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Darunavir: A Review of Its Use in the Management of HIV-1 Infection

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Abstract The latest HIV-1 protease inhibitor (PI) darunavir (Prezista™) has a high genetic barrier to resistance development and is active against wild-type HIV and HIV strains no longer susceptible to some older PIs. Ritonavir-boosted darunavir, as a component of antiretroviral therapy (ART), is indicated for the treatment of HIV-1 infection in adult and paediatric patients (aged ≥3 years), with or without treatment experience (details vary depending on region of approval). Several open-label or partially-blinded trials have evaluated the efficacy of ritonavir-boosted darunavir ART regimens for up to 192 weeks in these settings. In treatment-naïve adults, once-daily boosted darunavir was no less effective in establishing virological suppression than once- or twice-daily boosted lopinavir, yet was more effective at maintaining suppression long term. Moreover, treatment-experienced adults with no darunavir resistance-associated mutations (RAMs) had no less effective viral load suppression with once-daily than with twice-daily boosted darunavir. In treatment-experienced adults, including some with multiple major PI RAMs, twice-daily boosted darunavir was more effective than twice-daily boosted lopinavir or boosted control PIs in reducing viral load, and provided virological benefit as part of a salvage regimen in those with few remaining treatment options. Boosted darunavir also reduced viral load when administered once-daily in treatment-naïve adolescents or twice-daily in treatment-experienced children and adolescents. Boosted darunavir is generally well tolerated, with gastrointestinal disturbances and lipid abnormalities among the most common tolerability issues. It has a lipid profile more favourable than that of boosted lopinavir in terms of total cholesterol and triglyceride changes and, when administered once daily, its lipid effects are generally similar to those of boosted atazanavir. Thus, boosted darunavir is a useful option for the ART regimens of adult and paediatric patients with HIV-1 infection.

Darunavir in the management of HIV-1 infection: a summary

HIV protease inhibitor (PI) with a high genetic barrier to resistance and activity against wild-type HIV and HIV strains no longer susceptible to some older PIs

Like most PIs, darunavir must be coadministered with low-dose ritonavir to enhance its bioavailability

Twice-daily ritonavir-boosted darunavir regimens provide virological suppression in treatment-experienced paediatric and adult patients, including those with major PI resistance-associated mutations (RAMs)

Once-daily ritonavir-boosted darunavir regimens reduce viral load in treatment-naïve adults and adolescents, as well as in treatment-experienced adults with no darunavir RAMs

As is typical of PIs, gastrointestinal disturbances and lipid abnormalities are among the most common tolerability issues

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1 Introduction

HIV infection, a once fatal disease, is now considered a chronic but manageable illness thanks to antiretroviral therapy (ART) [1, 2]. ART reduces the morbidity and mortality of HIV/AIDS by suppressing viral replication and enabling immune system restoration [3], although the high genetic mutability of the virus is a continuous challenge, with drug resistance documented for all classes of antiretroviral agents in clinical practice [3, 4].

In order to minimize the likelihood of drug resistance developing, ART regimens generally include a combination of three antiretroviral agents from at least two different drug classes [3], with standard combinations comprising two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) [5–10], an integrase inhibitor [5–8] or a protease inhibitor (PI) boosted with ritonavir [5–10]. However, within these and other antiretroviral drug classes, there is a constant demand for agents with better genetic barriers to resistance development and activity against already resistant HIV [11].

Darunavir (Prezista™) is the most recently introduced PI [3] and provides a high genetic barrier to the emergence of resistance, as well as activity against HIV-1 strains no longer susceptible to some other PIs [12]. The drug is available as a tablet or suspension for oral administration and is coadministered with low-dose ritonavir (i.e. ritonavir-boosted darunavir) as part of a combination ART regimen [13, 14].

Darunavir is indicated in several countries, including the USA [14] and those of the EU [13], for the treatment of HIV-1 infection in ART-naïve and ART-experienced adults [13, 14], as well as in paediatric patients aged ≥3 years (weighing ≥10 [14] or ≥15 [13] kg) who have received ART previously [13, 14] or are ART naive [14] (provided they are aged 12–17 years, weighing ≥40 kg [13]). This article reviews the pharmacological, therapeutic efficacy and tolerability data relevant to the use of darunavir in these indications. Acronyms of the clinical studies discussed in this review are defined in Table 1.

2 Pharmacodynamic Properties

The pharmacodynamics of darunavir are well established and have been reviewed in detail in *Drugs* previously [15, 16]; this section provides an overview of the key pharmacodynamic properties of the drug, with discussion focusing on data pertaining to the pivotal trials and dosages discussed in Sect. 4 wherever possible. Some data were obtained from abstracts/posters [17–21], a US FDA review [22] and the EU [13] and US [14] prescribing information.

Darunavir is a non-peptidyl small molecule inhibitor of the protease of HIV-1. The drug inhibits the dimerization of the protease [23], as well as its catalytic activity [13], thereby selectively inhibiting the gag-pol polyproteins of HIV-1 from being cleaved, thus preventing virion maturation [13, 14].

Darunavir displays high affinity for the HIV-1 protease (binding constant 4.5×10^{-12} mol/L in vitro) and binds closely and predominantly within the substrate envelope [24], with rigid and flexible docking enabling it to form a highly stable complex with the enzyme [25]. As the drug's affinity for the wild-type protease is high, its affinity towards some proteases with PI resistance-associated mutations (RAMs) can be substantially lower without antiviral activity being compromised [26]. Moreover, a total of four protease mutations appear to be required to reduce the effectiveness with which darunavir inhibits protease dimerization [27]. These properties may help to explain the potent antiviral activity of darunavir against HIV strains with several mutations or multidrug resistance (Sect. 2.1) and its high genetic barrier to resistance development (Sect. 2.2).

Table 1 Clinical trial acronyms and definitions

Acronym	Definition
ACTG A5262	AIDS Clinical Trial Group study A5262
ANRS 139 TRIO	Agence Nationale de Recherches sur le SIDA et les hepatites virales study 139 TRIO
ARIEL	dArunavir in tReatment experIenced pEdiatric popuLation
ARTEMIS	AntiRetroviral Therapy with TMC114 ExaMined In naïve Subjects
DELPHI	Darunavir EvaLuation in Pediatric HIV-1-Infected treatment-experienced patients
DIONE	DarunavIr Once daily in treatment-Naive adolEscents
GRACE	Gender, Race, And Clinical Experience
ODIN	Once-daily Darunavir In treatment-experieNced patients
POWER	Performance Of TMC114/ritonavir When evaluated in treatment-Experienced patients with PI Resistance
TITAN	TMC114/ritonavir In Treatment-experienced pAtients Naïve to lopinavir

2.1 Antiviral Activity

Darunavir demonstrated antiviral activity against wild-type laboratory strains and/or clinical isolates of HIV-1 and HIV-2 in infected cells in vitro, with minimal cytotoxicity [22, 28, 29]. Across studies, the mean/median 50 % effective concentration (EC_{50}) of darunavir was 1.0–6.3 nmol/L for HIV-1 and 3–8.5 nmol/L for HIV-2 and was considerably lower than the 50 % cytotoxic concentration of the drug (≥74.4 to >100 μmol/L). Human serum proteins appeared to reduce the anti-HIV activity of darunavir [22, 28, 29], with the manufacturer's prescribing information reporting a median 5.4-fold increase in the EC_{50} of the drug in the presence of human serum [14].

Darunavir was active against a range of HIV-1 groups and clades [22, 29, 30], as well as circulating recombinant forms (CRFs) of the virus [29], in vitro. For instance, across a panel of 32 recombinant viruses derived from clinical isolates, the median EC_{50} of darunavir was 1.2–2.5 nmol/L for each group M clade assessed (B, C, D, F and H), 1.1–1.6 nmol/L for each group M CRF (CRF01_AE, CRF02_AG and CRF05_DF) and 2.2 nmol/L for group O virus [29].

Darunavir displayed varying degrees of antiviral activity against strains of HIV-1 selected for resistance against single PIs in vitro [28]. The mean EC_{50} was 3, 5, 25 and 29 nmol/L, respectively, for strains resistant to nelfinavir, saquinavir, ritonavir or indinavir, 220 nmol/L for a strain resistant to amprenavir and 3 nmol/L for wild-type virus.

Similarly, when the in vitro activity of darunavir was studied in clinical HIV-1 strains with resistance to other PIs, most appeared to be susceptible to darunavir [13, 14, 22, 28, 29]. For instance, among 1,501 recombinant clinical HIV-1 isolates with resistance (EC_{50} fold change [FC] of ≥4 vs. reference strain) to at least one PI, darunavir was highly active against the majority of isolates, with an EC_{50} of <10 nmol/L in 75 % of samples and an FC of <4 in 80 % [29].

No antagonism of antiviral activity was evident when darunavir was evaluated in combination with any one of several PIs, NRTIs, NNRTIs or enfuvirtide (a fusion inhibitor) in vitro, although there was evidence of synergism between darunavir and some PIs (ritonavir, amprenavir and nelfinavir) [29].

2.2 Viral Resistance

Darunavir exhibits a high genetic barrier to resistance development. The potential for a wild-type HIV strain to develop resistance to darunavir in in vitro selection experiments appeared to be lower than for amprenavir, nelfinavir or lopinavir [29]. Indeed, selection of darunavir resistance in vitro took >3 years and the growth of the selected strains could be suppressed with concentrations of the drug >400 nmol/L [13]. Development of two to four amino acid substitutions in the protease reduced the susceptibility of wild-type HIV-1 to darunavir 21- to 88-fold [13, 14], whereas emergence of at least eight protease amino acid substitutions in HIV-1 strains already harbouring multiple PI RAMs conferred a 50- to 641-fold reduction in darunavir susceptibility [14].

In the clinical setting, fewer than 16 % of ART-naïve adults who experienced virological failure (see Sect. 4 for details) over 192 weeks' treatment with once-daily ritonavir-boosted darunavir or once- or twice-daily ritonavir-boosted lopinavir in the ARTEMIS trial had developed PI RAMs (none of which were primary, i.e. major, RAMs) [4 of 43 vs. 9 of 57 evaluable recipients] or had developed NRTI RAMs (4 of 43 vs. 7 of 57) [31].

Moreover, use of once-daily ritonavir-boosted darunavir in ART-experienced adults with no darunavir RAMs did not increase the risk of resistance emerging to PIs or background therapy NRTIs when compared with twice-daily ritonavir-boosted darunavir in the 48-week ODIN study [32, 33]. Among evaluable patients with virological failure ($n = 41$–60), only one (in the once-daily group) had developed primary PI RAMs (M46I, V32I, L76V and I84V) and consequently lost susceptibility to darunavir and a number of other PIs (atazanavir, lopinavir, amprenavir, indinavir and nelfinavir).

Analysis of pooled 24-week data from the POWER 1–3 trials ($n = 458$) identified seven mutations that developed in ≥10 % of highly ART-experienced adults with virological failure on twice-daily ritonavir-boosted darunavir (I15V, V32I, L33F, M46I, I47V, I54L, L89V), five of which (V32I, L33F, I47V, I54L, L89V) were predictive of diminished virological response when present at baseline and are consequently among those termed darunavir RAMS (see Sect. 2.3) [34]. Many of these PI mutations were also among those most commonly associated with twice-daily ritonavir-boosted darunavir virological failures when data from the POWER trials were combined with data from the placebo arms of two etravirine studies that included ritonavir-boosted darunavir as part of the background therapy (V11I, I15V, V32I, L33F, I47V, I50V, I54L/M, L89V); these mutations were associated with a median darunavir FC at failure of 85 [14].

Among adults with a broader range of treatment experience who had virological failure after 96 weeks of twice-daily ritonavir-boosted darunavir or lopinavir therapy in the TITAN trial, up to 3.7-fold fewer darunavir than lopinavir recipients had developed primary PI RAMs (6 of 39 vs. 24 of 72) or NRTI RAMs (3 of 39 vs. 19 of 72) [$p < 0.05$] or had lost study PI (3 of 36 vs. 17 of 55) or NRTI [4 of 35 vs. 20 of 55] susceptibility [35]. The primary PI RAMs in the darunavir group were similar to those

identified in the POWER studies and included V32I, M46I, I47V, I54L/M and L76V [35].

Likewise, among the 24 ART-experienced paediatric patients aged 6–17 years with virological failure on twice-daily ritonavir-boosted darunavir in DELPHI, the PI mutations that developed most often were I13V, V32I, M36L, I50V, I54L, V77I and L89M [36]. However, no evaluable ART-experienced children aged 3 to <6 years who experienced virological failure after receiving twice-daily ritonavir-boosted darunavir for 24 weeks (six evaluable) [21] or 48 weeks (two evaluable) [20] in ARIEL had developed PI or NRTI RAMs.

2.2.1 *Cross Resistance*

In cell culture, HIV variants resistant to darunavir were no longer susceptible to a number of other PIs, including ritonavir, atazanavir, lopinavir, indinavir, nelfinavir, amprenavir and saquinavir [14]. By contrast, cross resistance between darunavir and tipranavir was limited, with the majority of variants selected in cell culture for darunavir resistance remaining susceptible to tipranavir (FC < 3) [14].

Indeed, minimal cross resistance was observed between these two PIs in ART-experienced adults who experienced virological rebound on twice-daily ritonavir-boosted darunavir in POWER 1–3 over 24 weeks' therapy (>80 % of isolates with tipranavir susceptibility at baseline were still susceptible to tipranavir after darunavir rebound) [34]. Longer-term data from these trials indicated that one-third of ritonavir-boosted darunavir recipients with reduced tipranavir susceptibility at baseline had their serum HIV-1 RNA level (i.e. viral load) suppressed to <50 copies/mL after 96 weeks' treatment [14]. Moreover, 41 % of the isolates from patients who experienced virological failure with ritonavir-boosted darunavir remained susceptible to tipranavir in this analysis (versus only 10 or <2 % of failures remaining susceptible to saquinavir or other PIs) [14]. Analysis of the Spanish AIDS Research Network database (105 genotypes evaluated) suggested that up to half of patients failing darunavir or tipranavir therapy may exhibit cross resistance [37].

The likelihood of retaining susceptibility to other PIs appeared to be greater with twice-daily ritonavir-boosted darunavir than with twice-daily ritonavir-boosted lopinavir in ART-experienced adults with virological failure after 96 weeks' therapy in TITAN (97–100 vs. 69–95 % of failures remained susceptible to atazanavir, amprenavir, indinavir, lopinavir, saquinavir and tipranavir) [35]. In addition, all evaluable ART-experienced children with virological failure on twice-daily ritonavir-boosted darunavir at 24 weeks in ARIEL were still susceptible to all PIs and background therapy NRTIs [21].

Moreover, ART-experienced adults (without darunavir RAMs at baseline) who experienced virological failure with once- or twice-daily ritonavir-boosted darunavir in the ODIN trial did not usually lose susceptibility to other PIs [33]. In the respective groups, 2 of 59 and 0 of 41 evaluable patients lost susceptibility to at least one PI; these included amprenavir, atazanavir, indinavir, lopinavir and nelfinavir in a patient who developed reduced darunavir susceptibility and atazanavir and indinavir in a patient without PI RAM emergence. All HIV isolates from ART-naïve adults with virological failure on once-daily ritonavir-boosted darunavir or once- or twice-daily ritonavir-boosted lopinavir in the ARTEMIS study ($n = 39$ and 52 evaluable) were still susceptible to darunavir, lopinavir and other PIs, including tipranavir, atazanavir, amprenavir, indinavir and saquinavir [31].

2.3 Predictors of Virological Response

Baseline darunavir FC is predictive of virological response to twice-daily ritonavir-boosted darunavir in highly ART-experienced adults, according to pooled data from the POWER 1–3 trials at 24 [34] and 96 [14] weeks. For example, at 96 weeks, a viral load of <50 copies/mL was achieved by 55, 30 and 12 % of patients with a baseline darunavir FC of 0–7, >7–20, or >20, respectively [14].

Baseline viral load and first-time enfuvirtide use were also correlated with viral load changes in this setting [34]. However, the POWER analyses found the number of baseline PI RAMs to be an unreliable predictor of virological response to twice-daily ritonavir-boosted darunavir in ART-experienced adults [34], although responses were influenced by the number of primary PI RAMs at baseline [14]. For instance, a viral load <50 copies/mL was achieved after 96 weeks' therapy by 50 % of patients with up to four such RAMs, 22 % with five RAMs and 9 % with six or more RAMs [14].

Certain baseline mutations were strongly predictive of diminished virological outcomes to darunavir in the 24-week POWER analysis [34]. These mutations, termed darunavir RAMs, included V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V, and were present in combination with a median of ≥10 PI RAMs; at least three darunavir RAMs were required to diminish virological response to the drug. The 96-week pooled analysis of these trials confirmed each of these mutations (with the exception of G73S) as darunavir RAMs and identified T74P as an additional darunavir RAM; a viral load <50 copies/mL was achieved by 59 % of patients with up to one RAM, 29 % with two RAMs and 12 % with at least three RAMs [14]. The number of baseline darunavir RAMs was also predictive of virological response to darunavir in ART-experienced paediatric patients in the DELPHI trial [36]. By

contrast, some PI RAMs (E35D, V82A) appear to have a positive impact on darunavir virological outcomes [38] and may, when considered along with RAMs with a negative impact, help predict virological response to darunavir [39].

Trough plasma concentrations (C_{min}) of darunavir generally do not appear to be predictive of virological response [19, 39–42] and whether the ratio of C_{min} to the number of darunavir RAMs (i.e. the genotypic inhibitory quotient) is predictive of response is currently unclear [39–42], perhaps because patient populations studied to date have had varying degrees of darunavir resistance. The best predictor of virological response to darunavir salvage therapy in one small ($n = 37$) prospective study was the virtual inhibitory quotient (i.e. ratio of C_{min} to change in virtual phenotype EC_{50}, multiplied by protein-binding-corrected darunavir EC_{50} for PI-resistant strains) [40].

2.4 Effects on Lipids

Ritonavir-boosted darunavir, administered once or twice daily in combination with background therapy, was generally associated with modest increases from baseline in mean/median lipid levels over up to 192 weeks' treatment in ART-naïve and -experienced adults, adolescents or children in the pivotal comparative and noncomparative trials, and their pooled analyses, discussed in Sect. 4 [31, 32, 35, 36, 43–50]. In some studies [36, 43, 49] and analyses [45, 50], triglyceride levels were reduced from baseline after 48–144 weeks' therapy in darunavir recipients; where reported, baseline triglyceride levels were above normal [36, 43, 45, 49] (the National Cholesterol Education Program [NCEP] cutoff is 1.7 mmol/L) and were associated with prior lopinavir use [36].

In comparison with once-daily [47] or twice-daily [35, 47] ritonavir-boosted lopinavir, once-daily [47] or twice-daily [35] ritonavir-boosted darunavir was associated with significantly ($p < 0.05$) smaller median increases from baseline in levels of triglyceride, total cholesterol and high-density lipoprotein (HDL)-cholesterol after 96 weeks' treatment in ART-naïve [47] or ART-experienced [35] adults, whereas changes in low-density lipoprotein (LDL)-cholesterol were similar between groups. At this timepoint, median levels of these lipids were generally within NCEP limits, although triglyceride levels in darunavir [35] and/or lopinavir [35, 47] recipients were above the 1.7 mmol/L cutoff. Longer term, lipids generally remained at similar median levels after 192 weeks' therapy [31] as at 96 weeks [47] in each treatment arm.

By contrast, the lipid profile of once-daily ritonavir-boosted darunavir was generally similar to that of once-daily ritonavir-boosted atazanavir in ART-naïve adults in randomized, open-label trials ($n = 55$ evaluable [51] or 180 randomized [18]). No significant [18] or clinically relevant [51] between-group differences in mean changes from baseline in triglyceride, LDL-cholesterol, HDL-cholesterol or total cholesterol were evident after 24 [18] or 48 [51] weeks of treatment, despite mean increases in total cholesterol being 4.4-fold greater among darunavir than atazanavir recipients at 12 weeks, where reported [51]. The daily doses of darunavir (800 mg) and atazanavir (300 mg) were boosted with ritonavir 100 mg.

Notably, once- and twice-daily ritonavir-boosted darunavir regimens had generally similar HDL- and LDL-cholesterol profiles over 48 weeks' therapy in ART-experienced adults in ODIN, although increases from baseline in median levels of triglyceride and total cholesterol were almost threefold greater with twice-daily administration [32]. Few gender-based differences in the darunavir lipid profile were evident after 48 weeks' therapy among ART-experienced adults receiving twice-daily ritonavir-boosted darunavir regimens in GRACE; however, the median increase from baseline in triglyceride level was significantly ($p = 0.006$) greater in men than women [52].

Some trials specified that lipid-lowering agents were used by some patients [31, 32, 45, 47, 52]. One study [51] prohibited the use of such agents until after week 12 of the trial; however, no patients received lipid-lowering therapy after the twelfth week.

2.5 Other Effects

The depletion of CD4+ cells that occurs during HIV-1 infection may be a result of increased apoptosis. In vitro data suggest darunavir may have anti-apoptotic properties, with levels of puromycin-induced apoptosis of peripheral blood mononuclear cells being 35–42 % with darunavir versus 60 % with media alone [17]. However, the clinical relevance of these findings remains to be determined.

The Fridericia-corrected QT (QTcF) interval did not appear to be prolonged to any clinically relevant extent with supratherapeutic dosages of darunavir plus ritonavir (1,600 plus 100 mg once daily or 800 plus 100 mg twice daily) over 7 days in a placebo- and active comparator-controlled crossover study in 40 healthy subjects, with the QTcF interval increasing by a mean of 2.2 ms (90 % CI −2.0 to 6.3 ms) at the mean maximum concentration (C_{max}) of darunavir (6,599 ng/mL) [14].

3 Pharmacokinetic Properties

This section provides an overview of the pharmacokinetics of darunavir, which have been reviewed previously [15, 16, 53]. Some data are available as abstracts and/or posters [54–59] or from the US [14] or EU [13] prescribing information. Darunavir exposure parameters following

administration of ritonavir-boosted darunavir in adult and paediatric patients infected with HIV-1 in multicentre trials (discussed in Sect. 4) are summarized in Table 2.

Absorption of darunavir is rapid after oral administration, with the C_{max} of the drug usually being reached within 2.5–4.0 h when boosted with low-dose ritonavir (i.e. 100 mg twice daily) [13, 14]. Coadministering a single dose of oral darunavir 600 mg with low-dose ritonavir increased the absolute bioavailability of darunavir to ≈82 versus ≈37 % when the darunavir dose was administered alone [13, 14]; the corresponding increase in darunavir systemic exposure upon coadministration with ritonavir was ≈14-fold [13].

Exposure to darunavir is increased by ≈30 % [60] or ≈40 % [14] when ritonavir-boosted darunavir is administered in the fed versus the fasted state, irrespective of the meal type; thus, ritonavir-boosted darunavir should always be administered with food [13, 14].

Darunavir is highly plasma protein bound (≈95 %), with α_1-acid glycoprotein being the predominant contributor to binding [13, 14]. Darunavir can also be detected in the cervicovaginal fluid [61], semen [62, 63] and cerebrospinal fluid (CSF) [64–66] of patients infected with HIV-1 receiving ritonavir-boosted darunavir at recommended dosages (Sect. 7), with most darunavir (97.2 %) in the CSF being protein unbound [65]. Notably, penetration of the drug into the CSF may be lower with once-daily darunavir 800 mg plus ritonavir 100 mg than with twice-daily darunavir 600 mg plus ritonavir 100 mg [64], the clinical relevance of which requires further investigation. The mean volume of distribution of intravenous darunavir is ≈1.5-fold higher when coadministered with twice-daily ritonavir 100 mg than when administered alone (131 vs. 88.1 L) [13].

Metabolism of darunavir is extensive and primarily oxidative, producing (in humans) at least three oxidative metabolites, all of which are at least tenfold less active than the parent drug against wild-type HIV [13]. The cytochrome P450 (CYP) isoenzyme CYP3A4 is almost exclusively responsible for the metabolism of darunavir [13].

Ritonavir-boosted darunavir has a terminal elimination half-life of ≈15 h [13, 14]. Elimination of darunavir was mainly via the faeces (≈79.5 %) and urine (13.9 %) after administration of a single dose of radiolabeled darunavir 400 mg plus ritonavir 100 mg, with ≈41.2 and 7.7 % of the darunavir dose recovered as unchanged parent drug via these routes [13, 14]. The clearance of intravenous

Table 2 Pharmacokinetic properties of darunavir following oral administration of ritonavir-boosted darunavir in adult and paediatric patients infected with HIV-1. Data for all but the DELPHI trial [36] are sourced from the US prescribing information [14]

Trial	Regimen (mg)	ART experience (no. of evaluable patients)	C_{trough} [range] (μg/mL)[a]	AUC_{24} [range] (μg·h/mL)[a]
Adult patients				
ARTEMIS	DRV 800 + RTV 100 od	Naïve (335)	2.0 [0.4–7.2]	87.9 [45–219]
ODIN	DRV 800 + RTV 100 od	Experienced[b] (280)	1.9 [0.2–7.9]	87.8 [45–237]
	DRV 600 + RTV 100 bid	Experienced[b] (278)	3.2 [0.3–11.9]	109.4 [49–324]
TITAN	DRV 600 + RTV 100 bid	Experienced (285)	3.3 [1.5–13.2]	111.6 [65–355]
POWER 1 and 2	DRV 600 + RTV 100 bid	Experienced (119)	3.5 [1.3–7.4]	123.3 [68–213]
Paediatric patients[c]				
DIONE	DRV 800 + RTV 100 od	Naïve (12)	2.2 [0.5–3.8]	86.7 [36–123]
DELPHI	DRV 11–19/kg + RTV 1.5–2.5/kg bid[d]	Experienced (76)	3.7 [1.8–7.2]	123 [72–202]
ARIEL		Experienced		
	DRV 20/kg + RTV 3/kg bid	BW 10 to <15 kg (10)	4.1 [2.5–9.4]	124 [89.7–261]
	DRV 380 + RTV 48[e] bid	BW 15 to <20 kg (13)	3.9 [3.0–10.3]	133 [112–295]

ART antiretroviral therapy, *AUC_{24}* area under the plasma concentration-time curve from time 0 to 24 h, *bid* twice daily, *BW* bodyweight, *C_{trough}* plasma concentration at end of dose administration interval, *DRV* darunavir, *od* once daily, *RTV* ritonavir

[a] Values are median population pharmacokinetic estimates

[b] Patients were treatment experienced but had no darunavir resistance-associated mutations

[c] Paediatric patients were aged 12 to <18 years weighing ≥40 kg (DIONE), 6–17 years weighing ≥20 kg (DELPHI) or 3 to <6 years weighing 10 to <20 kg (ARIEL)

[d] DELPHI had two parts; data presented are from part two. The weight-based DRV + RTV dosage of 11–19 mg/kg + 1.5–2.5 mg/kg bid was selected for evaluation in the second part of the trial because in part one (dosage selection phase; $n = 41$ evaluated for pharmacokinetics) it provided DRV exposure similar to that seen with the recommended dosage of 600 + 100 mg bid in adults

[e] Children received DRV suspension (3.8 mL) and RTV solution (0.6 mL)

darunavir 150 mg coadministered with low-dose ritonavir was 5.9 L/h.

3.1 Special Patient Groups

Exposure to darunavir following twice-daily bodyweight-based dosages of ritonavir-boosted darunavir in treatment-experienced children and adolescents (aged 3–17 years) was generally similar to that following twice-daily darunavir 600 mg plus ritonavir 100 mg in treatment-experienced adults (Table 2) [14, 36]. Likewise, once-daily darunavir 800 mg plus ritonavir 100 mg provided similar darunavir exposure in treatment-naïve adolescents (aged 12 to <18 years) to that in adults who were treatment naïve or experienced (Table 2) [14].

The once-daily ritonavir-boosted darunavir dosages recommended for paediatric patients aged 3 to <12 years in the USA (see prescribing information for details) are based on population pharmacokinetic models/simulations, with darunavir exposures predicted to be similar to those with once-daily darunavir 800 mg plus ritonavir 100 mg in treatment-naïve adults [14].

Relative to healthy subjects, exposure to darunavir (following twice-daily administration of darunavir 600 mg plus low-dose ritonavir for 6 days) was not significantly altered in patients with mild or moderate hepatic impairment (Child Pugh class A or B) [67]. In these patients, ritonavir-boosted darunavir requires no dosage adjustment [13, 14], although caution is advised in the EU [13]. Ritonavir-boosted darunavir is contraindicated [13] or not recommended [14] in patients with severe hepatic impairment, owing to a lack of data in these patients.

No dosage adjustments or special precautions are required in renally impaired patients [13]. As darunavir undergoes limited renal clearance, renal impairment should not reduce total body clearance of the drug [14]. There are no data on the pharmacokinetics of darunavir in HIV-infected patients with severely impaired renal function or end-stage renal disease [14], although moderate renal impairment (creatinine clearance 30–60 mL/min) had no significant impact on darunavir pharmacokinetics in a population pharmacokinetic analysis [13, 14]. Given the high plasma protein binding of darunavir and ritonavir, significant removal via haemodialysis or peritoneal dialysis is unlikely.

Exposure to darunavir does not appear to be affected to any clinically relevant extent by gender [14, 68], race [14, 68], hepatitis B and/or C virus (HBV and/or HCV) co-infection status [14, 69], age [68] or bodyweight [68], according to population pharmacokinetic analyses [14] (including GRACE [68]; see Sect. 4.2.1.3) and data from ARTEMIS [14], POWER 3 [69] and TITAN [14] (see Sects. 4.1.1 and 4.2.1). However, use of darunavir in elderly patients (aged ≥65 years) requires caution, given that data in this population are limited and the frequency of hepatic impairment, concomitant disease and cotherapy is greater [13, 14]. Furthermore, plasma concentrations of darunavir may decrease with increasing body mass index (BMI), according to a study in which 53 HIV-infected adults received darunavir plus ritonavir 800 mg plus 100 mg once daily or 600 mg plus 100 mg twice daily [54].

During pregnancy, ritonavir-boosted darunavir should be used only if the potential risk is justified by the potential benefit, as adequate well-controlled studies have not yet been conducted with darunavir in this setting [13, 14]. Use of ritonavir-boosted darunavir has been evaluated in pregnant women in several small studies ($n = 5$–33 evaluable recipients) [55–59, 70]. Overall exposure to darunavir appeared to vary during pregnancy and postpartum [55–58, 70], although where specified [70], no clinically relevant changes in exposure to unbound darunavir occurred; all babies were HIV negative where reported [55, 58, 59, 70]. Larger studies in this setting would be beneficial.

3.2 Drug Interactions

Potentially clinically significant drug interactions demonstrated or predicted to occur between ritonavir-boosted darunavir and agents likely to be administered in patients with HIV-1 infection are summarized in Table 3 [13, 14]. CYP3A is key to the metabolism of darunavir and ritonavir; thus, plasma concentrations of these drugs may be increased by agents that inhibit CYP3A and reduced by those that induce CYP3A (Table 3) [13, 14].

Ritonavir-boosted darunavir induces CYP2C9 and CYP2C19 activity and may therefore reduce the plasma concentration of agents that are metabolized predominantly by these enzymes (Table 3) [13]. Systemic exposure to drugs metabolized primarily by CYP2C8 (e.g. rosiglitazone, paclitaxel, repaglinide) may also be reduced if coadministered with darunavir and ritonavir, according to in vitro data [13]. In addition, ritonavir-boosted darunavir inhibits the activity of CYP3A, CYP2D6 [13, 14] and permeability–glycoprotein transporters [14] and may increase exposure to agents primarily metabolized or eliminated by these enzymes (Table 3).

Ritonavir-boosted darunavir is contraindicated for use in combination with drugs that have a narrow therapeutic index and depend highly on CYP3A for clearance. These agents include alfuzosin, cisapride, pimozide, ergot derivatives, triazolam, oral midazolam, lovastatin, simvastatin and sildenafil (for pulmonary arterial hypertension) in the USA [14] and EU [13], with the EU also contraindicating sertindole, astemizole, terfenadine, amiodarone, bepridil,

Table 3 Drug interactions of potential clinical significance associated with ritonavir-boosted darunavir. Recommendations apply to both the EU and USA, unless otherwise specified; data are derived from the US [14] and EU [13] prescribing information

Coadministered agent	Effect of coadministration with DRV + RTV on drug conc (mechanism, where known)	Recommendations regarding use in combination with DRV + RTV
Antiretroviral agents		
Indinavir	DRV ↑, indinavir ↑ (CYP3A inhib)	↓ indinavir dosage if intolerance occurs in EU; indinavir dosage recommendations not established in USA
Saquinavir	DRV ↓, saquinavir ↔	Not recommended
Lopinavir/ritonavir	DRV ↓ (CYP3A induc), lopinavir ↔	Contraindicated in EU and not recommended in USA
Didanosine	DRV ↔, didanosine ↔	Administer didanosine 1 h before or 2 h after DRV + RTV
TDF	DRV ↑, TDF ↑ (p-gp inhib)	Renal function may require monitoring in EU
Efavirenz	DRV ↓ (CYP3A induc), efavirenz ↑ (CYP3A inhib)	In EU, CNS toxicity monitoring may be required and DRV 600 mg + RTV 100 mg bid is recommended
Maraviroc	Maraviroc ↑	Maraviroc 150 mg bid is recommended
Antimicrobial agents (class)		
Clarithromycin (antibacterial)	DRV ↔, clarithromycin ↑ (CYP3A and p-gp inhib)	Use with caution in EU; adjust clarithromycin dosage in pts with renal impairment in USA
Rifabutin (antimycobacterial)	DRV ↑, rifabutin ↑	Adjust rifabutin dosage and ↑ AE monitoring
Rifampicin [rifampin] (antimycobacterial)	May cause profound PI ↓ (CYP3A induc)	Contraindicated
Voriconazole (antifungal)	Voriconazole ↓ (CYP induc)	Coadminister voriconazole only if benefit/risk ratio justifies its use
Ketoconazole, itraconazole, clotrimazole (antifungals)	DRV ↑, ketoconazole ↑, itraconazole ↑ (CYP inhib)	Coadminister with caution and monitor pts in EU. Ketoconazole and itraconazole dosage should be ≤200 mg/day
Other drugs (class)		
Digoxin (antiarrhythmic)	Digoxin ↑ (p-gp inhib)	Initiate digoxin at lowest possible dosage, then titrate as required
Bepridil, amiodarone, propafenone, quinidine, flecainide, systemic lidocaine (antiarrhythmics)	Antiarrhythmic ↑ (CYP2D6 or CYP3A inhib)	Coadminister with caution and monitor antiarrhythmic conc in USA. Bepridil, quinidine, amiodarone and systemic lidocaine contraindicated in EU
Warfarin (anticoagulant)	DRV ↔, warfarin ↓ (CYP2C9 induc)	Monitor international normalized ratio
Bosentan (endothelin receptor antagonist)	Bosentan ↑	Monitor bosentan tolerability in EU; in USA, temporarily discontinue bosentan therapy before starting DRV + RTV and use bosentan od or qod depending on tolerability
Artemether/lumefantrine (antimalarials)	DRV ↔, artemether ↓, lumefantrine ↑	Coadminister with caution as QT prolongation risk may increase with increased lumefantrine exposure
Carbamazepine (anticonvulsant)	DRV ↔, carbamazepine ↑	Monitor carbamazepine conc and titrate dosage. Monitor for AEs in EU
Phenytoin, phenobarbital (anticonvulsants)	DRV ↔ or ↓ (CYP induc), phenytoin ↓, phenobarbital ↓	Not recommended in EU. Monitor phenobarbital and phenytoin conc in USA
Trazodone, desipramine (antidepressants)	Trazodone ↑, desipramine ↑	In USA, coadminister with caution and consider reducing dosage of trazodone or desipramine
Midazolam, triazolam (benzodiazepines)	Midazolam ↑, triazolam ↑ (CYP3A inhib)	Triazolam and oral midazolam contraindicated. Use parenteral midazolam (caution in EU) and consider dosage adjustment
St John's wort [*Hypericum perforatum*] (herbal agent)	DRV ↓, RTV ↓ (CYP induc)	Contraindicated
Dexamethasone (corticosteroid)	DRV ↓ (CYP induc)	Administer systemic dexamethasone with caution in EU
Fluticasone propionate, budesonide (corticosteroids)	Fluticasone propionate ↑	In EU, do not coadminister unless benefit outweighs systemic effect risk; consider glucocorticoid dosage adjustment or a glucocorticoid not metabolized by CYP3A. In USA, consider alternatives to fluticasone propionate

Table 3 continued

Coadministered agent	Effect of coadministration with DRV + RTV on drug conc (mechanism, where known)	Recommendations regarding use in combination with DRV + RTV
Boceprevir, telaprevir (antivirals)	DRV ↓, boceprevir ↓, telaprevir ↓	Not recommended
Salmeterol (inhaled beta-adrenergic receptor agonist)	Salmeterol ↑	Not recommended
Metoprolol, timolol (beta-blockers)	Beta-blocker ↑	In USA, administer with caution and monitor pts – beta-blocker dosage reduction may be required
Felodipine, nifedipine, nicardipine (CCAs)	CCA ↑ (CYP3A inhib)	Administer with caution in USA. Clinical monitoring recommended
Pravastatin, atorvastatin, rosuvastatin (HMG-CoA reductase inhibitors)	HMG-CoA reductase inhibitor ↑	Start with/use lowest possible HMG-CoA reductase inhibitor dosage, titrating as necessary; atorvastatin dosage should be 10 mg od initially in EU and ≤20 mg/day in USA
Lovastatin, simvastatin (HMG-CoA reductase inhibitors)	Lovastatin ↑, simvastatin ↑ (CYP3A inhib)	Contraindicated
Ethinyl estradiol, norethindrone (oral contraceptive)	Ethinyl estradiol ↓, norethindrone ↓	Alternative contraception methods (or additional methods in EU) recommended. Clinical monitoring recommended in EU for pts on estrogen hormone replacement therapy
Sildenafil, vardenafil, tadalafil (phosphodiesterase type 5 inhibitor)	Phosphodiesterase type 5 inhibitor ↑	For erectile dysfunction, caution is advised (in EU) and dosage restrictions recommended. For PAH, sildenafil is contraindicated; tadalafil requires dosage/administration consideration in USA and is not recommended in EU
Risperidone, thioridazone (neuroleptics)	Neuroleptic ↑	Reduction in neuroleptic dosage may be required in USA
Colchicine (antigout agent)	Colchicine ↑	Interrupt colchicine or reduce its dosage in EU; dosage restrictions/adjustments recommended in USA. Not recommended in pts with renal or hepatic impairment
Cyclosporine, tacrolimus, sirolimus (immunosuppressant)	Immunosuppressant ↑	Monitor immunosuppressant conc
Sertraline, paroxetine (SSRIs)	DRV ↔, SSRI ↓	Titrate SSRI dosage according to antidepressant response
Methadone, buprenorphine, buprenorphine/naloxone (opioids/opioid antagonists)	Methadone ↓ (CYP2C19 induc), naloxone ↔, buprenorphine ↔, norbuprenorphine ↑	Clinical monitoring recommended. Methadone dosage adjustment may be required; dosage adjustment may not be necessary for buprenorphine in EU and is not needed for buprenorphine or buprenorphine/naloxone in USA

AE(s) adverse events, *bid* twice daily, *CCA* calcium channel antagonist, *conc* concentration, *CYP* cytochrome P450, *DRV* darunavir, *induc* induction, *inhib* inhibition, *od* once daily, *PAH* pulmonary arterial hypertension, *p-gp* permeability glycoprotein, *pts* patients, *qod* every other day, *RTV* ritonavir, *SSRI(s)* selective serotonin reuptake inhibitor(s), *TDF* tenofovir disoproxil fumarate, ↑ increase, ↓ decrease, ↔ no change

quinidine and systemic lidocaine [13]. For other drugs contraindicated in ritonavir-boosted darunavir recipients see Table 3.

No interactions requiring dosage adjustment have been demonstrated for ritonavir-boosted darunavir in combination with atazanavir, etravirine, nevirapine, rilpivirine, omeprazole, ranitidine [13, 14], efavirenz or tenofovir disoproxil fumarate [14] in clinical studies (monitoring may be required with the latter two drugs in the EU; Table 3) and none are expected to occur between ritonavir-boosted darunavir and emtricitabine, lamivudine, stavudine, zidovudine, abacavir [13, 14] or zalcitabine [14]. Raltegravir may reduce plasma concentrations of darunavir, according to some clinical studies/literature references, although at present these reductions do not appear to be of any clinical relevance [13, 14].

4 Therapeutic Efficacy

This section reviews the efficacy of oral ritonavir-boosted darunavir in combination with other antiretroviral agents in the treatment of adult (Sects. 4.1 and 4.2) and paediatric (Sect. 4.3) patients with HIV-1 infection, as evaluated in several key open-label [21, 32, 36, 44, 46, 48, 71–75] or partially-blinded [76, 77] trials (n > 80, except where data

are limited). Trials were multicentre (or not specified as such [74]), with one study [72] including data from two trials (13 sites of one study and one site of another). Some data were sourced from abstracts/posters [20, 21, 49, 78, 79], conference reports [75] or the US prescribing information [14].

In general, patients were required to have a plasma viral load ≥5,000 copies/mL if treatment naïve or >1,000 copies/mL if treatment experienced. Where specified, trials conducted in adults generally excluded patients with active AIDS-defining illness (other than wasting syndrome or stable Kaposi sarcoma [32, 44, 73]), clinically significant disease or HBV/HCV coinfection (e.g. if clinically unstable or expected to require treatment during the study). Among other exclusion criteria were reduced hepatic function [32, 44, 46, 76], hepatic decompensation [32, 46], acute viral hepatitis [32, 46, 73] (specifically hepatitis A [76]) and active hepatic disease [76, 77] (specifically hepatitis B [48]). Exclusion criteria were not reported for paediatric studies.

Several randomized trials stratified patients by factors such as screening viral load [32, 44, 46, 76, 77], CD4+ cell count [46], number of primary PI mutations [76, 77] or use of NNRTIs [44] or enfuvirtide [76, 77] in the background therapy. Efficacy was evaluated using surrogate endpoints of virological and immunological response (i.e. viral load and CD4+ cell count); virological failure was also assessed in some trials, and included patients who failed to achieve virological suppression (criteria varying between studies) as well as those who experienced viral rebound.

4.1 Treatment-Naïve Adults

Discussion in this section focuses on the 192-week, randomized, phase III study, known as ARTEMIS [31, 46, 47], designed to assess the noninferiority of ritonavir-boosted darunavir versus ritonavir-boosted lopinavir, when used in combination with NRTI background therapy in ART-naïve adults (see Table 4 for details). Data from two 48-week phase IIb [48] or pilot [74] studies evaluating the efficacy of ritonavir-boosted darunavir as part of an NRTI-sparing regimen in ART-naïve adults are also briefly discussed (patients with two or more darunavir RAMs or known major integrase RAMs were excluded where specified [48]).

In ARTEMIS, noninferiority analyses were generally conducted in the per-protocol population, with subsequent superiority testing in the intent-to-treat (ITT) population if noninferiority was established; primary efficacy analyses in other studies used an ITT [48] or modified ITT [74] approach. Across trials, at baseline, patients had a mean/median age of ≈35–42 years, a mean/median viral load of ≈4.8 $\log_{10}$ copies/mL and, where specified, a mean duration of infection of ≈2.5 years [46]; the viral load was

Table 4 Efficacy of once-daily oral ritonavir-boosted darunavir in combination with background therapy in antiretroviral therapy-naïve adults with HIV-1 infection. Results of the phase III, ARTEMIS trial

Treatment (mg/day)[a]	Week of eval	Ref	Pts (%) with plasma HIV-1 RNA level <50 copies/mL[b]				Median change from BL[c] in CD4+ cell count (cells/μL)	Pts (%) with virological failure
			PP[d]	ITT[d]	PP BGD (95 % CI)	ITT BGD (95 % CI)		
DRV 800 + RTV 100	48	[46]	84	84	5.6 (−0.1 to −11)[e]	5.5 (−0.3 to −11)	137[f]	10[f]
LPV 800 + RTV 200			78	78			141[f]	14[f]
DRV 800 + RTV 100	96	[47]	NR	79	8.4 (1.9–14.8)[e]	8.3 (1.8–14.7)*	171	12*
LPV 800 + RTV 200			NR	71			188	17
DRV 800 + RTV 100	192	[31]	69	69	12.0 (4.8–19.2)[e]	11.6 (4.4–18.8)[e]**	258[f]	16
LPV 800 + RTV 200			57	57			263[f]	21

BGD between-group difference, *bid* twice daily, *BL* baseline, *DRV* darunavir, *eval* evaluation, *ITT* intent-to-treat, *LPV* lopinavir, *NR* not reported, *od* once daily, *PP* per-protocol, *pts* patients, *ref* reference, *RTV* ritonavir

* $p < 0.05$, ** $p < 0.005$ vs. LPV + RTV group

[a] DRV + RTV was administered od and the LPV + RTV dosage was 800 + 200 mg od (15 % of pts) or 400 + 100 mg bid (75–77 %), with a switch from bid to od permitted for intolerance (8–11 %); all pts received tenofovir disoproxil fumarate + emtricitabine. LPV + RTV was initially administered as capsules, with a subsequent switch to tablets permitted subject to local approval and availability; by week 48, most pts (83 %) had switched to tablets

[b] Primary endpoint at 48 weeks, determined using the US FDA time-to-loss-of-virological-response algorithm

[c] The median CD4+ cell count at BL was 228 and 218 cells/μL in DRV and LPV recipients

[d] ITT population included 343 DRV and 346 LPV recipients and the PP population 340 and 346 recipients

[e] Noninferiority of DRV + RTV vs. LPV + RTV was established (criterion for noninferiority was a 95 % CI lower limit for the BGD in response of greater than −12 %). Key noninferiority analyses were conducted in the PP population (at week 48 [primary objective] and 96) or ITT population (at week 192), with subsequent testing for superiority in the ITT population if noninferiority was established

[f] Between-group statistical analyses were NR

≥100,000 copies/mL in 34 % [46] and 44 % [48] of patients.

4.1.1 ARTEMIS Study

When used in combination with a dual NRTI background therapy in treatment-naïve adults, once-daily darunavir 800 mg plus ritonavir 100 mg was noninferior to lopinavir 800 mg plus ritonavir 200 mg (administered in one or two divided doses) in establishing virological suppression, as measured by the proportion of patients who achieved a viral load <50 copies/mL (i.e. a response) after 48 weeks of therapy (primary endpoint) [Table 4] [46]. The between-group difference in this measure did not reach statistical significance at this timepoint in subsequent superiority analyses (Table 4).

However, the darunavir regimen was significantly more effective than the lopinavir regimen in maintaining virological suppression during longer-term use. Noninferiority of ritonavir-boosted darunavir versus ritonavir-boosted lopinavir in terms of the proportion of patients achieving a viral load <50 copies/mL was established at 96 and 192 weeks, with subsequent superiority testing finding darunavir to be significantly more effective in this regard at both timepoints (Table 4) [31, 47]. Moreover, post hoc analyses at 192 weeks suggested that once-daily darunavir provided significant ($p \leq 0.018$) benefit over lopinavir, regardless of whether lopinavir was administered once or twice daily [31].

According to the results of stratification, significantly ($p < 0.05$) more patients with a high baseline viral load (≥100,000 copies/mL) achieved a response with ritonavir-boosted darunavir than with ritonavir-boosted lopinavir after 48, 96 and 192 weeks' therapy [31, 46, 47]. Likewise, significantly ($p = 0.038$) more darunavir than lopinavir recipients with a baseline viral load <100,000 copies/mL achieved a response at 192 weeks [31]; the between-group difference was not significant at week 48 [46] or 96 [47].

When stratified via baseline CD4+ cell count, response rates did not significantly differ between darunavir and lopinavir at 48 weeks among patients with <200 or ≥200 CD4+ cells/μL at baseline [46]. However, longer term, significantly ($p < 0.02$) more darunavir than lopinavir recipients achieved a response after 96 weeks' therapy among those with <200 cells/μL at baseline [47] and after 192 weeks' therapy among those with ≥200 cells/μL at baseline [31].

When other baseline patient characteristics were assessed to determine their impact on darunavir efficacy at 96 weeks, ritonavir-boosted darunavir appeared to provide virological benefit regardless of gender, age, race or HBV/HCV co-infection status; response rates varied slightly in some subgroups, although these subgroups were generally small (<55 patients) [80]. Compared with ritonavir-boosted lopinavir, response rates at 192 weeks favoured ritonavir-boosted darunavir across all patient subgroups evaluated, although the between-group difference was not statistically significant for some patient groups, including those aged ≤30 years or infected with HIV-1 of clade C or B [31].

With regard to other efficacy measures, median changes from baseline in CD4+ cell count were reported to not significantly differ between the darunavir and lopinavir groups at 96 weeks (Table 4) [47]. However, significantly fewer darunavir than lopinavir recipients had experienced virological failure at this timepoint [47], although the between-group difference was no longer significant at 192 weeks (Table 4) [31].

The proportion of patients adherent to treatment at 192 weeks, as assessed by the modified medication adherence self-report inventory (M-MASRI) questionnaire, did not differ significantly between the darunavir and lopinavir regimens (83 vs. 78 %) [31].

4.1.2 Other Studies

Data from a noncomparative study, ACTG A5262 ($n = 112$), suggested that once-daily darunavir 800 mg plus ritonavir 100 mg used in combination with twice-daily raltegravir 400 mg may be a useful NRTI-sparing regimen for some ART-naïve adults [48]. Virological failure occurred in 16 % (95 % CI 10–24) of patients after 24 weeks' therapy (primary endpoint), meeting the prespecified definition of satisfactory efficacy (95 % CI upper limit of <35 % for virological failure at week 24), and in 26 % of patients after 48 weeks. Of note, baseline viral loads were significantly ($p = 0.002$) higher and baseline CD4+ cell counts significantly ($p = 0.007$) lower among those who experienced virological failure than among those who did not. With regard to other endpoints, a viral load of <50 or <200 copies/mL was achieved by a large proportion of patients at weeks 24 (79 and 93 %) and 48 (71 and 86 %), and a significant ($p < 0.001$) improvement in CD4+ cell count was seen at both timepoints (median change of 142 and 200 cells/μL; 271 cells/μL at baseline).

However, when this regimen was compared with a standard regimen comprising once-daily ritonavir-boosted darunavir (at the same dosage) plus two NRTIs in ART-naïve patients in another 48-week study ($n = 85$ randomized), significantly fewer patients achieved a viral load <48 copies/mL at study end with the class-sparing regimen than with the standard regimen (62.5 vs. 83.7 %; $p = 0.045$), although mean changes from baseline in CD4+ cell count did not significantly differ between the groups [74].

4.2 Treatment-Experienced Adults

4.2.1 Twice-Daily Administration

This section reviews the clinical efficacy of twice-daily darunavir 600 mg plus ritonavir 100 mg in ART-experienced adults. Discussion focuses on randomized, active comparator-controlled, phase IIb [76, 77] or III [44] trials, known as POWER 1 [76], POWER 2 [77] and TITAN [44], that compared the efficacy of this darunavir regimen with that of twice-daily ritonavir-boosted lopinavir [44] or investigator-selected control PIs (CPIs) [76, 77], when used in conjunction with background therapy. Noncomparative phase II [71] or IIb [72] trials, POWER 3 [72] and ANRS 139 TRIO [71], that evaluated the efficacy of ritonavir-boosted darunavir in combination with background therapy [72] or as part of a salvage regimen containing etravirine and raltegravir [71] are also discussed. See Table 5 for further details of these trials. The key findings of a phase IIIb trial known as GRACE [73, 81] designed to assess gender- and race-based differences in darunavir response are also briefly summarized.

Across the pivotal studies [44, 71, 72, 76, 77], patients had a mean or median age of 41–46 years and, where specified, a mean duration of infection of ≈9–13 years [44, 72, 76]. Patients enrolled in TITAN had a broad range of treatment experience and had received ≥12 weeks of highly active ART (HAART) [although were naïve to lopinavir]; at baseline, most patients had susceptibility to at least two NRTIs (92 %) and at least four PIs (82 %) and the median number of primary PI RAMs was zero (range 0–6) [44].

By contrast, the POWER [72, 76, 77] and ANRS 139 TRIO [71] trials enrolled highly treatment-experienced patients. Eligibility criteria included the use of NRTIs [72] (two or more [76, 77]) for ≥12 weeks, at least one NNRTI [72, 77] (in a failing regimen [76]), at least one PI for ≥12 weeks [72, 76, 77] or stable combination ART for ≥8 weeks [71]. Patients were also required to be infected with a HIV-1 strain with at least one [72, 76, 77] or three [71] primary PI RAMs. Where specified, at baseline, most patients (63 % [76] or 80 % [72]) were resistant to all PIs commercially available at the time of the trial, with FC values for individual PIs exceeding clinical cut-offs in 71–97 % of patients [72, 77]. At baseline, patients had a median of three [72, 76] or four [71] primary PI RAMs, eight [76] or nine [72] PI RAMs, six NRTI RAMs and one NNRTI RAM [71].

Twice-daily ritonavir-boosted darunavir provided both virological and immunological benefit for up to 144 weeks

Table 5 Efficacy of twice-daily oral ritonavir-boosted darunavir in treatment-experienced adults with HIV-1 infection in phase II/IIb or III trials. Primary efficacy analyses used an intent-to-treat approach unless otherwise specified; some data are from posters [49, 79]

Study	Regimen[a] (mg bid) [no. of pts[b]]	Week of eval	Ref	Pts (%) with a plasma viral load			Mean change from BL [BL]	
				Decrease from BL ≥1 $\log_{10}$ copies/mL[c]	<50 copies/mL	<400 copies/mL	Plasma viral load ($\log_{10}$ copies/mL)	CD4+ cell count (cells/μL)
Comparative studies								
POWER 1[d]	DRV 600 + RTV 100 [60]	24	[76]	77**	53**	67**	−2.03** [4.5]	124** [176]
	CPI + RTV [60]			25	18	25	−0.63 [4.4]	20 [197]
POWER 2[d]	DRV 600 + RTV 100 [39]	24	[77]	62**	39**	49*	−1.7** [4.7]	59** [99]
	CPI + RTV [42]			14	7	10	−0.3 [4.6]	12 [113]
POWER 1 and 2 (pooled)	DRV 600 + RTV 100 [110]	48	[45]	61***	45***		−1.63*** [4.6]	102*** [153]
	CPI + RTV [120]			15	10		−0.35 [4.5]	19 [163]
	DRV 600 + RTV 100 [131]	96	[50]		39**			133**
	CPI + RTV [124]				9			15
	DRV 600 + RTV 100 [131]	144	[79]	51***	37**			128**
	CPI + RTV [124]			10	9			15
TITAN	DRV 600 + RTV 100 [286]	48	[44]	77*	71**	77*[e] [77[f]][g]	−1.95* [4.3]	88[h,i] [235]
	LPV 400 + RTV 100 [293]			69	60	67[e] [68[f]][g]	−1.72 [4.3]	81[h,i] [230]
	DRV 600 + RTV 100 [280]	96	[35]		60.4	66.8*[e] [67.5[f]]		81[h,i]
	LPV 400 + RTV 100 [294]				55.2	58.9[e] [59.5[f]]		93[h,i]
Noncomparative studies								
POWER 3	DRV 600 + RTV 100 [246]	24	[72]	65	40	57	−1.65 [4.6]	80 [115]
	[336]	96	[50]		42			103
	[325]	144	[49]	39	32			118

Table 5 continued

Study	Regimen[a] (mg bid) [no. of pts[b]]	Week of eval	Ref	Pts (%) with a plasma viral load			Mean change from BL [BL]	
				Decrease from BL ≥1 log_{10} copies/mL[c]	<50 copies/mL	<400 copies/mL	Plasma viral load (log_{10} copies/mL)	CD4+ cell count (cells/μL)
ANRS 139 TRIO	DRV 600 + RTV 100 + RAL 400 + ETR 200 [103]	24	[71]		90[g]		−2.3[j] [4.2]	105[j] [255]
	[103]	48	[71]		86		−2.4[h]	108[h]
	[100]	96	[43]		88		−2.3	150[h]

Rates of virological response (except viral load <400 copies/mL in POWER 1 and 2 and decrease in viral load ≥1 log_{10} copies/mL in TITAN) were specified as being determined using the US FDA time-to-loss-of-virological-response algorithm in all trials other than ANRS 139 TRIO

bid twice daily, *btwn-grp diff* between-group difference, *BL* baseline, *CPI* control protease inhibitor, *DRV* darunavir, *ETR* etravirine, *eval* evaluation, *LPV* lopinavir, *NRTIs* nucleoside (nucleotide) reverse transcriptase inhibitors, *PP* per-protocol, *pts* patients, *RAL* raltegravir, *Ref* reference, *RTV* ritonavir

* $p < 0.05$, ** $p \leq 0.005$, *** $p < 0.0001$ vs. comparator group

[a] Pts (generally [71]) also received a background regimen comprising NRTIs (≥2 where specified [76, 77]) +/− enfuvirtide [71, 72, 76, 77] or ≥2 antiretrovirals (NRTIs +/− non-nucleoside reverse transcriptase inhibitors) [44]. In TITAN, pts randomized to LPV + RTV could switch from the capsule to the newer tablet formulation (59 % had switched before week 96)

[b] Number of pts enrolled in ANRS 139 TRIO, in the PP population in TITAN (primary analysis population), or who had reached the specified treatment timepoint at the time of analysis in the POWER studies, where specified [45, 49, 72, 76, 77, 79]

[c] Primary efficacy measure in the POWER studies; primary efficacy analysis was at week 24

[d] Dose-ranging study; however, only data for the DRV + RTV dosage approved for use in this patient population (i.e. 600 + 100 mg bid) are presented. BL values for the DRV + RTV group are for all dosages evaluated (individual values for approved dosage were not reported)

[e] Superiority of DRV vs. LPV was demonstrated in the intent-to-treat population ($n = 298$ and 297) in a secondary analysis; criteria for superiority (95 % CI lower limit >0 % for btwn-grp diff in response) was met both at 48 weeks (btwn-grp diff 10 %; 95 % CI 2–17) and 96 weeks (8.7 %; 95 % CI 0.7–16.7)

[f] PP data. Mean PP btwn-grp diff was 9 % (95 % CI 2–16) at 48 weeks and 8.7 % (95 % CI 0.7–16.8) at 96 weeks; noninferiority of DRV vs. LPV in this population (primary analysis) was established at both timepoints (criteria for noninferiority was a 95 % CI lower limit for the btwn-grp diff in response not exceeding −12 %)

[g] Primary endpoint

[h] Median change

[i] Statistical analyses for btwn-grp diff were not reported

[j] Value estimated from a graph

of treatment when used in combination with other antiretroviral agents in ART-experienced adults in these comparative and noncomparative trials.

4.2.1.1 TITAN Trial In combination with NRTI-based background therapy, twice-daily ritonavir-boosted darunavir provided significantly better virological suppression than twice-daily ritonavir-boosted lopinavir, according to primary endpoint analyses of the TITAN trial. Having established the noninferiority of the darunavir versus the lopinavir regimen, subsequent superiority testing found significantly more darunavir than lopinavir recipients achieving a viral load of <400 copies/mL after 48 weeks' therapy (primary endpoint), with this benefit being maintained at 96 weeks (Table 5) [35, 44]. Other measures of virological suppression also significantly favoured the darunavir over the lopinavir regimen in most instances, and improvements in CD4+ cell count were seen in both groups (Table 5). Moreover, approximately twofold fewer darunavir than lopinavir recipients experienced virological failure at 48 weeks (10 vs. 22 %) [44] or 96 weeks (13.8 vs. 25.6 %; $p < 0.001$) [35].

In protocol-specified subgroup analyses, ritonavir-boosted darunavir was generally noninferior or superior to ritonavir-boosted lopinavir in achieving a viral load <50 copies/mL at 48 weeks, although did not meet noninferiority criteria in some patient groups, including those with a viral load ≥100,000 copies/mL or <100 CD4+ cells/μL at baseline or lacking sensitivity to background therapy antiretrovirals [44]. Further subgroup analyses (post hoc) suggested that the darunavir regimen was significantly ($p \leq 0.007$) better than the lopinavir regimen in achieving this level of virological suppression at 96 weeks among patients who had used at least one PI previously or had at least one primary PI RAM [35].

4.2.1.2 POWER Trials In POWER 1 and 2, adults with extensive treatment experience receiving NRTI-based background therapy had significantly better virological suppression with twice-daily ritonavir-boosted darunavir than with ritonavir-boosted CPIs after 24 weeks' treatment, as assessed by measures such as the proportion of patients who achieved a viral load reduction of ≥1 log_{10} copies/mL (primary outcome) or a viral load of <400 or <50 copies/mL

(Table 5) [76, 77]. The darunavir regimen continued to provide significant benefit over the CPI arm in terms of virological suppression at 48, 96 and 144 weeks, according to a pooled analysis (Table 5) [45, 50, 79]. Moreover, improvements in CD4+ cell counts were significantly greater in darunavir than CPI recipients at all timepoints (Table 5). These virological and immunological findings are generally supported by data from the noncomparative POWER 3 study (Table 5) [49, 50, 72].

According to subgroup analyses of these studies, the proportion of patients who achieved $\geq$1 $\log_{10}$ reduction in viral load [45, 76, 77] or a viral load <50 copies/mL [50] after 24 [76, 77], 48 [45] or 96 [50] weeks of therapy was numerically [45, 50, 76, 77] or significantly ($p \leq 0.01$) [45] higher with ritonavir-boosted darunavir than with ritonavir-boosted CPIs, regardless of factors such as baseline viral load, number of primary PI mutations at baseline or use of enfuvirtide in the background therapy.

Of note, treatment exposure to the darunavir and CPI regimens differed considerably, mainly due to a high discontinuation rate in the CPI group caused predominantly by virological failure. For instance, at 48 weeks, the respective groups had received 62.3 and 31.5 weeks of therapy and 21 and 81 % of patients had discontinued (8 and 67 % because of virological failure) [45]. However, between-group differences in efficacy were not driven by the discontinuation difference, as at week 12 (when 95 % of CPI recipients were still receiving therapy) a viral load decrease of $\geq$1 $\log_{10}$ copies/mL had already been achieved by significantly more darunavir than CPI recipients (76 vs. 23 %; $p < 0.0001$) [45].

4.2.1.3 Other Studies In the ANRS 139 TRIO study, twice-daily ritonavir-boosted darunavir used in combination with etravirine and raltegravir, with or without background therapy (NRTIs or enfuvirtide), provided virological and immunological benefit in highly treatment-experienced adults with resistance to multiple antiretroviral agents and few remaining treatment options. The majority of patients achieved a viral load of <50 copies/mL after 24 weeks' therapy (primary endpoint), and this benefit was maintained for up to 96 weeks (Table 5) [43, 71]. Moreover, factors such as baseline viral load, CD4+ cell count, background therapy genotypic sensitivity score and using enfuvirtide for the first time had no significant effect on this outcome [71]. Changes from baseline in viral load and CD4+ cell count were also favourable (Table 5) [43, 71]; 19 % of patients experienced virological failure over 96 weeks [43].

In GRACE, no significant differences in rates of virological response (i.e. viral load <50 copies/mL) were observed with twice-daily ritonavir-boosted darunavir plus background therapy (NRTIs and NNRTIs) on the basis of gender (50.9 % in women [$n = 287$] vs. 58.5 % in men [$n = 142$]) after 48 weeks' therapy (primary endpoint analysis in ITT population) [73]. However, a significant ($p = 0.045$) difference in this measure was observed across races, with 61.5 % of Hispanic ($n = 96$), 60.0 % of Caucasian ($n = 65$) and 48.5 % of Black ($n = 264$) patients achieving a virological response [81].

4.2.2 Once-Daily Administration

The efficacy of once-daily and twice-daily ritonavir-boosted darunavir, each used in conjunction with NRTI background therapy, has been compared in ART-experienced adults with HIV-1 infection with no darunavir RAMs in the 48-week randomized, phase III, noninferiority trial known as ODIN [32] (see Table 6 for details).

Eligible patients had a CD4+ cell count of >50 cells/μL and had received a stable HAART regimen for $\geq$12 weeks, without use of darunavir, tipranavir and/or enfuvirtide [32]. At baseline, patients had a mean age of $\approx$40 years and a mean viral load of 4.16 $\log_{10}$ copies/mL and most (75.6 %) had a viral load $\leq$50,000 copies/mL. Almost half of patients were PI naïve (46.1 %) and a large proportion had previously used at least three NRTIs (57.2 %) and/or one or more NNRTIs (87.5 %).

When used in combination with at least two NRTIs, once-daily darunavir 800 mg plus ritonavir 100 mg was noninferior to twice-daily darunavir 600 mg plus ritonavir 100 mg in terms of the proportion of patients who achieved a viral load <50 copies/mL after 48 weeks of therapy (primary endpoint) [Table 6] [32]. In exploratory subgroup analyses, no clinically relevant differences in this measure were evident between the two treatment regimens, irrespective of baseline patient demographics and disease characteristics, such as age, gender, race, HIV-1 clade or viral load ($\leq$50,000 or >50,000 copies/mL), or the number of active NRTIs in the background therapy [82].

The incidence of virological failure did not significantly differ between once- and twice-daily recipients and improvements in CD4+ cell count were observed in both groups (Table 6) [32].

There was no significant difference between the two treatment regimens with regard to improvements in health-related quality of life, as measured by mean changes from baseline in Functional Assessment of HIV-Infection (FAHI) questionnaire total scores and the proportion of patients who achieved a clinically meaningful difference from baseline (i.e. a relative increase of 10 %) in FAHI total score (quantitative data not reported; 262 once-daily and 268 twice-daily recipients evaluable) [78].

Similarly, patient adherence to the once- and twice-daily regimens did not markedly differ, as assessed by the M-MASRI questionnaire (63.1 vs. 55.6 % of patients were

Table 6 Comparative efficacy of once- versus twice-daily oral ritonavir-boosted darunavir in treatment-experienced adults with HIV-1 infection and no darunavir resistance-associated mutations. Summary of the 48-week, phase III ODIN trial [32]

Endpoint	DRV 800 mg + RTV 100 mg od[a] ($n = 294$[b])	DRV 600 mg + RTV 100 mg bid[a] ($n = 296$[b])
Pts (%) with plasma HIV-1 RNA level <50 copies/mL	72.1[c]	70.9[c]
Median change from BL [BL] in CD4+ cell count (cells/μL)	100[d] [219]	94[d] [236]
Pts (%) with virological failure	22.1	18.2

bid twice daily, *BL* baseline, *DRV* darunavir, *od* once daily, *pts* patients, *RTV* ritonavir

[a] Pts also received ≥2 nucleoside reverse transcriptase inhibitors

[b] Intent-to-treat pts (population used to evaluate noninferiority)

[c] Primary endpoint, determined using the US FDA time-to-loss-of-virological-response algorithm. Between-group difference was 1.2 % (95 % CI −6.1 to 8.5); noninferiority of DRV + RTV od vs. bid was established, as the criterion for noninferiority was a 95 % CI lower limit greater than −12 % for the between-group difference in this outcome

[d] Between-group statistical analyses were not reported

adherent; between-group difference not significant), pill count (57.5 vs. 54.1 %) and darunavir plasma concentrations (83.2 vs. 87.6 %) [32].

4.3 Children and Adolescents

Three noncomparative phase II trials, known as DIONE [75], DELPHI [36] and ARIEL [21] have evaluated the efficacy of ritonavir-boosted darunavir plus background therapy for up to 48 weeks in the treatment of HIV-1 infection in ART-naïve adolescents [75] and ART-experienced children [21, 36] and adolescents [36] (see Table 7 for further details). Patients in these trials were required to weigh 10 to <20 kg [21], ≥20 kg [36] or ≥40 kg [75] and, where reported, have a stable CD4+ percentage [36], less than three darunavir RAMs [21] and have received HAART for ≥12 weeks [21].

At baseline, patients had a mean viral load of 4.4–4.7 $\log_{10}$ copies/mL [21, 36, 75] and, where specified, a mean/median age of 4.6 [21] or 14.6 [75] years (70 % of patients were aged 12–17 years in one study [36]) and a mean duration of infection of 11 years [36]. A median of 4 [21, 75] or 11 [36] PI RAMs and a median of zero (range 0–3 [21] or 0–0 [75]) or three [36] primary PI RAMs were detected.

4.3.1 Treatment-Naïve Patients

Once-daily darunavir 800 mg plus ritonavir 100 mg used in combination with NRTI background therapy provided effective virological suppression in treatment-naive adolescents aged 12 to <18 years. The majority of patients achieved a viral load of <50 (primary endpoint) or <400 copies/mL after 24 weeks' therapy and these benefits were sustained at 48 weeks (Table 7) [14, 75]. Improvements in CD4+ count were observed at each of these timepoints (Table 7) [14, 75] and only 1 of 12 patients experienced virological failure at 24 weeks [75].

4.3.2 Treatment-Experienced Patients

ART regimens containing twice-daily, bodyweight-based dosages of ritonavir-boosted darunavir provided virological benefit in some treatment-experienced children and adolescents (aged 3 to <6 years [20, 21] or 6–17 years [36]). After 24 weeks' therapy, a large proportion of patients had achieved a decrease from baseline in viral load of ≥1 $\log_{10}$ copies/mL (primary endpoint of DELPHI [36]) and at least half had achieved a viral load of <50 copies/mL (primary endpoint of ARIEL [21]) [Table 7]. These benefits were largely sustained at 48 weeks and additional measures of virological suppression generally supported these findings (Table 7) [20, 36].

Virological suppression was well maintained throughout the DELPHI trial, with most patients (88 %) who had achieved a viral load decrease of ≥1 $\log_{10}$ copies/mL or a viral load of <50 copies/mL at week 24 retaining this degree of suppression at 48 weeks [36]. However, response rates in adolescents (aged 12–17 years) were up to ≈1.9-fold lower than in younger patients (aged 6 to <12 years), with 57 versus 83 % of patients in these groups achieving a viral load decrease of ≥1 $\log_{10}$ copies/mL and 38 versus 71 % achieving a viral load <50 copies/mL. The fact that adolescents are likely to be more treatment experienced and drug resistant than younger children may explain this finding.

The proportion of patients considered to have virological failure in ARIEL was 40.7 % (11 of 27 patients, 8 of whom had achieved an unconfirmed viral load <50 copies/mL) after 24 weeks [21] and 14.3 % (3 of 21 patients) after 48 weeks [20]; the corresponding rate after 48 weeks in DELPHI was 30 % [36].

Table 7 Efficacy of oral ritonavir-boosted darunavir in paediatric patients with HIV-1 infection. Results of three noncomparative phase II trials; some data were obtained from abstracts/posters [20, 21], a conference report [75] or the US prescribing information [14]

Study	Ref	No. of pts[a]	Treatment regimen (mg/kg bid [21, 36] or mg od [75])[b]	Week of eval	Pts (%) with plasma HIV-1 RNA level			Change[c] from BL [BL] in CD4+ cell count (cells/μl)
					Decrease from BL ≥1 $\log_{10}$ copies/mL	<50 copies/mL	<400 copies/mL	
Treatment-experienced children and adolescents (aged 6–17 [36] or 3 to <6 [21] years)								
DELPHI	[36]	80	DRV 11–19 + RTV 1.5–2.5	24	74[d]	50[e]	65[e]	NR
				48	65	48	59	110 [330]
ARIEL	[21]	27	DRV 20 + RTV 2.6–3.2[f]	24	85	56[d]	89	109 [927]
	[20]	21		48		81		187
Treatment-naïve adolescents (aged 12 to <18 years)								
DIONE	[75]	12	DRV 800 + RTV 100	24		92[d]	100	175 [282]
	[14]			48		83.3	91.7	221 [282]

All analyses (except DIONE at 48 weeks) specified that virological response rates were assessed using the US FDA time-to-loss-of-virological-response algorithm

bid twice daily, *BL* baseline, *DRV* darunavir, *eval* evaluation, *NR* not reported, *NRTI* nucleoside reverse transcriptase inhibitor, *od* once daily, *pt(s)* patient(s), *ref* reference, *RTV* ritonavir

[a] All pts enrolled and treated [21, 75] (with ≥1 dose of study drug [36]) where specified

[b] All pts also received background therapy consisting of ≥2 NRTIs [21, 75] or ≥2 of the following: a paediatric-approved NRTI, efavirenz or nevirapine, or the fusion inhibitor enfuvirtide [36])

[c] Changes from BL are means in all but one study [36], which reported the median

[d] Primary endpoint

[e] Value estimated from a graph

[f] Initial dosage, with DRV administered as an oral suspension. After pharmacokinetic analyses at 2 weeks, DRV + RTV dosages were modified to 25 + 2.6–3.2 mg/kg bid (for pts weighing 10 to <15 kg) or 375 + 50 mg fixed bid (for pts weighing 15 to <20 kg)

Ritonavir-boosted darunavir regimens improved CD4+ cell counts in both trials (Table 7) [20, 21, 36]. In DELPHI, patients ($n = 74$ evaluable) also experienced significant ($p \leq 0.003$) improvements from baseline in certain growth parameters after 48 weeks' treatment, including weight (mean change 4.3 kg), weight z-score (0.2) and height (4.1 cm), but not height z-score (0.1); baseline mean age-adjusted z-score for both weight and height was −1.4 [36]. By contrast, in ARIEL, mean improvements in growth parameters, including height (2.6 cm; baseline 101 cm) and weight (0.8 kg; baseline 15.3 kg), were not significant after 24 weeks of therapy [21].

5 Tolerability

Tolerability data concerning the use of oral darunavir plus ritonavir (800 plus 100 mg once daily, 600 plus 100 mg twice daily or twice-daily bodyweight-based dosages) are available from the trials discussed in Sect. 4. This section focuses on data from randomized studies and pooled analyses of the POWER trials, except where data are limited. Some data were obtained from the EU [13] and US [14] prescribing information.

5.1 General Profile

Ritonavir-boosted darunavir, administered once or twice daily for up to 192 weeks, was generally well tolerated in adult and paediatric patients infected with HIV-1 in pivotal trials discussed in Sect. 4, with adverse events and/or laboratory abnormalities generally being grade 1 or 2 in severity. Diarrhoea was very common (incidence ≥10 %) with ritonavir-boosted darunavir during clinical trials and postmarketing experience, with other common adverse events (incidence ≥1 to <10 %) including nausea, vomiting, abdominal pain, headache, insomnia, hyperlipidaemia, lipodystrophy, increased ALT, fatigue and rash [13].

Rash is usually mild to moderate with ritonavir-boosted darunavir, occurs within 4 weeks of initiating treatment and resolves during continued therapy [13, 14]. However, some patients developed severe skin reactions during the clinical development programme (0.4 % of 3,063 patients), including Stevens-Johnson syndrome (<0.1 % of patients), and there have been post marketing reports of acute generalized exanthematous pustulosis and toxic epidermal necrolysis; immediate discontinuation of ritonavir-boosted darunavir is recommended if severe skin reactions develop [13, 14].

Hepatitis is uncommon with ritonavir-boosted darunavir therapy, occurring in 0.5 % of recipients during the clinical development programme [13, 14]. However, the likelihood of hepatic abnormalities, including severe and potentially fatal events, is increased in patients with pre-existing hepatic dysfunction, such as chronic HBV/HCV infection. Cases of liver injury (some resulting in death) have occurred with ritonavir-boosted darunavir post marketing, although a causal relationship has not been determined [14]. Appropriate laboratory parameters should be monitored before starting ritonavir-boosted darunavir as well as during treatment, with interruption or discontinuation of the regimen if hepatic dysfunction develops or worsens [13, 14].

5.2 Treatment-Experienced Adults

In 48-week analyses of TITAN [44], POWER 1 and 2 (pooled) [45] and ODIN [32], the majority of treatment-experienced adults (with no darunavir RAMs [32]) who received once-daily [32] or twice-daily [32, 44, 45] ritonavir-boosted darunavir or a comparator PI regimen experienced adverse events, where specified (Table 8) [32, 44]. Those considered to be serious occurred in up to 20 % of darunavir recipients [32, 44, 45], although were possibly related to therapy in fewer than 1 %, where reported [32] (Table 8). Across darunavir and comparator PI groups, <10 % of patients discontinued therapy because of adverse events and few deaths occurred, all of which were considered unrelated or doubtfully related to study treatment (Table 8) [32, 44, 45].

Generally similar findings were reported with twice-daily ritonavir-boosted darunavir in 96-week analyses of POWER 1–3 (pooled) [50] and TITAN [35] and 144-week analyses of POWER 1 and 2 (pooled) [79] and POWER 3 [49]. For instance, in the latter analysis, 98 % of darunavir recipients had adverse events, 30 % had serious adverse events and 10 % had discontinued because of adverse events [49]. Notably, among the six deaths that occurred in darunavir recipients in the 144-week analysis of POWER 1 and 2, one (sudden death) was considered possibly related to therapy [79].

The most common adverse events associated with [44, 45], or considered possibly related to [32], once-daily [32] or twice-daily [32, 44, 45] ritonavir-boosted darunavir over 48 weeks' therapy were diarrhoea and nausea (Table 8). The nature and incidence of adverse events with comparator PI regimens were broadly similar, although ritonavir-boosted darunavir recipients had a 2.8-fold lower rate of diarrhoea and headache and a 3.9-fold higher rate of herpes simplex infection than ritonavir-boosted CPI recipients (after adjusting for differences in treatment exposure) [45] and a 2.3-fold higher incidence of rash-related events than ritonavir-boosted lopinavir recipients [44]. Longer term, diarrhoea and nausea remained among the most common adverse events associated with twice-daily ritonavir-boosted darunavir over up to 144 weeks' treatment (incidence 16–28 %) [50, 79].

Grade 2–4 adverse events (excluding laboratory abnormalities) at least possibly related to therapy occurred in 40.9 % of twice-daily darunavir recipients and 44.8 % of twice-daily ritonavir-boosted lopinavir recipients over 96 weeks' therapy in TITAN, with the most common being gastrointestinal in nature (15.8 vs. 19.5 %), such as diarrhoea (8.1 vs. 15.2 %) and nausea (4.0 vs. 4.4 %) [35]. Generally similar findings were reported with twice-daily ritonavir-boosted darunavir in the 96- and 144-week POWER trial analyses [49, 50, 79], with diarrhoea, vomiting and nausea being the most frequent grade 2–4 adverse events at least possibly related to study drug in the largest 144-week analysis (incidence 2.4–3.9 %) [49]. Notably, the incidence of grade 3–4 adverse events considered to be at least possibly related to treatment did not significantly differ between once- and twice-daily ritonavir-boosted darunavir over 48 weeks' therapy in ODIN (1.7 vs. 4.1 % of patients) [32].

5.2.1 Laboratory Abnormalities

After 48 weeks' therapy, the most common grade 3 or 4 laboratory abnormality with twice-daily ritonavir-boosted darunavir was increased triglycerides in POWER 1 and 2 (15 vs. 7 % of CPI recipients) [45] and the most frequent grade 2–4 abnormalities in TITAN were increased total cholesterol (32 vs. 29 % of ritonavir-boosted lopinavir recipients), increased triglycerides (19 vs. 25 %) and increased LDL-cholesterol (19 vs. 17 %) [44]. Longer-term data were consistent with these findings, with increased total cholesterol, increased LDL-cholesterol and increased triglycerides being the most commonly reported grade 2–4 laboratory abnormalities with ritonavir-boosted darunavir at 96 weeks in TITAN (20–35 vs. 23–37 % of ritonavir-boosted lopinavir recipients) [35] and POWER 1–3 (21–25 %) [50] and at 144 weeks in POWER 3 (22–28 %) [49].

Other common (incidence >8 %) grade 2–4 laboratory abnormalities that occurred over 96 weeks of treatment with ritonavir-boosted darunavir in TITAN included increased pancreatic amylase (12.2 vs. 10.0 % of ritonavir-boosted lopinavir recipients), hyperglycaemia (11.4 vs. 11.7 %), increased ALT (10.3 vs. 9.0 %) and increased AST (8.6 vs. 9.7 %) [35], with similar results reported at 96 and 144 weeks in POWER trial analyses [49, 50].

Once-daily administration of ritonavir-boosted darunavir was associated with a more favourable lipid profile than twice-daily administration in patients with no darunavir

Table 8 Tolerability of oral ritonavir-boosted darunavir in treatment-experienced adults with HIV-1 infection. Data from 48-week analyses of phase IIb [45] or III [32, 44] trials; values are percentages of patients, unless otherwise specified

AE	POWER 1 and 2 (pooled) [45]		TITAN [44]		ODIN [32]	
	DRV 600 mg + RTV 100 mg bid ($n = 131$)	CPI + RTV ($n = 124$)	DRV 600 mg + RTV 100 mg bid ($n = 298$)	LPV mg 400 + RTV 100 mg bid ($n = 297$)	DRV 800 mg + RTV 100 mg od ($n = 294$)	DRV 600 mg + RTV 100 mg bid ($n = 296$)
AEs	NR	NR	93	92	76.2	77.0
Serious AEs	20 [16.6[a]]	14 [22.6[a]]	9	10	5.4[b,c]	9.1[b,c]
Deaths[d]	5	1	2	3	2	6
AEs causing discontinuation	9.2	4.8	7	7	3.4	4.7
Most common AEs (incidence >10 %)[e]						
Diarrhoea	20 [16.6[a]]	28 [46.7[a]]	32	42	9.9[b]	15.2[b]
Nausea	18 [15.3[a]]	13 [21.3[a]]	18	21	10.9	10.5
Headache	15 [12.1[a]]	20 [33.3[a]]	11	NR		
Nasopharyngitis	14	11	12	11		
Fatigue	12	17				
URTI	12	7	10	NR		
Rash-related			16	7		
Herpes simplex infection	12 [10.2[a]]	2 [2.6[a]]				

AEs adverse events, *bid* twice daily, *CPI* control protease inhibitor, *DRV* darunavir, *LPV* lopinavir, *NR* not reported, *od* once daily, *pt(s)* patient(s), *RTV* ritonavir, *URTI* upper respiratory tract infection

[a] Incidence rate per 100 pt-years after correcting for difference in treatment exposure between DRV and CPI recipients attributable to discontinuation because of virological failure (see Sect. 4.2.1 for details); adjusted data for some tabulated AEs were not reported

[b] Difference between the od and bid groups was not significant

[c] The incidence of serious AEs possibly related to treatment was 0.3 and 1.0 % in the od and bid groups

[d] Number of pts are reported

[e] In ODIN, these AEs were considered possibly related to treatment, as were vomiting, rash and headache which occurred with an incidence of <6 % with DRV + RTV od or bid

RAMs. Over 48 weeks' therapy in ODIN, significantly ($p < 0.05$) fewer patients in the once-daily than in the twice-daily group had grade 2–4 treatment-emergent increases in total cholesterol (10.1 vs. 20.6 %), LDL-cholesterol (9.8 vs. 16.7 %) and triglycerides (5.2 vs. 11.0 %) [32]. Other grade 2–4 laboratory abnormalities reported in >5 % of patients in either the once- or twice-daily group included increased glucose (7.3 vs. 6.4 %) and increased pancreatic amylase (5.9 vs. 3.9 %).

5.3 Treatment-Naïve Adults

The overall tolerability profile of once-daily ritonavir-boosted darunavir in treatment-naïve patients in the ARTEMIS trial was generally consistent with that reported in studies evaluating twice-daily administration in treatment-experienced patients. Diarrhoea, nausea, headache, upper respiratory tract infection, nasopharyngitis, abdominal pain, vomiting and cough were the adverse events most frequently reported over 48 weeks of therapy (no further details reported) [46].

Once-daily ritonavir-boosted darunavir had some tolerability benefits over ritonavir-boosted lopinavir (administered once or twice daily) in ARTEMIS. Over 192 weeks' treatment, significantly ($p \leq 0.005$) fewer recipients of the darunavir than of the lopinavir regimen experienced at least one adverse event possibly related to therapy (56.6 vs. 74.9 %) or permanently discontinued treatment because of adverse events (7.6 vs. 14.5 %), although no significant between-group difference was seen in the incidence of adverse events that were grade 3 or 4 in severity (30.0 vs. 31.8 %), serious (16.0 vs. 20.8 %) or led to death (1.2 vs. 2.0 %) [31].

Over 192 weeks, the overall incidence of grade 2–4 adverse events possibly related to therapy, including those of a gastrointestinal nature and specifically diarrhoea, was significantly lower in the darunavir than in the lopinavir group, whereas the incidence of grade 2–4 nausea and rash did not differ significantly between the groups (Fig. 1) [31]. However, significantly fewer patients had grade 2–4 increases in total cholesterol or triglycerides or developed hyperbilirubinaemia with ritonavir-boosted darunavir than

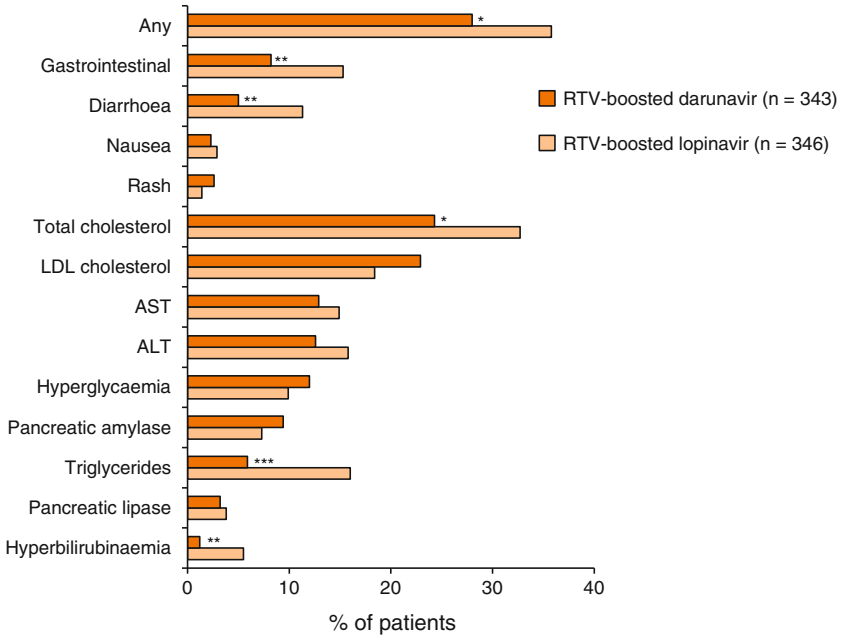

Fig. 1 Tolerability of oral ritonavir-boosted darunavir versus ritonavir-boosted lopinavir in treatment-naïve adults infected with HIV-1. Grade 2–4 adverse events possibly related to treatment and grade 2–4 laboratory abnormalities that occurred with an incidence of ≥2 % over 192 weeks of treatment in the ARTEMIS trial (see Sect. 4.1.1 for details). *LDL* low density lipoprotein, *RTV* ritonavir. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$ vs. RTV-boosted lopinavir

with ritonavir-boosted lopinavir, although between-group differences were not significant for other laboratory abnormalities (Fig. 1) [31]. Earlier analyses of ARTEMIS conducted at 48 [46] and 96 [47, 83] weeks reported similar findings, including an analysis of metabolic parameters [83].

5.4 Children and Adolescents

The tolerability profile of ritonavir-boosted darunavir in paediatric patients was generally similar to that seen in adult patients, in terms of the type, frequency and severity of adverse events [14].

In treatment-naïve adolescents (aged 12 to <18 years) participating in the 48-week DIONE trial, the most common clinical adverse reactions with once-daily ritonavir-boosted darunavir included vomiting (33 %), nausea (25 %), diarrhoea (16.7 %), abdominal pain, decreased appetite, rash and pruritus (8.3 % each) [14]. Many of these adverse reactions were also among those that occurred most frequently with twice-daily ritonavir-boosted darunavir in treatment-experienced children and adolescents (aged 3–17 years) in the 48-week ARIEL and DELPHI trials (diarrhoea [24 and 11 %], vomiting [19 and 13 %], rash [19 and 5 %] and abdominal pain [5 and 10 %]), with the addition of anorexia in ARIEL (5 %) and headache in DELPHI (9 %) [14].

A small proportion of patients in DELPHI experienced grade 3 increases in certain laboratory parameters, including pancreatic amylase (4 %), ALT (3 %), LDL cholesterol (3 %), AST (1 %), pancreatic lipase (1 %) and total cholesterol (1 %), with some of these abnormalities also occurring with grade 4 severity (increased pancreatic amylase and increased ALT; 1 % each) [14]. No laboratory abnormalities grade 3 or 4 in severity were considered to be adverse reactions in DIONE or ARIEL [14].

6 Pharmacoeconomic Analyses

This section provides an overview of modelled pharmacoeconomic analyses of darunavir therapy in treatment-naïve (Sect. 6.1) and treatment-experienced (Sect. 6.2) adults infected with HIV, with discussion focusing on fully published analyses based on head-to-head trials. As with all pharmacoeconomic studies, those evaluating darunavir are subject to several inherent limitations. Pharmacoeconomic analyses based on clinical trials extrapolate the results of such trials to the general population; however, patient populations, rates of compliance and major outcomes in clinical trials may differ from those observed in real-life practice. Modelled analyses, such as those presented in this section, rely on a number of assumptions and use data from a variety of sources. Moreover, results of pharmacoeconomic analyses may not be applicable to other geographical regions because of differences in healthcare systems, medical practice and unit costs.

6.1 Treatment-Naïve Patients

This section focuses on a US pharmacoeconomic analysis [84] that used data from the ARTEMIS study (discussed in Sect. 4.1.1) to estimate the cost utility of ritonavir-boosted darunavir relative to ritonavir-boosted lopinavir, when used

as a first-line treatment option in combination with a dual NRTI background therapy in adults infected with HIV-1.

The study used a discrete event simulation model with a lifetime horizon and was from a third-party payer perspective, including only direct medical costs (e.g. ART and non-ART agents, routine medical care, treatment of AIDS-related and adverse events) [84]. Costs were based on various sources, including healthcare databases and literature, and were inflated to 2011 US dollars; utility values were based on literature. Annual discounts (costs and benefits) were 3 %.

Used in conjunction with a dual NRTI background therapy, ritonavir-boosted darunavir did not appear to be a cost-effective first-line treatment option for adults infected with HIV compared with ritonavir-boosted lopinavir in the USA [84]. The lopinavir regimen was associated with lower total healthcare costs ($US462,636 vs. $US488,023) and slightly more quality-adjusted life-years (QALYs) [12.130 vs. 12.083] than the darunavir regimen. Assuming a willingness-to-pay threshold of $US50,000 per QALY gained, the net monetary benefit of the lopinavir versus the darunavir regimen was $US27,762 in the base case analysis and $US12,808–31,357 in sensitivity analyses [84].

In addition, three modelled pharmacoeconomic analyses (some available only as abstracts [85, 86]) have estimated the cost effectiveness of ritonavir-boosted darunavir relative to ritonavir-boosted atazanavir and various other PIs in the first-line treatment setting in Germany [85], Belgium [86] and the USA [87], from a payer perspective where specified [86, 87]. However, data from these analyses should be interpreted with caution given that some comparisons were of an indirect nature owing to limited/no trials comparing agents head-to-head.

In the European analyses, darunavir appeared to be cost effective relative to atazanavir over a 48-week horizon in Belgium, when used in combination with ritonavir and NRTI-based background therapy (incremental cost-effectiveness ratio [ICER] of €18,011) [86], whereas in Germany, ritonavir-boosted atazanavir was cost effective compared with ritonavir-boosted darunavir over a 25-year horizon (ICER €11,241 per QALY gained) [85]; a widely accepted cost-effectiveness threshold is €30,000 per QALY gained. However, using an efficacy frontier approach, the US analysis predicted darunavir to be the most efficient (i.e. best value for money) ritonavir-boosted PI for first-line use in combination with NRTI-based background therapy relative to atazanavir, lopinavir, fosamprenavir and saquinavir, based on ART costs over 1 year and virological efficacy over 48 weeks [87].

6.2 Treatment-Experienced Patients

This section provides an overview of pharmacoeconomic analyses that have estimated the cost utility of twice-daily ritonavir-boosted darunavir relative to that of ritonavir-boosted lopinavir [88, 89] or CPIs [90, 91] in the treatment of HIV infection in ART-experienced adults from the payer perspective (see Table 9 for details).

In the USA [88, 90] and several European countries [89, 91], twice-daily ritonavir-boosted darunavir ART regimens appeared to be cost effective with regard to the cost per QALY gained compared with ART regimens containing ritonavir-boosted lopinavir [88, 89] or CPIs [90, 91] in treatment-experienced adults (Table 9). Over a lifetime horizon, the darunavir regimens increased costs but also QALYs relative to the comparator PI regimens, resulting in incremental costs per QALY gained below the widely accepted cost-effectiveness thresholds of €30,000 or $US50,000 per QALY gained (Table 9). Moreover, when a 5-year horizon was evaluated in the base-case analysis of one of the US studies, ritonavir-boosted darunavir was predicted to dominate ritonavir-boosted CPIs with regard to the cost per QALY gained [90].

At these cost-effectiveness thresholds, the likelihood of ritonavir-boosted darunavir regimens being cost effective relative to regimens containing ritonavir-boosted lopinavir or other CPIs was estimated to be >70 % over a lifetime horizon in probabilistic sensitivity analyses [88–91], with some studies reporting a likelihood of >90 % in Belgium, Italy, Sweden [91] and the USA [90].

The findings of these models were generally robust to variations in key input parameters, modelling assumptions and treatment patterns in sensitivity and scenario analyses [88–91].

7 Dosage and Administration

Oral darunavir, coadministered with low-dose ritonavir and other antiretroviral agents, is indicated in several countries, including the USA [14] and those of the EU [13], for the treatment of HIV-1 infection in ART-naïve and ART-experienced adults [13, 14], as well as in paediatric patients aged ≥3 years (weighing ≥10 kg [14] or ≥15 kg [13]) who have received ART previously [13, 14] or are ART naive [14] (provided they are aged 12–17 years, weighing ≥40 kg [13]). Darunavir should be taken with food and is available in the form of tablets (75–800 mg) and an oral suspension (100 mg/mL), which may be more suitable for patients who find swallowing tablets difficult [13, 14].

For adults who are ART naïve or are ART experienced with no darunavir RAMs, the recommended dosage in the USA [14] and EU [13] is darunavir 800 mg plus ritonavir 100 mg, once daily, whereas the dosage recommended for ART-experienced adults with at least one darunavir RAM or an unavailable genotype is darunavir 600 mg plus ritonavir 100 mg, twice daily [13, 14]. For paediatric

Table 9 Cost utility of twice-daily ritonavir-boosted darunavir relative to comparator protease inhibitor regimens in treatment-experienced adults infected with HIV from a payer perspective. Base case results of Markov models with a lifetime horizon are shown

Study[a]	Treatment regimen[b]	Country (year of costs)	Incremental cost	Incremental QALY	Incremental cost per QALY gained
ART-experienced adults with evidence of protease inhibitor resistance					
Moeremans et al. [89]	DRV + RTV vs. LPV + RTV	Belgium (2009)	€5,664	0.785	€6,964
		Italy (2009)	€5,643	0.608	€9,277
		Sweden (2009)	€4,013	0.584	€6,868
		UK (2008)	€8,122	0.550	€14,778
Brogan et al. [88][c]	DRV + RTV vs. LPV + RTV	USA (2008)	$US11,358	0.493	$US23,057
Highly ART-experienced adults with failure to prior ART (>1 PI regimen [91])					
Moeremans et al. [91]	DRV + RTV vs. CPIs + RTV	Belgium (2009)	€16,049	1.397	€11,484
		Italy (2009)	€14,197	1.171	€12,122
		Sweden (2009)	€12,495	1.142	€10,942
		UK (2008)	€17,933	1.091	€16,438
Mauskopf et al. [90][c]	DRV + RTV vs. CPIs + RTV	USA (2008)	$US38,071	1.27	$US30,046

ART antiretroviral therapy, *CPIs* control protease inhibitors, *DRV* darunavir, *LPV* lopinavir, *QALY* quality adjusted life-year, *RTV* ritonavir

[a] All analyses used a Markov model with six health states (based on CD4+ cell count) plus a state of death and 3-month cycles; sources of data included the TITAN [88, 89] and POWER 1 and 2 [90, 91] trials. Costs were direct (e.g. ART and inpatient/outpatient costs, including management of complications and disease monitoring) and were based on a variety of sources, including official local sources (e.g. healthcare databases/tariffs) and literature; utilities were based on literature. Annual discounts (costs and benefits) were 3 % in the US, Italian and Swedish analyses, 3.5 % in the UK analyses and 3 and 1.5 %, respectively, in the Belgian analyses

[b] Each regimen was administered in combination with optimized background therapy

[c] These analyses were reported to be from a societal perspective, although did not directly include loss of productivity costs. Only direct costs were included; QALY estimates were assumed to include indirect costs

patients, the dosage of ritonavir-boosted darunavir is determined by bodyweight and should not exceed that recommended for adults; for those weighing ≥40 kg, dosage recommendations are the same as those for adults [13, 14].

Use of ritonavir-boosted darunavir should be guided by genotypic or phenotypic testing (when available) as well as treatment history [13, 14], and in the EU, ART-experienced patients with no darunavir RAMs must have a viral load <100,000 copies/mL and a CD4+ cell count ≥100 cells × 10^6/L [13]. Darunavir requires caution or is contraindicated/not recommended in some special patient populations and coadministration of the drug with certain agents may require dosage adjustments/caution or is contraindicated/not recommended (Sect. 3). Local prescribing information for darunavir should be consulted for further information regarding bodyweight-determined dosages in paediatric patients, drug interactions, contraindications and other warnings and precautions.

8 Place of Darunavir in the Management of HIV-1 Infection

A key objective of ART in patients with HIV is to achieve and maintain maximal virological suppression [7–10], thus restoring and preserving immune system function [7–10] and reducing morbidity and mortality [5, 7, 10]. To this end, numerous antiretroviral agents are available for use in ART regimens, including NRTIs, NNRTIs, PIs and entry and integrase inhibitors, with three agents from at least two different drug classes generally being used in combination [3].

First-line ART regimens currently recommended for adult [5–8], adolescent [7] and paediatric [9, 10] patients in European [5, 6, 9] and US [7, 8, 10] guidelines combine two NRTIs with either an NNRTI [5–10], an integrase inhibitor [5–8] or a ritonavir-boosted PI [5–10], with agent selection depending on factors such as the characteristics of the patient (e.g. comorbidities) and the regimen (e.g. tolerability) [7–10] and the resistance profile of the viral strain [7, 9, 10]. Boosting PIs with ritonavir is near universal, as it increases exposure to the active PI thus reducing the risk of viral resistance [4, 7].

Compared with agents such as NNRTIs or the integrase inhibitor raltegravir, PIs have a higher genetic barrier to resistance [7], with multiple mutations generally being required to reduce phenotypic susceptibility [92]. However, like all antiretroviral drug classes, resistance can still develop to PIs and cross-resistance has proven to be a challenge [3, 92]. A variety of PIs are currently available, including first-generation (saquinavir, indinavir, nelfinavir) and second-generation (amprenavir/fosamprenavir, lopinavir, atazanavir, tipranavir) agents, the latest of which is

darunavir [3, 93]. Darunavir is a non-peptidyl PI that provides a high genetic barrier to the emergence of resistance and has activity against both wild-type HIV-1 and strains no longer susceptible to some of the older PIs (Sect. 2). Consequently, darunavir was first approved for use in treatment-experienced patients, although has since also received approval for first-line therapy (Sect. 7).

Ritonavir-boosted darunavir is one of the PIs preferred/recommended for use in initial ART regimens in adults [5–8] and adolescents [7] in current treatment guidelines, with the other being ritonavir-boosted atazanavir [5–8]. When given along with a dual NRTI background therapy in ART-naïve adults in the randomized ARTEMIS trial, once-daily ritonavir-boosted darunavir was no less effective in establishing virological suppression over 48 weeks' therapy than once- or twice-daily ritonavir-boosted lopinavir, yet was more effective at maintaining suppression longer term (Sect. 4.1.1). No robust trials have yet compared the virological efficacy of once-daily ritonavir-boosted darunavir with that of once-daily ritonavir-boosted atazanavir in this setting, although phase III and IV trials are currently ongoing or recruiting patients [94].

Ritonavir-boosted darunavir is also considered as an alternative to ritonavir-boosted atazanavir (preferred for those aged ≥6 years [10] or teenagers [9]) or lopinavir (preferred for infants [9, 10] and young children aged <6 [9] or ≥3 [10] years) in the initial ART regimens of paediatric patients aged ≥3 or ≥6 years. However, data supporting its virological efficacy in ART-naïve paediatric patients are currently limited to a small 48-week noncomparative study conducted in adolescents who received once-daily ritonavir-boosted darunavir plus background therapy (Sect. 4.3.1). Further robust comparative trials in this setting would therefore be beneficial, although it is recognized that conducting randomized HIV studies in the paediatric population is difficult [95].

In ART-experienced patients, choice of therapy is determined largely by treatment history and resistance testing [7]. For those with multidrug-resistant HIV, the introduction of novel antiretrovirals, such as the CCR5 antagonist maraviroc and the integrase inhibitor raltegravir, as well as newer members of existing antiretroviral drug classes, including the NNRTI etravirine and the nonpeptidyl PIs darunavir and tipranavir, has enabled many of these patients to achieve full virological suppression [4].

Twice-daily ritonavir-boosted darunavir, plus NRTI-based background therapy, provides virological suppression for up to 144 weeks' therapy in ART-experienced adults, including those with multiple major PI RAMs, according to randomized and noncomparative studies (TITAN and POWER; Sect. 4.2.1). Moreover, the virological suppression observed with this regimen was better than that seen with twice-daily ritonavir-boosted lopinavir or ritonavir-boosted CPIs in comparative trials (Sect. 4.2.1). Twice-daily ritonavir-boosted darunavir also appears to provide durable virological suppression when used in combination with raltegravir and etravirine in treatment-experienced adults with resistance to multiple antiretrovirals and few remaining treatment options, according to a noncomparative study (ANRS 139 TRIO; Sect. 4.2.1.3). Virological benefit has also been observed with twice-daily ritonavir-boosted darunavir regimens in some ART-experienced paediatric patients (aged 3–17 years) in noncomparative studies of limited size (Sect. 4.3.2).

Like darunavir, tipranavir provides a relatively high genetic barrier to resistance and is active against most HIV strains resistant to earlier-generation PIs [96]. The drug is indicated for use in highly treatment-experienced patients with multiple PI resistance, but in contrast to darunavir and most other PIs, is not approved for use in ART-naïve patients [97, 98]. Its narrow indication, along with its hepatotoxicity risk (see later discussion) and a paucity of agents with reasonable tolerability to use in combination with the drug, have limited tipranavir use [93], and comparative data versus darunavir are limited to a retrospective cohort study [99] and a randomized trial with insufficient statistical power due to early termination [100].

Suboptimal adherence to ART can result in therapy failure and emergence of resistance [101] and has been associated with factors such as regimen complexity (e.g. high dosing frequency) and administration difficulties (e.g. problems swallowing pills) [7]. Most second-generation PIs, including darunavir (Sect. 7), are taken once or twice daily depending on factors such as ART experience, resistance profile, patient age and local recommendations, and are available as capsules/tablets as well as liquid solution/suspension formulations. Atazanavir can be administered once daily regardless of ART experience, although it is available only in the form of capsules which some patients, particularly children, may find hard to swallow. The only PI to currently offer the convenience of co-formulation with ritonavir is lopinavir.

Given the potential adherence advantages of once-daily administration and the benefits observed with once-daily ritonavir-boosted darunavir in ART-naïve adults in ARTEMIS (Sect. 4.1.1), the efficacy of this regimen was evaluated in ART-experienced adults with no darunavir RAMs (indicating early treatment experience) in a randomized 48-week trial (ODIN). In this study, ritonavir-boosted darunavir, used in combination with NRTI-based background therapy, reduced viral load no less effectively when taken once daily than when taken twice daily, although once-daily administration was not associated with a marked adherence benefit (Sect. 4.2.2) perhaps because of the trial setting [32]. Notably, ODIN was not specifically

designed to assess adherence and its findings in this regard may not necessarily be replicated during routine clinical use.

The prevalence of darunavir RAMs generally appears to be low, according to analyses of resistance data from large numbers (>1,000) of clinical and drug resistance database specimens of HIV [102–105], with the largest analysis (of ≈232,000 clinical samples) detecting no darunavir RAMs in 94 % of isolates submitted for resistance testing in 2009 (vs. 85 % of isolates in 2003) [104]. Thus, ritonavir-boosted darunavir 800 mg once daily may be a suitable option for a number of treatment-experienced patients, including those who may wish to simplify their treatment regimen, with the availability of an 800 mg darunavir tablet (Sect. 7) further reducing the complexity of the regimen versus use of two 400 mg tablets. However, if genotypic testing is not feasible [14] or available [13], ritonavir-boosted darunavir 600 mg twice daily is recommended in this setting.

The efficacy of ritonavir-boosted darunavir has also been evaluated as part of more novel ART strategies, including NRTI-sparing initial ART (Sect. 4.1.2, as well as two phase III trials which have recently been completed or terminated due to inferior efficacy relative to NRTI-based therapy [94]). NRTI-sparing regimens currently have limited data [106] and are not among the recommended treatment options for ART-naïve patients, although may be considered in ART-naïve adults in special circumstances according to some guidelines [8]. Similarly, attempts to limit ART exposure and cost have driven evaluation of PI monotherapy regimens [106]. Ritonavir-boosted darunavir has shown promise as maintenance monotherapy in treatment-experienced patients with virological suppression in randomized studies [107–109], but is not approved for use in this setting. Although PI monotherapy is not a recommended treatment strategy in most guidelines, the European AIDS Clinical Society include monotherapy with ritonavir-boosted darunavir or lopinavir as a possible switch option for virologically suppressed adults without treatment failure on PI-based therapy who require regimen simplification, are intolerant of NRTIs or use illicit drugs and have interrupted ART frequently [6].

Patient adherence to ART can also be affected by its adverse effects [7]. Once- and twice-daily ritonavir-boosted darunavir regimens were generally well tolerated in adult and paediatric patients (Sect. 5). As is typical of PIs [7, 106], ritonavir-boosted darunavir is generally associated with gastrointestinal disturbances and metabolic abnormalities, such as increased lipid levels (Sect. 5). However, once-daily ritonavir-boosted darunavir had some tolerability advantages over once- or twice-daily ritonavir-boosted lopinavir in ART-naïve adults in the ARTEMIS trial, with fewer darunavir recipients experiencing treatment-related adverse events, including grade 2–4 diarrhoea and increased total cholesterol and triglyceride levels (Sect. 5.3). Of note, interpretation of the gastrointestinal findings of this study is complicated by the trial's use of both capsule and tablet formulations of ritonavir-boosted lopinavir (Table 4), as the tablet tends to be associated with fewer gastrointestinal adverse events than the capsule [31].

With regard to lipids, ritonavir-boosted darunavir is associated with more favourable changes in levels of total cholesterol and triglyceride than ritonavir-boosted lopinavir and, when administered once daily, its lipid profile does not markedly differ from that of ritonavir-boosted atazanavir (Sect. 2.4). Notably, ritonavir-boosted darunavir appears to have a more favourable lipid profile when administered once daily than twice daily (Sect. 2.4), which may in part be due to the lower ritonavir dose in the once-daily regimen (100 vs. 200 mg/day), as ritonavir can increase the likelihood of hyperlipidaemia [7]. Lipid-lowering agent requirements may be minimized by antiretrovirals with more favourable lipid profiles, helping to reduce the risk of the adverse events that can occur with such agents (e.g. myopathy, hepatotoxicity) as well as the complexity and cost of therapy [110]. Current data suggest that, within the PI class, darunavir and atazanavir have the best lipid profiles [110].

In addition to metabolic and gastrointestinal effects, some PIs have other tolerability issues that require consideration. For instance, among the second-generation agents, atazanavir can cause PR interval prolongation (which may be of consequence if taken with other drugs that prolong the interval), is associated with indirect hyperbilirubinaemia that can lead to jaundice, and depends on low gastric pH for absorption (resulting in interactions with acid-reducing agents, such as proton pump inhibitors) [7]. PR interval prolongation may also occur with lopinavir and there have been reports of QT interval prolongation and torsades de pointes with the drug [7]. Moreover, tipranavir carries a boxed warning in the USA regarding reports of intracranial haemorrhage, hepatitis and hepatotoxicity, some of which have been fatal [97]; however, hepatotoxic effects have also been observed with other PIs, including darunavir (Sect. 5) and are considered a class disadvantage [7].

Consideration must also be given to the drug interaction potential of PIs, which is more pronounced when boosted with ritonavir [7]. Ritonavir is a nonselective inhibitor of CYP3A and is also capable of inducing the activity of CYP3A and a variety of other enzymes [111, 112], leading to a plethora of drug interactions. Recently, a more selective CYP3A inhibitor with a lower potential for drug interactions than ritonavir was approved for use in the EU as a pharmacokinetic enhancer of darunavir and atazanavir

in adults [113]. The drug is known as cobicistat and is an emerging alternative to ritonavir for the pharmacokinetic enhancement of these PIs.

Given there are currently >30 million people infected with HIV worldwide [114], it follows that cost effectiveness may also be an important consideration in ART selection. Modelled pharmacoeconomic analyses of darunavir suggest that ritonavir-boosted darunavir regimens are cost effective in treatment-experienced adults in several countries relative to regimens containing ritonavir-boosted CPIs, including lopinavir (Sect. 6.2). However, analyses of ritonavir-boosted darunavir versus other PIs in the first-line setting have produced mixed findings (Sect. 6.1), although most are limited by a lack of clinical trials comparing agents directly and should therefore be interpreted with caution. The only comparative pharmacoeconomic analysis based on a head-to-head study predicted that ritonavir-boosted darunavir may not be cost-effective relative to ritonavir-boosted lopinavir in treatment-naïve adults in the USA (Sect. 6.1). Further pharmacoeconomic analyses would be beneficial in the event of directly comparative trials.

In conclusion, although additional comparative data are needed to position darunavir more definitively with respect to other PIs, particularly in the paediatric setting, current clinical data indicate that ritonavir-boosted darunavir is an effective and generally well tolerated option for use in the ART regimens of adult and paediatric patients with HIV-1 infection, including those with multiple major PI RAMs.

Data selection sources: Relevant medical literature (including published and unpublished data) on darunavir was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 8 November 2013], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Darunavir, Prezista, HIV infections, human immunodeficiency virus infection.
Study selection: Studies in patients with HIV-1 infection who received darunavir. When available, large, well-designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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