

Overview of boosted protease inhibitors in treatment-experienced HIV-infected patients

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Antiretroviral drug combinations that include two nucleoside reverse transcriptase inhibitors and a protease inhibitor (PI) can suppress HIV replication to undetectable levels, improving the prognosis of HIV-infected individuals. The aim of therapy is complete virological suppression, with a current goal of <50 copies/mL HIV-1 RNA, in order to minimize the occurrence of drug resistance. Improved understanding of the pharmacology of PIs, primarily the importance of adequate drug exposure, has led to the widespread administration of PIs combined with a low 'boosting' dose of ritonavir. The combination of PIs with ritonavir can improve treatment responses in both treatment-naïve and -experienced patients. Boosted PIs are an important therapeutic option for HIV and extensive data exist supporting their use. Use of individual agents should be guided by a resistance test at all stages of treatment from naïve through to highly treatment-experienced patients. Currently, seven boosted PIs have both US and European licensing approval: indinavir, saquinavir, lopinavir, fosamprenavir, atazanavir, tipranavir and darunavir (formerly TMC114). The preferred first-line option in the USA is lopinavir. Many of the older PIs are less effective and/or have less favourable tolerability profiles. Emergent PI resistance is a major challenge in treatment, and it can be accelerated by partial suppression of viral load through inappropriate therapy combinations. Using the newer boosted PIs, which have more robust resistance profiles, with an optimized background regimen may increase the likelihood of complete viral suppression. This review discusses the relative strengths and weaknesses of boosted PIs in current practice.

Keywords: antiretroviral therapy, PIs, antiviral

Introduction

Since the mid-1990s, antiretroviral drug combinations comprising two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI) have provided HIV patients with potent options to durably suppress HIV replication to undetectable levels, reducing the likelihood of the emergence of drug resistance. Subsequently, clinical practice has seen the introduction of newer PIs (most recently tipranavir and darunavir) and re-formulated versions of already approved PIs [saquinavir and lopinavir/ritonavir (Kaletra®)]. A major advance in the use of PIs has been their administration in combination with a low 'boosting' dose of the PI ritonavir. This has followed from an improved understanding of the pharmacology of PIs and of the importance of adequate drug exposure. A shift in the treatment paradigm towards the widespread use of boosted PIs has raised the benchmark for virological

response in treatment-experienced patients with multiple drug resistance from suppression of viral load to specifically the suppression of HIV-1 RNA to <50 copies/mL.¹

Boosted PIs are an important therapeutic option in HIV disease and good data exist for their use in people who are naïve to therapy.² However, commencing therapy with a non-NRTI (NNRTI) plus two NRTIs has remained popular with clinicians and patients alike, mainly for reasons of simplicity and proven efficacy.³ Sequencing currently approved NNRTIs is unlikely to be successful after the failure of the initial NNRTI, because of within-class cross-resistance, meaning that boosted PIs usually constitute key agents of a new class in the subsequent regimen for NNRTI-experienced patients.

Seven potent boosted PIs currently have licensing approval for treatment-experienced patients: indinavir, saquinavir, lopinavir, fosamprenavir, atazanavir, tipranavir and, most recently, darunavir

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Table 1. Comparison of the key utilities of boosted PIs

Drug	IDV/r	SQV/r ^a	LPV/r ^a	ATZ/r ^a	FPV/r ^b	TPV/r ^c	DRV/r ^d
Dosing frequency	BID	BID/QD	BID/QD	QD	BID/QD ^e	BID	BID
Ritonavir dose (mg)	200	200/100	200	100 ^f	200 ^f	400/200 ^g	200
Total daily pill burden	8	6	4	3	4	6	6
Food required	no	yes	no	no	yes	yes	no

ATZ, atazanavir; BID, twice daily; DRV, darunavir; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir; QD, once daily; r, ritonavir; SQV, saquinavir; TPV, tipranavir.

^aBritish HIV association-preferred option.

^bBritish HIV association-recommended alternative option.

^cEU licence for treatment-experienced patients only.

^dInvestigational compound, EU licence applied for.

^eUnlicensed dose.

^fCan be used unboosted but poor data in treatment-experienced subjects.

^gData available for boosting with 100 or 200 mg ritonavir once daily and twice daily.

(formerly TMC114) (Table 1). Nelfinavir is not boosted, because drug exposure is relatively unaffected by co-administration of ritonavir; it has tended to be reserved for use during pregnancy.⁴ Possible contamination of nelfinavir stock with the potential carcinogen ethyl methanesulphonate has recently prompted the withdrawal of nelfinavir stock and the suspension of its European marketing authorization pending the results of further toxicology studies.⁵

Pharmacology of boosted PIs

The boosting effect of ritonavir is mediated substantially through its inhibitory effect on the cytochrome P450 iso-enzyme CYP 3A4.⁶ CYP 3A4 is found primarily in the intestines and liver and is important in the first-pass metabolism of many drugs, including PIs.⁷ Inhibition of CYP 3A4 by ritonavir reduces hepatic and intestinal metabolism of concurrently administered PIs, increasing drug exposure, minimum plasma concentration and elimination half-life.⁷ Low doses of ritonavir (100–200 mg) given concurrently with another PI can therefore boost the bio-availability of PIs without resulting in an unacceptable increase in the risk of adverse effects. Ritonavir may also boost the levels of PIs in a number of other ways, which include interference with the P-glycoprotein and multidrug resistance-associated protein efflux channels that take part in the active transport of PIs out of cells.⁷ It has also been suggested that ritonavir may boost levels of unbound fractions of PIs in the circulation by saturating protein binding sites or by active competition with the primary PI for these binding sites.⁷

Ritonavir is an absolute requirement for some PIs, such as lopinavir and tipranavir, to achieve adequate serum levels. More generally, boosting plasma levels of PIs through concomitant administration of ritonavir has several potential advantages, including increased PI potency and efficacy, a reduced risk of viral resistance, lower pill burden and simplification of treatment regimens, allowing, for example, the use of the boosted PI once daily.⁸ Increasing the plasma concentration of a PI raises the pharmacological barrier to the development of resistance and reduces the likelihood of the development of mutations within the protease gene. Furthermore, raising the exposure to a PI may provide the PI with activity against what would otherwise be resistant viruses. Some early evidence that boosted PIs were more robust against the development of drug resistance than

their unboosted counterpart PIs was provided by the Abbott M98-863 study in which lopinavir/ritonavir was compared with nelfinavir.⁹ Recently, similar evidence has also been seen with boosted saquinavir in the Staccato study.¹⁰

Although the boosting of plasma concentrations of PIs with ritonavir can be advantageous, ritonavir may adversely affect the pharmacological handling of other medications. Studies have shown that tipranavir/ritonavir results in significantly reduced levels of other PIs such as lopinavir, saquinavir and amprenavir, and thus boosted tipranavir should not be administered with other currently available PIs.¹¹ In addition, the NNRTIs nevirapine and efavirenz induce CYP 3A4 metabolism, and patients receiving a boosted PI plus these agents may experience a drop in the PI level, requiring dose increases to counter this and any potential loss of activity.⁶ In certain cases, drug interactions may prohibit co-administration of particular drugs; whereas in others, dose adjustment, close monitoring for efficacy and toxicity and therapeutic drug monitoring may be sufficient to allow co-administration.¹²

The enhanced PI exposure that ritonavir boosting provides may increase the frequency of dose-dependent adverse events such as diarrhoea and lipid abnormalities, and this is a consideration to weigh against the other advantages; for example, nephrotoxicity was significantly increased when indinavir was compared with ritonavir-boosted indinavir in the BEST study.¹³

Specific boosted PIs

Indinavir/ritonavir

Indinavir was frequently used unboosted in the early era of highly active antiretroviral therapy (HAART). However, it has not sustained widespread clinical use as a boosted PI because of its narrow therapeutic window when boosted with ritonavir. Less toxic PIs with improved potency are now preferred.

In the MaxCmin 1 study, indinavir/ritonavir 800/100 mg twice daily was compared with saquinavir/ritonavir (soft gel capsules) 1000/100 mg twice daily in a study population composed of 25% antiretroviral-naïve patients, 14% antiretroviral-experienced but PI-naïve patients and 61% PI-experienced patients.¹⁴ The rate of virological failure in the two arms at 48 weeks was similar (27% versus 25%, respectively), but a greater number of treatment-limiting adverse events were seen in

the indinavir/ritonavir-treated patients. When a switch from the randomized treatment was included within the definition of virological failure, the rate of virological failure was significantly higher in the indinavir/ritonavir arm when compared with the saquinavir/ritonavir arm (49% versus 34%, respectively, $P = 0.009$).

Saquinavir/ritonavir

Saquinavir initially received approval from the US Food and Drug Administration (FDA) in 1994 and has twice been re-formulated since then in order to address bioavailability and tolerability issues. The activity of the original hard gel capsule formulation (Invirase®) given without ritonavir boosting was limited by the drug's poor pharmacokinetics, resulting in limited long-term virological suppression, despite the administration of six capsules three times daily.¹⁵ Replacement with a soft gel capsule formulation (Fortovase®) also failed to provide adequate drug exposure and was also associated with poor gastrointestinal tolerability. Only when saquinavir was combined with ritonavir, initially at a dose of 400/400 mg twice daily, has it been shown to be potent with durable activity.^{14,16} Recently, saquinavir has been re-formulated to a 500 mg tablet, thereby reducing daily pill burden to four tablets plus two ritonavir capsules.¹⁷

The MaxCmin 1 study (in which 61% of patients were PI experienced) established the superior tolerability of saquinavir/ritonavir over indinavir/ritonavir.¹⁴ The MaxCmin 2 study (in which 52% of patients were already PI experienced), failed to show equivalence between saquinavir/ritonavir 1000/100 twice daily and lopinavir/ritonavir 400/100 mg twice daily: there was a higher proportion of protocol-defined treatment failures with saquinavir/ritonavir, although there were no statistically significant differences in the percentages of patients with a viral load of <50 copies/mL in the intent-to-treat or on-treatment analysis.¹⁸ The risk of both virological failure and treatment discontinuation was greater in the saquinavir/ritonavir arm at week 48 due in part to the use of soft gel capsules, which were not as well tolerated as the hard gel capsule formulation.¹⁹ However, it should be noted that indinavir and saquinavir are now rarely used in the treatment-experienced patient population.

Lopinavir/ritonavir

Lopinavir was the first and remains the only PI to be co-formulated with ritonavir, as Kaletra®, initially as a capsule formulation containing lopinavir/ritonavir 133/33 mg. A tablet formulation, produced by a novel melt-extrusion process, is now approved and reduces the daily pill burden (from six capsules to four tablets daily), with additional benefits of no dietary restrictions, or requirement for refrigeration, and a reduced incidence of self-reported diarrhoea.^{20,21}

The BMS-043 study compared lopinavir/ritonavir (400/100 mg twice daily) with unboosted atazanavir (400 mg once daily) in 300 patients who had failed an initial PI-containing regimen, of whom 25% had at least four major PI mutations at baseline.²² Lopinavir/ritonavir was shown to be virologically superior with a $0.3 \log_{10}$ greater reduction in viral load at week 24 than that achieved with atazanavir ($P < 0.01$). Although those receiving lopinavir/ritonavir fared better virologically in this study, atazanavir-treated patients exhibited fewer rises in lipid parameters. Additionally, lopinavir/ritonavir has been compared with atazanavir/ritonavir in the BMS-045 study, as described below.²³

The benefits of lopinavir/ritonavir have also been demonstrated in combination with the fusion inhibitor enfuvirtide (T20). The TORO studies randomized approximately 1000 patients with documented resistance to drugs from each of the three drug classes available at that time, with a sustained viral load above 5000 copies/mL, to receive antiretroviral therapy consisting of an optimized background regimen chosen by resistance testing with or without enfuvirtide.²⁴ In those patients with no previous therapy with lopinavir/ritonavir, the use of this agent in the background regimen resulted in greater numbers of patients with a virological response and greater mean increases in CD4 counts than was observed in patients without concomitant use of lopinavir/ritonavir. In contrast, in patients previously treated with lopinavir/ritonavir, the use of lopinavir/ritonavir made no difference to the response to treatment.

Atazanavir/ritonavir

In the UK, unlike the USA, atazanavir/ritonavir is only licensed for the treatment of HIV-infected adults who are antiretroviral treatment experienced, used in combination with other antiretroviral agents.²⁵ Atazanavir/ritonavir has been compared with lopinavir/ritonavir and atazanavir/saquinavir in the BMS-045 study—a randomized, open label, multinational trial.²³ HIV-infected individuals, who had failed two or more prior HAART regimens that cumulatively included at least one drug from all three antiretroviral classes approved at the time of study design (NRTIs, NNRTIs and PIs), were randomized to receive atazanavir/ritonavir 300/100 mg once daily ($n = 120$), or lopinavir/ritonavir capsules 400/100 mg twice daily ($n = 123$), given with tenofovir and a second NRTI chosen by drug resistance testing; a third arm evaluated the double PI combination of atazanavir/saquinavir 400/1200 mg once daily. Mean reduction in HIV RNA levels from baseline at week 96 was $2.29 \log_{10}$ copies/mL in the atazanavir/ritonavir arm versus $2.08 \log_{10}$ copies/mL in the lopinavir/ritonavir arm [time-averaged difference (97.5% confidence interval): $0.14 \log_{10}$ copies/mL ($-0.13, 0.41$)]. An intent-to-treat analysis (non-completer = failure) at that time point demonstrated that 33% of patients receiving atazanavir/ritonavir achieved the secondary endpoint of HIV-1 RNA <50 copies/mL when compared with 36% of patients receiving lopinavir/ritonavir, not a significant difference. The atazanavir/saquinavir arm was discontinued at 24 weeks after an interim analysis showed that this combination to be inferior to both the other arms.

Although response rates were similar when fewer than 4 of the 16 PI-associated mutations of the Stanford Resistance Panel were present (amino acid substitutions at positions 10, 20, 24, 32, 33, 36, 46, 48, 50, 54, 63, 71, 73, 82, 84 and 90), lopinavir/ritonavir was superior to atazanavir/ritonavir in patients with four or more protease mutations at baseline. This suggests that atazanavir/ritonavir is of similar efficacy to lopinavir/ritonavir in drug-experienced patients with limited protease resistance, but inferior when a greater level of PI resistance is present.²⁶ Less than 30% of atazanavir/ritonavir-treated patients were responders if mutations were present at positions 46, 73, 84 or 90 at baseline, whereas in comparison, lopinavir/ritonavir response was $<30\%$ when protease substitutions at positions 46, 54 or 84 were present at baseline.²⁶ Additionally, there was a difference between the treatment groups in the impact of baseline phenotypic susceptibility on virological response. Suppression rates were similar for the two drugs for HIV-1 isolates, with baseline

phenotypes of up to a 5-fold reduction in susceptibility versus the wild-type HIV reference. However, for baseline isolates with >5-fold reductions in susceptibility, the atazanavir/ritonavir response rate was 11% when compared with 27% for lopinavir/ritonavir. These data provide little support for atazanavir/ritonavir for the highly treatment-experienced patient with multiple PI mutations.

Key benefits of atazanavir/ritonavir are a limited effect on lipid levels and its once daily administration. In the BMS-045 study, there were significant reductions in total cholesterol and fasting triglycerides in the atazanavir/ritonavir (300/100 mg once daily) arm when compared with the lopinavir/ritonavir arm. Atazanavir/ritonavir has also been shown to impair glucose uptake *in vitro* and insulin sensitivity *in vivo* significantly less than lopinavir/ritonavir (400/100 mg) in a group of 26 healthy HIV-negative men treated for 10 days in a randomized, cross-over study.²⁷

Fosamprenavir/ritonavir

Amprenavir has been re-formulated as its pro-drug, fosamprenavir, to improve bioavailability and to allow for a lower daily pill burden. In treatment-experienced patients, fosamprenavir is usually given twice daily when boosted by ritonavir. This dosing regimen is based on the findings of the randomized CONTEXT study, in which fosamprenavir/ritonavir (given either 1400/200 mg once daily or 700/100 mg twice daily) was compared with lopinavir/ritonavir (400/100 mg twice daily) in 315 PI-experienced patients, with background NRTI therapy selected by baseline resistance testing.^{28,29} By week 24, a greater proportion of virological failures occurred in both the fosamprenavir/ritonavir arms (34% for once daily and 27% for twice daily) when compared with the lopinavir/ritonavir arm (21% twice daily); at week 48, the once-daily arm was shown to have underperformed when compared with the twice-daily arms. Because twice-daily fosamprenavir/ritonavir failed to meet the protocol-defined threshold for non-inferiority to lopinavir/ritonavir in this study, it is still a less favourable option for the treatment of PI-experienced patients.

New boosted PIs

Two new PIs—tipranavir and darunavir—have recently entered clinical practice. These agents are currently being used in highly treatment-experienced populations and have shown impressive virological responses in clinical trials.

Tipranavir/ritonavir

Tipranavir was approved in the European Union in late 2005 for highly treatment-experienced patients with resistance to multiple PIs. Tipranavir is a novel, non-peptidic PI, with a resistance profile distinct from other PIs and is given at a dose of 500 mg twice daily boosted with twice-daily ritonavir 200 mg, double the ritonavir dosage administered with other boosted PIs.

The registrational trials for tipranavir—the RESIST 1 and 2 studies—were large, similarly designed, randomized, multinational studies conducted in the USA, Canada and Australia and in Europe and Latin America, respectively.³⁰ Together, the studies treated 1483 patients: 746 with tipranavir/ritonavir

(500/200 mg twice daily) and 737 with a comparator PI [chosen using clinical judgement and the resistance profile; lopinavir ($n = 359$), saquinavir ($n = 162$), amprenavir ($n = 194$) and indinavir ($n = 22$)] boosted with ritonavir. One-fifth (20.5%) of patients in the RESIST studies also used enfuvirtide as part of the background regimen. The mean baseline CD4 cell counts were 196 and 195 cells/mm³ and the mean baseline viral loads were 4.73 and 4.73 log₁₀ HIV-1 RNA copies/mL in the tipranavir/ritonavir and comparator PI/ritonavir arms, respectively, and the median prior number of antiretroviral drugs used was 12.

Patients were required to have taken at least 3 months of therapy with drugs from the three main antiretroviral drug classes, including at least two PI-containing regimens, and to have HIV-1 RNA levels of >1000 copies/mL at study entry. Additionally, patients had to have at least one primary protease mutation documented by resistance testing at baseline (approximately two-thirds of patients had two or more mutations); there were no CD4 cell count limitations and patients with hepatitis were not excluded, provided that they were stable with no greater than Grade 1 liver function test abnormalities at baseline. Week 96 results have been presented, and week 24 and 48 data have been recently published.^{30–33}

In both studies, virological responses were superior in the tipranavir/ritonavir arm when compared with the standard-of-care comparator-boosted PI arm at week 48.³⁴ The mean change in HIV-1 RNA viral load was -1.14 log₁₀ copies/mL in patients taking tipranavir/ritonavir and -0.54 log₁₀ copies/mL in the comparator PI/ritonavir arm. In the combined RESIST study population, 22.8% (170/746) of patients who received tipranavir/ritonavir achieved a viral load of <50 copies/mL at week 48, compared with 10.2% (75/737) of control patients ($P < 0.0001$) with no effect of PI experience, because patients who took tipranavir/ritonavir were always more likely to have a viral load of <50 copies/mL at week 48 than those who took a comparator PI/ritonavir. Even in patients who had only taken two previous PIs, the difference in treatment responses was considerable: 35.0% (28/80) with a viral load of <50 copies/mL in the tipranavir/ritonavir arm versus 24.3% (17/70) in the control arm. In patients with more extensive PI experience, the difference between the two arms was greater; patients who had taken six prior PIs were 8.8-fold more likely to have an undetectable viral load on tipranavir/ritonavir treatment when compared with any of the comparator PIs/ritonavir.³⁵ Mean CD4 cell counts increased by 45 cells/mm³ in patients on tipranavir/ritonavir and by 21 cells/mm³ in the control arm [last observation carried forward (LOCF)]. CD4 cell responses were significantly blunted in both arms when patients received didanosine with tenofovir as the nucleoside backbone, even when the lower dose of didanosine 250 mg once daily was used.³⁶ The risk of treatment failure through week 48 was reduced in the tipranavir/ritonavir arm (HR 0.63, $P < 0.0001$) and patients who initiated tipranavir/ritonavir with higher baseline CD4 cell counts or lower baseline viral loads achieved better therapeutic responses (>50% of patients who started tipranavir/ritonavir with a baseline HIV-1 RNA viral load of <10 000 copies/mL experienced a treatment response by week 48).³⁰ In addition, the health-related quality-of-life (HRQOL) scores, using validated measures, showed stable or improved HRQOL in the tipranavir/ritonavir arm, despite a higher incidence of treatment-associated adverse events.³⁷

Review

The 96 week results from the RESIST 1 and 2 studies confirm the durable superiority of tipranavir/ritonavir when compared with other boosted-PI regimens in achieving viral load declines and delaying treatment failure in highly treatment-experienced patients. The median time to treatment failure was 115 days for tipranavir/ritonavir and 0 days for the comparator PI/ritonavir, because more than half the patients in the comparator arm did not achieve a treatment response ($P < 0.0001$).³³ Combining tipranavir/ritonavir with another active agent resulted in a greater rate of virological response and the mean change in the viral load at week 96 was $-1.07 \log_{10}$ copies/mL on tipranavir/ritonavir and $-0.50 \log_{10}$ copies/mL in the control arm (LOCF). The proportion of patients achieving viral load of <50 copies/mL was 20.4% of those receiving tipranavir/ritonavir, compared with 9.0% of those receiving comparator-boosted PIs ($P < 0.0005$): co-administration of the fusion inhibitor enfuvirtide increased these proportions to 28.8% and 13.3%, respectively ($P < 0.0002$). In an analysis of all the 24 week data presented to the FDA from Boehringer-Ingelheim-sponsored studies (RESIST 1 and 2), by baseline PI mutations, patients with five or more mutations began to lose antiviral response between weeks 4 and 8; however, if enfuvirtide was used concurrently, then a $>1.5 \log_{10}$ reduction in HIV RNA was seen.³⁸ Owing to the non-randomized use of enfuvirtide, those patients who used it tended to be those with lower CD4 levels, higher viral loads and greater baseline resistance, potentially underestimating the benefits of combining the two agents.

Hepatic and lipid-related adverse events occurred at a greater frequency in the tipranavir/ritonavir arm, but were rarely a cause for study discontinuation.³⁹ In RESIST 1 and 2, 10.3% of patients in the tipranavir/ritonavir arm and 15.3% of patients treated with a comparator-boosted PI were co-infected with hepatitis B or C virus (HBV or HCV). By week 48, the Kaplan–Meier probability of emergent Grade 3/4 alanine aminotransferase (ALT) elevation was 9.9% with tipranavir/ritonavir when compared with 2.8% with comparator PI/ritonavir. Cox multivariate regression analyses (including treatment, baseline ALT/AST grade, hepatitis co-infection, baseline CD4 count, race and gender) showed that tipranavir/ritonavir treatment (HR = 2.77, 95% CI 1.65–4.67), hepatitis co-infection (HR = 2.01, 95% CI 1.17–3.46) and baseline CD4 count >200 cells/mm³ (HR = 1.64, 95% CI 1.07–2.53) were the most significant independent risk factors for the development of Grade 3/4 ALT/AST.

Elevated baseline ALT was also a risk factor for both treatment arms (RR = 2.03, 95% CI 0.88–4.70), but did not reach statistical significance ($P = 0.10$). Only 1.9% of patients who received tipranavir/ritonavir discontinued therapy because of emergent Grade 3/4 liver function tests and among these patients, hepatic serious adverse events were rare; the majority of patients (81.1%) who developed Grade 3/4 liver function tests were able to continue therapy and the clinical significance of liver function abnormalities seen with tipranavir remains ill-defined. Nevertheless, it is probably advisable to consider switching therapy in patients who experience c 3/4 liver function test abnormalities.

In summary, the RESIST studies provide good evidence that tipranavir/ritonavir is virologically and immunologically superior to comparator-boosted PIs in a population of highly treatment-experienced patients.

Tipranavir/ritonavir has been linked with both fatal and non-fatal intracranial haemorrhage: 14 cases, including 8 fatalities were reported in clinical trials involving 6840 HIV-1-infected patients, many of whom had other medical conditions or were receiving concomitant medications that may have contributed to these events. Tipranavir has been observed to inhibit human platelet aggregation and should therefore be used with caution in patients known to be at risk of increased bleeding.⁴⁰

Although *in vitro* studies have suggested that the interaction potential of enfuvirtide with PIs is low, an unexpected interaction between enfuvirtide and tipranavir/ritonavir was observed in patients undergoing routine therapeutic drug monitoring while receiving tipranavir/ritonavir (500/200 mg twice daily) with or without enfuvirtide (90 mg subcutaneously twice daily). Tipranavir trough concentrations were significantly higher in the presence of enfuvirtide ($41\,069 \pm 20\,174$ versus $27\,261 \pm 17\,516$ ng/mL, mean \pm SD, $P = 0.011$), although the clinical significance of this is unclear and these results have not been confirmed by other investigators.^{41,42}

Data indicate that co-administration of boosted tipranavir with some other PIs may alter their pharmacokinetics.¹¹ A 24 week, open-label study investigated the safety and PK of tipranavir/ritonavir (500/200 mg twice daily) alone or in combination with a second boosted PI (amprenavir, lopinavir or saquinavir) in 315 highly treatment-experienced patients (three or more PI mutations). At a planned interim analysis (conducted when all patients had reached week 4), there were reductions in plasma pharmacokinetic variables for saquinavir, amprenavir and lopinavir when co-administered with tipranavir/ritonavir. All the combinations appeared to be well tolerated. Increased doses of lopinavir/ritonavir co-administered with tipranavir 500 mg twice daily have been investigated (lopinavir/ritonavir 400/300 mg or 533/233 mg twice daily) and found to be generally safe and well tolerated, but the authors recommend therapeutic drug monitoring because of inter-patient variability in lopinavir trough concentrations.⁴³

A tipranavir mutation score developed by an expert panel of retrovirologists was recently published: it lists 21 mutations at 16 protease positions that confer resistance to tipranavir (10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D and 84V).⁴⁴ The scoring system lists viruses with ≤ 4 of these mutations as susceptible, with 5–7 as partially resistant and with ≥ 8 mutations as resistant.⁴⁴ This score has been subsequently used to evaluate the relationship between tipranavir genotypic inhibitory quotient (gIQ) and early virological response.⁴⁵ Tipranavir gIQ was calculated as the ratio between mean tipranavir C_{\min} and number of tipranavir-associated mutations. In 38 treatment-experienced patients, tipranavir gIQ was an independent predictor of both viral load decrease and virological response (defined as a decrease in HIV-1 RNA by at least 1 \log_{10} copies/mL and/or a reduction in HIV-1 RNA to <50 copies/mL) by multivariate analysis. It has also been shown, using published scores (>3) for lopinavir resistance, that tipranavir/ritonavir was more likely to achieve a viral load of <50 copies/mL than comparator PIs.⁴⁶ Finally, in a report of combined data sets from RESIST and B11182.51, clinical isolates exposed to other boosted PIs retained susceptibility to tipranavir [fold change (FC) IC_{50} <4 -fold], whereas high-level resistance (FC IC_{50} <10 -fold) was seen in $<2.5\%$.⁴⁷

Darunavir/ritonavir

Darunavir is a non-peptidic PI that was approved in the European Union in February 2007 for highly pre-treated adult patients who have failed more than one PI-containing regimen.

Studies of this drug suggest that it has good activity against HIV isolates resistant to currently approved PIs and it is now licensed at a dose of darunavir/ritonavir 600/100 mg twice daily.^{39,48} Selection in cell culture of darunavir-resistant HIV-1 from nine strains harbouring multiple PI resistance mutations led to the emergence of 22 mutations in the protease gene, including L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S and Q92R.⁴⁹ Mutations at residues 10, 32, 33, 37, 46, 47, 50, 63, 71 and 84 were most prevalent. These darunavir-resistant viruses with at least eight protease gene mutations exhibited a 50–641-fold decrease in susceptibility to darunavir, with final EC₅₀ values ranging from 125 to 3461 nM.

The POWER 1 and 2 studies randomized triple-class-experienced patients, who had failed at least one PI-based combination and had viral loads >1000 copies/mL, to one of four darunavir/ritonavir doses (400 mg once daily, 800 mg once daily, 400 mg twice daily or 600 mg twice daily) or to a comparator-boosted PI.^{50–53} A total of 397 patients were randomized to darunavir/ritonavir treatment and 100 to the control arm; 48% and 41% of patients, respectively, also received enfuvirtide. Week 24 and 48 data from these two Phase IIb studies have been presented. Those who combined darunavir/ritonavir with enfuvirtide achieved the best virological responses, although the sample size in this subgroup was small.

The primary analysis at 24 weeks in POWER 1 and 2 showed that 69.5% of patients in the darunavir/ritonavir arm achieved a virological response ($\geq 1.0 \log_{10}$ reduction), compared with 21% of patients in the control arm.⁵⁰ In addition, darunavir/ritonavir recipients were more likely to achieve a viral load of <50 copies/mL (45% versus 12%, respectively) and to have an increase in CD4 cell count from baseline (92 versus 17 cells/mm³, respectively), compared with patients in the control arm. An *ad hoc* analysis of 110 patients who had reached 48 weeks of treatment in the darunavir/ritonavir arm (total $n = 131$) showed 61% with $\geq 1.0 \log_{10}$ reduction in viral load from baseline versus 15% for the 120 patients in the control arm (total $n = 124$) by intent-to-treat analysis. In this 48 week analysis, 46% of patients receiving darunavir/ritonavir had a viral load of <50 copies/mL and the mean CD4 cell increase was 102 cells/mm³, compared with 10% of patients in the control arm and a mean CD4 cell increase of 19 cells/mm³. The most frequently reported adverse events by week 48 in the darunavir/ritonavir arm versus control arm were diarrhoea (20% versus 28%), nausea (18% versus 13%), headache (15% versus 20%), nasopharyngitis (14% versus 11%) and fatigue (12% versus 17%), whereas discontinuations due to adverse events were similar: 7% in the darunavir/ritonavir arm versus 5% in the control arm.⁵²

POWER 3 was an open-label, non-randomized study conducted to assess further the long-term efficacy and safety of darunavir/ritonavir 600/100 mg twice daily in 327 treatment-experienced patients. Mean baseline viral load was $4.6 \log_{10}$ copies/mL and CD4 count was 115 cells/mm³.⁵³ Patients had a median of three primary PI mutations; only 20% had viruses sensitive to another PI at screening by phenotype (excluding tipranavir, which was not available at the time of

recruitment). Among enrolled patients, 99% had used one or more PIs and 98% had received four or more NRTIs and one or more NNRTIs, similar to patients in POWER 1 and 2.

The primary efficacy endpoint of $\geq 1 \log_{10}$ viral load reduction was observed in 65% of patients at week 24, with a viral load of <50 copies/mL in 40% of patients and a mean viral load reduction of $1.65 \log_{10}$ copies/mL; CD4 counts at week 24 (LOCF) increased by a mean of 80 cells/mm³. The most frequent adverse events were diarrhoea (14%), nasopharyngitis (11%) and nausea (10%), whereas Grade 3/4 triglyceride, cholesterol and ALT/AST liver function enzyme elevations occurred in 6%, 4%, 2% and 2% of patients, respectively, similar to rates seen in previous darunavir/ritonavir studies.

Overall, 8% of patients discontinued therapy during POWER 3. Notably, there was a low rate of treatment discontinuation because of adverse events or HIV-related events (2%) and virological failure (2%). When all three POWER studies were analysed together, similar rates of viral suppression were seen across the studies for patients who received darunavir/ritonavir 600/100 mg twice daily, but lower rates of reported adverse events, notably, diarrhoea occurred in Power 3.⁵⁴ In the clinical trial development programme, rash was reported in 7% of patients, including several cases of erythema multiforme and Stevens–Johnson syndrome.⁴⁹

Amprenavir and darunavir share structural similarities, which suggest the possibility of impaired response to darunavir in those patients previously treated with amprenavir. A pooled analysis of 317 patients taking either lopinavir/ritonavir, fosamprenavir/ritonavir or tipranavir/ritonavir as part of a failing combination when they entered the three studies shows similar rates of response to darunavir/ritonavir, regardless of which boosted PI was failing at the time of darunavir/ritonavir initiation, with a reduced susceptibility when ≥ 10 PI-associated mutations were present.^{55,56} Researchers did not report whether first-time enfuvirtide use differed in the three groups analysed. Virological response to darunavir/ritonavir differed hardly at all by sensitivity or exposure to comparator.⁵⁷

Phenotypic cut-offs, corresponding to predicted darunavir/ritonavir FC values associated with a 20% ($n = 319$) or 80% ($n = 83$) loss of the wild-type darunavir/ritonavir response, were calculated and validated using data from 402 patients who received darunavir/ritonavir 600/100 mg twice daily in the POWER studies.⁵⁸ The analysis showed that a 20% loss of anti-retroviral activity for darunavir/ritonavir is predicted with a 3.4-fold phenotypic change in the 50% effective concentration (EC₅₀) and an 80% loss of activity is predicted with a >97-FC.

Darunavir/ritonavir has a number of important PI pharmacokinetic interactions and should not be co-administered with lopinavir/ritonavir or saquinavir/ritonavir.⁵⁹ A study in 33 HIV-positive patients demonstrated that the AUC of darunavir at a dose of 1200 mg twice daily plus lopinavir/ritonavir was ~40% of the AUC with darunavir/ritonavir at 600/100 mg twice daily without lopinavir.⁶⁰ A separate study showed that the pharmacokinetics of darunavir/ritonavir is affected by the co-administration of saquinavir/ritonavir; researchers found that the C_{min} , C_{max} and AUC₁₂ of darunavir were decreased by 42%, 17% and 26%, respectively, whereas saquinavir parameters were unaffected by the addition of darunavir/ritonavir.⁶¹ Co-administration of darunavir/ritonavir and saquinavir/ritonavir was associated with a higher incidence of adverse events and discontinuations because of adverse events.

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Other pharmacokinetic interactions with darunavir/ritonavir that may be clinically relevant include a reduction by darunavir/ritonavir in methadone (S-isomer) C_{min} , C_{max} and AUC_{12} by 40%, 44% and 36%, respectively, although no *a priori* dose adjustment is suggested for methadone in those stable on the therapy. Four of 22 patients developed symptoms associated with withdrawal;⁶² therefore, careful monitoring and a potential methadone increase may be required. In addition, when patients were treated with darunavir/ritonavir (400/100 mg) together with the selective serotonin reuptake inhibitors paroxetine and sertraline, drug exposure was reduced by 49% and 39%, respectively, although the clinical implications of these findings are not yet clear.⁶³

Patients co-infected with HBV or HCV were allowed to enter the POWER 1 trial or the POWER 3 analysis if their condition was clinically stable and they were not on treatment for hepatitis during the studies. In these trials, HBV or HCV co-infection was present in 15% of the 634 patients who received darunavir/ritonavir and 21% of the 63 patients who received a comparator PI (active infections were present in 12% and 16% of patients, respectively).⁶⁴ Darunavir/ritonavir efficacy was similar in both HBV or HCV subgroups when compared with HBV- and HCV-uninfected HIV patients, but a difference was seen in the incidence of liver-related adverse events, mainly AST and ALT elevations (darunavir/ritonavir: 13% versus 8% and comparator PI: 20% versus 12%).⁶⁴ Lipid levels at week 48 were similar between patients treated with darunavir/ritonavir and comparator PIs.⁶⁵ Mean low-density lipoprotein, high-density lipoprotein and total cholesterol levels remained within the normal range as per the National Cholesterol Education Project (NCEP) guideline recommendations.

To date, there has been no randomized, comparative trial of darunavir/ritonavir and tipranavir/ritonavir in treatment-experienced patients, and the safety and efficacy of darunavir/ritonavir require further evaluation in long-term studies, especially with the availability of new antiretroviral classes.

Which boosted PI to choose?

PIs may select for unique resistance patterns when they are taken without ritonavir (D30N for nelfinavir and I50L for atazanavir) and may lose activity when common PI mutations are selected, which in turn may contribute to broad cross-resistance as they accumulate.

An analysis of 9860 HIV-1 isolates by Monogram Biosciences had several interesting findings concerning resistance to ritonavir-boosted tipranavir, lopinavir, amprenavir, atazanavir and saquinavir.⁶⁶ In particular, the study showed that the I84V mutation had a greater effect on susceptibility to all these PIs than other mutations, such as L33F/I, V82A and L90M. Other data indicate that the I84V mutation also has a substantial effect on susceptibility to darunavir.⁴⁹ The V82A mutation, without other critical PI mutations, had no effect on susceptibility to tipranavir/ritonavir, even when found with a second seminal PI mutation, whereas L90M had the least impact on resistance to any boosted PI studied, except saquinavir.

For the newer boosted PIs—tipranavir and darunavir—the available data suggest minimal cross-resistance between these two agents (Figure 1).^{67,68} For example, the I50V mutation is

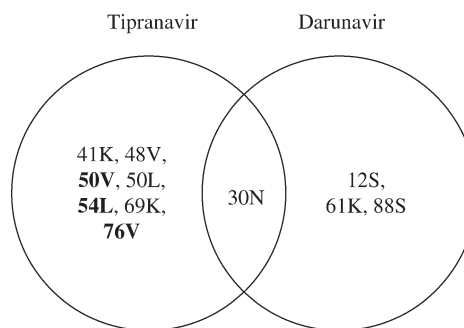


Figure 1. Single mutations associated with increased susceptibility to tipranavir and darunavir (adapted from two presentations of the vircoTYPE analysis). Mutations (I50V, I54L and L76V) associated with resistance to darunavir are associated with increased susceptibility to tipranavir. Similar to amprenavir, N88S is associated with increased susceptibility to darunavir. Note: it does not show combinations of two mutations that are associated with increased susceptibility.^{67,68}

associated with reduced susceptibility to fosamprenavir and darunavir, but increased susceptibility to tipranavir.

It is clear that resistance testing should be used in patients failing HAART to select both the most appropriate PI and background antiretrovirals to secure a durable viral response to HIV-1 RNA <50 copies/mL.³ Phenotypic resistance testing may theoretically provide additional benefit over genotyping, but this has not yet been demonstrated in clinical trials, and practical and cost issues have rendered this assay useful mainly within clinical trials. The use of vircoTYPE tests could provide an acceptable alternative and combines an analysis of resistance-associated mutations in the protease and reverse transcriptase genes of the virus, classified by drug class, with a prediction of the phenotype.

Few cohort-based studies comparing the benefits of different boosted PIs have been performed. One study of 389 Spanish patients examined the outcomes of those who received saquinavir/ritonavir ($n = 139$), indinavir/ritonavir ($n = 35$), lopinavir/ritonavir ($n = 129$), amprenavir/ritonavir ($n = 35$), atazanavir/ritonavir ($n = 29$) and tipranavir/ritonavir ($n = 22$), while excluding those who received enfuvirtide in the background regimen.⁶⁹ In multivariate analyses, only the total number of primary PI mutations was associated with a lower virological response (95% CI 0.68–0.87, $P < 0.001$), and the threshold of <5 or ≥ 5 mutations at baseline provided the most discrimination with regard to viral response.

The introduction of tipranavir and darunavir into clinical practice enhances the choice of PIs for inclusion in second- and third-line regimens. Until further informed by a head-to-head comparison study of these, the clinician must consider which of the two are most compatible with the needs of specific patients in the context of the whole regimen. The choice will specifically take into account differences in the safety profiles of these agents, the comparable robustness of their genetic barriers to resistance and their drug–drug interaction profiles with existing and potentially new drugs. Tipranavir/ritonavir cannot be co-administered with etravirine (TMC125, a salvage NNRTI in Phase III development) because of the significant reduction in exposure to the latter that occurs.⁷⁰ Reductions in exposure to the integrase inhibitor raltegravir (MK-0518) when combined with tipranavir/ritonavir have also been reported.⁷¹ Drug–drug

interaction studies have not been reported for the combination of darunavir/ritonavir and raltegravir, but there is no significant pharmacokinetic interaction between either darunavir/ritonavir or tipranavir/ritonavir and another integrase inhibitor in development, elvitegravir (GS-9137).^{72,73} Maraviroc, the first licensed member in the new class of CCR5 receptor antagonists, requires dose adjustments when used in combination with PIs, with the exception of tipranavir/ritonavir.^{74,75}

Selecting the optimal concomitant drugs in an antiretroviral combination is critical to the success or failure of a boosted PI regimen in treatment-experienced patients. In cases where patients have failed multiple prior combinations, where extensive NRTI and NNRTI resistance is present, it is critical to add at least one or two drugs from a new class (or classes), such as the fusion inhibitor enfuvirtide, the CCR5 receptor antagonist maraviroc⁷⁶ or the integrase inhibitor raltegravir.⁷⁷

This principle is supported by data from three sets of randomized, prospective clinical trials: TORO, RESIST and POWER. The large TORO studies of enfuvirtide showed the importance of combining lopinavir/ritonavir, which at the time was the new potent PI, with enfuvirtide for maximum success.²⁴ Similarly, both the large RESIST studies of tipranavir/ritonavir,³¹ as well as preliminary results of the somewhat smaller POWER studies of darunavir/ritonavir,⁵⁰ demonstrate the importance of combining a potent PI, to which the virus is susceptible, with enfuvirtide when treating PI-experienced patients.⁷⁸

What should be the goal of therapy for highly experienced patients?

The aim of therapy for all HIV-infected patients is complete virological suppression, regardless of whether a patient is treatment-naïve or treatment-experienced, because this is the only proven way to achieve long-term clinical benefit. It is essential to use drug resistance testing with expert interpretation to choose the boosted PI with maximum remaining activity. Recent analyses of the TORO, RESIST, POWER, BENCHMARK and MOTIVATE studies suggest that undetectable HIV-1 RNA levels can be achieved even in patients who have failed multiple PI regimens, especially when a new class of antiretrovirals is used.^{79–82} For those in whom complete HIV-1 RNA suppression cannot be obtained with currently available agents, maintaining immunological function and preventing clinical progression should be the main objectives of therapy.

The major risk to the patient of maintaining a partially suppressed viral load on treatment is the continued emergence of resistance mutations that reduce future drug options. This cost is a strong argument for aggressive modification of HIV therapy following virological failure. For some, a fully suppressive regimen may not be possible and the clinician should weigh the risk of rapidly losing future drug options by switching therapy early, with the risk of losing benefit from future drug options by maintaining a partially suppressive regimen. In a cohort of 106 treatment-experienced HIV-positive patients who were maintained in partially suppressive regimens, an estimated 44% of patients developed at least one new drug resistance mutation over 1 year (18% developed at least one new PI mutation at 1 year, whereas 30% lost the phenotypic equivalent of one susceptible drug over this period). Although researchers

observed a significant risk of viral evolution overall, the risk of accumulating genotypic resistance to tipranavir and darunavir was relatively low, suggesting that it may be prudent to defer switching until at least two new effective antiretroviral agents are available.⁸³ The risk of developing new mutations that may compromise future treatment options should also be balanced against the risk of clinical progression. Consequently, the need to change therapy in partially suppressed patients with limited therapeutic options should consider their immunological status. Patients with relatively preserved CD4 counts may delay changing therapy until potent suppressive regimens can be designed, whereas those who are more severely immunodepressed may be at a higher risk of developing opportunistic illnesses and could therefore benefit from an earlier switch.

The combination of using a newer boosted PI with greater activity against resistant viruses, alongside an optimized background therapy chosen by resistance testing, has significantly increased the likelihood of effective therapy for treatment-experienced patients. With the optimal use of the fusion inhibitor enfuvirtide, as well as new classes of antiretroviral agents, this represents a new standard-of-care for treatment-experienced patients. The goal of therapy for highly treatment-experienced patients should now be to achieve HIV-1 viral load <50 copies/mL.⁸⁴

Patients who are highly experienced benefit from the care of highly experienced doctors. It seems that the Art of Medicine has once more come to the fore: the use of new agents in drug classes to which a patient has previous exposure is usually limited by selected resistant mutants, making the adopt and considered combination of agents from novel classes, as well as a thorough understanding of boosted PIs, paramount for the best choice of regimen for individual patients. The goal of therapy now is success and nothing less is acceptable.

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