy recruited 10 patients and achieved the aim of obtaining a darunavir AUC24 similar (i.e. within 80%–130%) to that in adults. The darunavir geometric mean AUC24 was 115 000 (SD: 40 600) ng.h/mL in children, which was 128% of the adult AUC24. Similarly, the C0 geometric mean was 149% of the adult value. All patients remained virologically suppressed during the 2 week substudy and no treatment-related AEs of grade 2 or higher were reported.92

**Future directions**

Daranavir is currently available in tablets of 75, 150, 600 and 800 mg. A 100 mg/mL oral suspension is available for paediatric use and for adults who have difficulty in swallowing.93

Current treatment guidelines recommend the use of at least two, preferably three, active antiretroviral agents maintained for...
a patient’s lifetime, even after viral suppression is achieved (viral load ≤50 copies/mL). However, the European treatment guidelines also suggest that boosted HIV PI monotherapy using twice-daily lopinavir/ritonavir or once-daily darunavir/ritonavir as possible switch strategies for virologically suppressed patients (confirmed plasma viral load <50 copies/mL) who are intolerant to NRTIs or for treatment simplification. The findings of both the MONET and MONOI trials suggest that darunavir/ritonavir monotherapy of 800/100 mg once daily may represent a feasible treatment option for some treatment-experienced patients who are virologically suppressed. This strategy may have the future potential to avoid toxicities associated with the multiple antiretroviral classes that typically constitute combination therapy. However, monotherapy strategies are unlikely to become widely used until further long-term data become available. An alternative future option may be once-daily dual therapy with darunavir/ritonavir combined with either etravirine or an integrase inhibitor for antiretroviral-naive or early treatment-experienced patients. A recently completed Phase II study (NCT01199939) has shown adequate viral suppression and tolerability over 48 weeks with 400 mg of etravirine and 800/100 mg of darunavir/ritonavir each given once daily in a nucleoside-sparing regimen in early treatment-experienced patients. Data on dual therapy consisting of darunavir/ritonavir plus an integrase inhibitor are so far only available for raltegravir that is given twice daily. Finally, cobicistat is currently being evaluated as a potential alternative to ritonavir, with a fixed-dose product in development that coformulates darunavir with cobicistat as a single 800/150 mg tablet. Also under investigation is a single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (GS-7340; a pro-drug of tenofovir) (NCT01565850).

Summary and relationship to HIV treatment guidelines

Antiretroviral-naive adult patients

Until relatively recently, lopinavir/ritonavir was the preferred boosted HIV PI and, for this reason, was selected as the comparator for darunavir/ritonavir in the ARTEMIS trial. Compared with lopinavir/ritonavir (800/200 mg total daily dose), virological superiority of once-daily darunavir/ritonavir (800/100 mg) at weeks 96 and 192 was demonstrated, along with a higher virological response in the hard-to-treat subset of patients with high baseline viral load (i.e. >100,000 copies/mL) as well as in those with adherence ≤95%. The favourable lipid profile of darunavir/ritonavir observed in ARTEMIS has been confirmed in a meta-analysis of 12 clinical trials that examined the effect of different ritonavir-boasted HIV PIs on lipid changes at 48 weeks in >4000 treatment-naive patients.

There is a lack of studies comparing the efficacy, safety and pharmacokinetics/pharmacodynamics of darunavir/ritonavir with atazanavir/ritonavir. Results from one Phase I study in healthy volunteers and two randomized, controlled trials in antiretroviral-naive patients (METABOLIK and ATADAR) suggest that darunavir/ritonavir and atazanavir/ritonavir have similar metabolic profiles. In addition, the Phase III 96 week ARDENT trial in antiretroviral-naive patients (ACTG 5257, NCT00811954) has shown equivalent efficacy between darunavir/ritonavir, atazanavir/ritonavir and raltegravir (each given with tenofovir DF/emtricitabine). On the coprimary endpoint of failure due to tolerability problems, both darunavir/ritonavir and raltegravir were superior to atazanavir/ritonavir.

For initial therapy in adults, the current guidelines of the Department of Health and Human Services (USA) recommend the use of once-daily regimens consisting of tenofovir DF/emtricitabine combined with one of the following: darunavir/ritonavir, atazanavir/ritonavir or efavirenz. Twice-daily raltegravir with tenofovir DF/emtricitabine is also recommended. The guidelines of the European AIDS Clinical Society (EACS) are comparable except that rilpivirine is also a recommended first-line agent (for patients with viral load <100,000 copies/mL) and abacavir/lamivudine is a recommended NRTI backbone option as well as tenofovir DF/emtricitabine.

Antiretroviral-experienced adult patients

For patients with extensive antiretroviral experience, twice-daily darunavir/ritonavir at 600/100 mg has been identified as the optimal dosage (POWER 1 and 2 trials). However, in these studies a subgroup of patients with no darunavir RAMs responded favourably to a once-daily dose of 800/100 mg of darunavir/ritonavir. This once-daily regimen of darunavir/ritonavir was therefore studied in treatment-experienced patients with no darunavir RAMs in the ODIN trial and its efficacy in this patient group was established.

A twice-daily dose of 600/100 mg is licensed in the USA and EU for use in patients who have one or more darunavir RAMs, as this was the regimen that proved most efficacious for this subpopulation of patients in the POWER trials. Genotypic testing prior to initiation of darunavir/ritonavir therapy is recommended and if genotypic testing is not feasible, the once-daily dosing schedule is recommended in treatment-naive patients whereas the twice-daily dosing schedule is recommended for treatment-experienced patients.

Paediatric patients

Darunavir/ritonavir twice daily is currently recommended for use in paediatric patients ≥3 years old and weighing ≥10 kg (USA) or ≥15 kg (EU). A weight-based once-daily dosing option is also available for paediatric patients ≥3 years old in the USA and for adolescents (≥12 years old) in the EU. The once-daily dosing for paediatric patients aged 3–12 years in the EU is under development. Darunavir is not recommended for paediatric

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patients below the age of 3 years due to morbidity observed in juvenile rat toxicity studies.\textsuperscript{22}

**Conclusions**

Large clinical trials have established the efficacy and tolerability of once-daily darunavir/ritonavir at 800/100 mg in treatment-naive patients and treatment-experienced patients lacking darunavir RAMs. Pharmacokinetic analyses have confirmed that adequate plasma concentrations of darunavir required for suppression of wild-type HIV are achieved with this once-daily dosing schedule. Both treatment-naive patients and treatment-experienced patients with no darunavir RAMs can therefore benefit from the greater convenience and improved tolerability of once-daily dosing compared with twice-daily darunavir/ritonavir dosing, without reduction in efficacy. Finally, fixed-dose combinations of darunavir and cobicistat currently under development may extend the range of once-daily options.

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**Supplementary data**

Figure S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

**References**


