Antiretroviral Therapy: Darunavir: An Overview of an HIV Protease Inhibitor Developed to Overcome Drug Resistance

March 01, 2007 | Cholesterol Disorders [1], HIV/AIDS [2], Sleep Disorders [3], Infection [4]
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Darunavir (TMC114) is a second-generation, sulfonamide, nonpeptidic protease inhibitor (PI) with a unique, flexible, 3-dimensional structure that contributes to its high potency and slow selection of resistant virus. Darunavir has to be coadministered with low-dose ritonavir and food to optimize its pharmacokinetics. Ritonavir-boosted darunavir is effective in many heavily pretreated patients, including those with multiple PI resistance mutations. In vitro, the coexistence of numerous PI mutations was required for its virological potency to be significantly reduced.

Preliminary findings suggest that it is active against some tipranavir-resistant strains. [AIDS Reader. 2007;17:151-156, 159-161]

Key words: HIV/AIDS • Antiretroviral therapy • Protease inhibitors • Darunavir • Drug resistance • Ritonavir boosting

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The HIV protease inhibitor (PI) class of antiretroviral agents is one of the cornerstones of effective antiretroviral therapy.1 However, the clinical usefulness of PIs is limited by several factors, including their adverse effect profile and drug resistance that emerges during treatment or, less frequently, is acquired at the time of infection.2-4 These limitations underscore the need for new, better-tolerated compounds with activity against multi-PI-resistant HIV.

Darunavir (formerly TMC114) is a second-generation, nonpeptidic PI that evolved from a prototype compound synthesized using structure-based design strategies.5,6 In vitro and in vivo animal and human clinical studies have demonstrated its safety and potency against a wide range of HIV strains found in treatment-naive and treatment-experienced patients, including viral strains with numerous PI resistance mutations. Of note, darunavir must be coadministered with low-dose ritonavir to optimize its pharmacokinetic characteristics.7 Following favorable clinical trials results, expanded access to the drug was begun in October 2005; darunavir was granted accelerated approval by the US FDA in June 2006 and approved by Health Canada in August 2006.

RELATIONSHIP OF STRUCTURE TO FUNCTION

Darunavir has novel structural features that are believed to account for a high level of potency, a relatively slow selection of darunavir-resistant virus during exposure to the compound, and preserved activity against viruses resistant to other PIs. Darunavir is structurally related to amprenavir9 and was selected from approximately 200 other synthetic compounds being screened for development based on its pharmacokinetic and antiviral properties.10 Darunavir binds to the HIV protease enzyme with high affinity partly because of the formation of additional hydrogen bonds at the active binding site.11,12 As a result, darunavir has a tighter binding affinity than amprenavir, indinavir, saquinavir, lopinavir, ritonavir, and nelfinavir.13 Despite this relatively tighter bonding, the molecular structure of darunavir remains highly flexible with some ability to adapt to the shape of mutant virus.14

IN VITRO EFFICACY

In line with the initial suggestion of efficacy,15 darunavir has been shown to be highly potent in suppressing the replication and infectivity of laboratory strains of HIV-1. For example, it was more potent against HIV-1LA1 (inhibitory concentration [IC]50, 0.003 µM) than saquinavir, amprenavir, indinavir, nelfinavir, lopinavir, and ritonavir, which had IC50 ranging from 0.017 µM to 0.047 µM.12 De Meyer and colleagues13 showed that darunavir had comparable activity against HIV group M (subtypes A-H), group O, and different circulating recombinant forms. Also, darunavir demonstrated
more potency against laboratory HIV-2 strains than did any other tested PIs with the exception of saquinavir.\textsuperscript{12}

In vitro replication of HIV variants that were selected during exposure to other PIs was, in general, suppressed by darunavir, although the degree of suppression was variable. Specifically, darunavir remained potent against strains selected by saquinavir and nelfinavir; was somewhat less active against strains selected by indinavir and ritonavir; and was least active against strains that were selected by the structurally-related PI amprenavir.\textsuperscript{12} Overall, among 1051 viral strains with decreased susceptibility, which was defined as less than 4-fold increase in the effective concentration or $EC_{50}$ (ie, plasma concentration/area under the curve [AUC] ratio required for obtaining 50% of the maximum effect in vivo), to at least 1 of the tested PIs, 80% of the strains remained susceptible to darunavir; only 10% demonstrated a greater than 10-fold change in $EC_{50}$ to darunavir.\textsuperscript{13}

Clinical isolates from 5 of 7 extensively antiretroviral-exposed patients remained highly susceptible to darunavir ($IC_{50}$, 0.003 to 0.013 $\mu$M) despite the presence of 9 to 14 PI resistance mutations and phenotypic resistance to all tested PIs (except saquinavir in some cases).\textsuperscript{12} The remaining 2 of the 7 isolates were also susceptible to darunavir, although at a higher $EC_{50}$. Modest synergy was demonstrated between darunavir and ritonavir, nelfinavir, and amprenavir; no antagonism was found between darunavir and any of the approved NRTIs or NNRTIs.\textsuperscript{13}

**IMPORTANT CLINICAL TRIALS**

**Study C207**

The first clinical trial of darunavir (C207) was a multicenter 14-day proof-of-principle study.\textsuperscript{16} Enrolled participants had to have HIV RNA levels above 2000 copies/mL, have 2 or more months of exposure to 2 to 4 PIs, and be currently receiving a regimen containing PI(s) plus NRTIs. There was extensive baseline PI resistance: 51% demonstrated phenotypic resistance to the PIs amprenavir, indinavir, ritonavir, lopinavir, nelfinavir, and saquinavir. All primary PI mutations, with the exception of the I50L and V82S mutations, were represented.

Participants were randomized to 1 of 3 darunavir/ritonavir (DRV/r) treatment groups: 300/100 mg twice daily (group 1, n = 13); 900/100 mg daily (group 2, n = 13); or 600/100 mg twice daily (group 3, n = 12). A fourth group continued its current PI regimen (group 4, n = 12). The patients' baseline NRTI backbones were continued in all groups.

After 14 days, an HIV RNA level below 400 copies/mL was achieved in 46%, 31%, 42%, and 8% in groups 1 to 4, respectively. Median increases in CD4$^+$ cell counts were 16, 5, 63, and 0.5/µL, respectively. There was no development of darunavir resistance mutations during the short duration of the study.

**POWER 1 and POWER 2 Trials**

The first 2 POWER trials are multinational, randomized, controlled clinical trials evaluating the efficacy and safety/tolerability of ritonavir-boosted darunavir. Both studies are scheduled to go through 96 weeks.

At baseline, enrolled patients had to be 3-class-experienced and be on a failing PI-based regimen (ie, HIV RNA level greater than 1000 copies/mL).\textsuperscript{17-19} Patients had previous exposure to an average of 4 PIs with a median of 8 current primary and secondary PI mutations. All patients received an optimized background regimen of NRTIs with or without enfuvirtide (added at the discretion of the investigator) and randomized to different doses of darunavir plus ritonavir or an investigator-selected comparator PI.

Combined interim analysis of POWER 1 and POWER 2 was conducted after at least 150 patients in each study had been treated for 24 weeks or had discontinued treatment earlier.\textsuperscript{18} Overall, DRV/r was remarkably potent in this highly PI-resistant cohort (Figure 1), and the 600/100 mg twice-daily dosing was selected for further clinical development.

Separate 24-week data from POWER 1 and POWER 2 have also been presented.\textsuperscript{17,19} The data for DRV/r 600/100 mg versus control are shown in Figure 2. In summary, in this highly PI-resistant cohort, DRV/r was superior to the PIs in the control arm (all currently FDA-approved PIs except tipranavir). Viral suppression improved when enfuvirtide was included in the regimen (Table). Of note, patients in POWER 1 had better average virological response than those in POWER 2, perhaps because of their lower baseline HIV RNA level and higher baseline CD4 counts.

The durability of the antiviral efficacy of ritonavir-boosted darunavir through week 48 was recently reported.\textsuperscript{20} Boosted darunavir was found to be superior to a comparator PI for the end points of 1-log\textsubscript{10} or greater decline in HIV RNA level (61% vs 15%); HIV RNA level below 50 copies/mL (46% vs 10%); and mean CD4$^+$ cell increase from baseline (102/µL vs 19/µL).
Data demonstrating the 24-week efficacy of DRV/r has been buttressed by POWER 3 (N = 327), an
open-label safety and efficacy study among patients with triple-class experience and a median of 3
primary PI mutations. At week 24, 40% of patients had achieved viral suppression to below 50
copies/mL, including 45% of patients receiving enfuvirtide for the first time and 31% of patients
previously exposed to tipranavir. Mean CD4+ cell increase was 80/µL.

**DRUG RESISTANCE**

Preliminary in vitro data suggested slower development of drug-resistant viral mutations with
darunavir than with some other PIs. Breakthrough viral replication occurred in the presence of high
centrations of nelfinavir after 20 days, amprenavir after 30 days, and lopinavir after 90 days. In
contrast, replicating virus was not selected with exposure to darunavir, even after 260 days. The
mutations that eventually emerged (R41T and K70E), which have reduced viral replication capacity,
confered reduced susceptibility to darunavir, but cross-resistance to PIs (greater than 10-fold
reduced susceptibility to darunavir, but less than 10-fold reduced susceptibility to amprenavir,
lopinavir, indinavir, and nelfinavir) was uncommon. Only to saquinavir did the mutated virus show a
greater than 10-fold decreased susceptibility.

The baseline mutations associated with decreased 24-week virological response to darunavir in the
POWER 1 and POWER 2 studies were V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, and
L89V. Among participants who had virological rebound after initial response, more than 10%
developed a drug-resistant mutation: V32I, L33F, I47V, I54L, or L89V. In vitro tests showed that each
mutation, by itself or combined with 1 or 2 additional mutations, did not greatly reduce susceptibility to darunavir (ie, less than a 4-fold change), confirming that coexistence of multiple
mutations is needed before darunavir's efficacy is compromised. The virological potency of darunavir
only became substantially reduced when there were at least 10 PI mutations.

Recent studies have shed light on the potential role of genotypic and phenotypic testing in predicting
response to darunavir. However, it is important to recognize the preliminary and sometimes
controversial nature of some of these findings, especially those that involve fold-changes and clinical
cutoffs derived using complicated statistical assumptions and permutations. Bearing this in mind, the
11 mutations that have been associated with resistance to darunavir usually occur along with many
other PI mutations.

Darunavir appears to have a high genetic barrier to resistance with virological efficacy, which is
probably best predicted by baseline phenotypic fold-change estimations. At week 24 in the POWER
1, POWER 2, and POWER 3 studies, 50%, 25%, and 13% of patients with changes in susceptibility of
10-fold or less, 10- to 40-fold, and greater than 40-fold, respectively, reached HIV RNA levels below
50 copies/mL. Because a change of less than 10-fold was predictive of clinical response in the three
pivotal studies, this was proposed by the drug's manufacturer as the lower clinical cutoff, and a
change of greater than 40-fold, which was predictive of poor response, was proposed as the upper
clinical cutoff.

Of note in these studies, the coexistence of several different viral mutants associated with reduced
darunavir susceptibility was required for a change of greater than 10-fold to occur. Using
site-directed mutants engineered by the investigators, none of the mutants alone or combined with 1
or 2 other mutants caused a greater than 10-fold change in susceptibility to darunavir.

Nevertheless, the clinical cutoffs for darunavir are still uncertain. In a different analysis of the POWER
study data from all 3 trials, using the Virco Antivirogram assay and a benchmark of 8-week
virological response, the lower clinical cutoff (defined as the fold-change that correlates with 20%
loss of virological response) was estimated to be 3.4-fold, while the upper cutoff (defined as a
fold-change that correlates with 80% loss of virological response) was estimated to be 96.9-fold. The
investigators cautioned that these findings may apply only to patient populations similar to
those in the POWER studies.

The efficacy of ritonavir-boosted darunavir is influenced by the number of coadministered
antiretroviral agents active against target virus during phenotypic testing. This number is described
as the phenotypic susceptibility score (PSS). In one study, an HIV RNA level below 50 copies/mL was
achieved by 34% of patients whose PSS was under 0.5 compared with 49% of those with a PSS of 0.5
to 1.5. Of those with a higher PSS, 52% achieved full viral suppression.

Similarities and differences in the resistance profiles of darunavir and tipranavir have drawn
considerable interest. One study found somewhat decreased susceptibility to darunavir, but not
tipranavir, in 24 patients whose lopinavir-based treatment was failing. In that cohort, change in
susceptibility to darunavir went from 1.4-fold before lopinavir was introduced to 2.7-fold after
lorinavir failure was established (both fold-changes are still below the proposed lower cutoff for
darunavir). The fold-changes in susceptibility to tipranavir, on the other hand, were 1.9 and 1.8,
respectively. There are conflicting data on cross-resistance between darunavir and tipranavir. According to the manufacturer's analysis of 9968 isolates, 70% of isolates that were resistant to tipranavir remained susceptible to darunavir, while 53% of isolates resistant to darunavir were susceptible to tipranavir. These findings are in contrast to those of another study that reported maximal susceptibility (defined as fold-change at or below the lower cutoff of 3.4) to darunavir in only 28% of tipranavir-resistant isolates. Approximately one third of patients with prior tipranavir exposure in the POWER 3 trial achieved viral suppression to below 50 copies/mL.

SAFETY PROFILE

Darunavir is generally safe and well tolerated. In vitro, the drug concentration that resulted in a 50% reduction in the viability of mock-infected cells compared with drug-free control (CC_{50}) was greater than 100 µM, indicating a selectivity index (defined as the ratio CC_{50}/EC_{50}) of greater than 20,000. Darunavir is generally safe and well tolerated. In vitro, the drug concentration that resulted in a 50% reduction in the viability of mock-infected cells compared with drug-free control (CC_{50}) was greater than 100 µM, indicating a selectivity index (defined as the ratio CC_{50}/EC_{50}) of greater than 20,000. Darunavir is generally safe and well tolerated. In vitro, the drug concentration that resulted in a 50% reduction in the viability of mock-infected cells compared with drug-free control (CC_{50}) was greater than 100 µM, indicating a selectivity index (defined as the ratio CC_{50}/EC_{50}) of greater than 20,000.

Oral Solution

The first clinical formulation of darunavir was an oral solution that contained polyethylene glycol (PEG). In a phase 2a trial, the most common adverse events were grade 1 or 2: diarrhea, 32%; flatulence, 18%; headache, 16%; and dizziness 11%. Non-treatment-limiting grade 3 or 4 laboratory abnormalities occurred in 13% (5 of 38) of ritonavir-boosted darunavir recipients and in 33% (4 of 12) of the control arm. One patient had grade 4 hepatotoxicity that resolved with drug discontinuation. There was a grade 4 rash described as recrudescent eczema plus oral blisters. It resolved without treatment interruption. Owing to the unacceptably high incidence of GI adverse effects caused by the PEG component of the darunavir oral solution, a direct compression tablet formulation was developed.

Direct Compression Tablet

In follow-up through week 24, the approximate incidences of the most common adverse events among DRV/r recipients in the POWER 1 and POWER 2 studies, which used the direct compression tablet, were headache (17% to 18%), diarrhea (16% to 8%), nausea (14% to 17%), and fatigue and insomnia (10% to 16%). Adjusted for duration of drug exposure in POWER 2, headache and diarrhea were more common in the control arm, and there was no difference in the incidence of nausea.

Rash has emerged as one the most important adverse reactions attributed to darunavir, which is a sulfonamide. In the POWER 2 trial, rash (mainly grade 1 or 2) occurred in 5% of DRV/r recipients but in none in the control arm, and there was no dose-response relationship. Across all darunavir clinical trials, the incidence of rash, regardless of grade or causation, was 7%. The rash was generally self-limited and did not require drug discontinuation. Severe cases, such as Stevens-Johnson syndrome, have been reported.

In both the POWER 1 and POWER 2 trials, changes in laboratory parameters (alanine aminotransferase, aspartate aminotransferase, total cholesterol, and triglyceride levels) with ritonavir-boosted darunavir were of mild to moderate severity and typically were neither clinically significant nor dose-related. Overall, these laboratory abnormalities with boosted darunavir were not more commonly reported than with the control PIs. In addition, an analysis of 31 patients coinfected with hepatitis in the POWER 1 study showed that the safety profile of boosted darunavir in this subgroup was comparable to that of the overall study population (N = 255). Nonetheless, clinical experience with darunavir is still limited, and current prescription guidelines call for caution when the drug is prescribed for persons with hepatic dysfunction, pending additional data on hepatic toxicity and optimal dosing in the presence of hepatic disease. At week 24 in the POWER 1 study, 12 of 255 participants (5%) discontinued DRV/r treatment as a result of an adverse event, versus 4 of 63 controls (6%); in the POWER 2 study, 8% of DRV/r recipients dropped out because of adverse events, compared with 4% in the control arm. These discontinuation rates should be cautiously interpreted because duration of treatment was longer among those receiving darunavir. For example, by week 24 in POWER 2, 47% of the patients in the control arm had discontinued their regimen early as a result of virological failure, compared with 4% of DRV/r recipients.

The safety of darunavir through week 48 has been demonstrated in an ad hoc analysis of the POWER 1 and POWER 2 studies. The most common adverse events were diarrhea (20%) and nausea (18%). Other commonly reported adverse effects were headache, 15% (20% in control arm); nasopharyngitis, 14% (11% in control arm); and fatigue, 12% (17% in control arm). Discontinuations because of adverse events occurred in 7% of DRV/r recipients versus 5% of controls. Ritonavir-boosted darunavir did not cause any major increase in lipid levels. There is limited information on the effects of darunavir on glucose metabolism, but ritonavir has been associated
with insulin resistance.\textsuperscript{33}

**PHARMACOKINETIC PROFILE**

Darunavir has been shown to have good bioavailability. When administered alone at dosages of 400 mg twice daily, 800 mg twice daily, 800 mg 3 times daily, or 1200 mg 3 times daily, darunavir was rapidly absorbed, with a time to peak plasma concentration ($C_{\text{max}}$) of approximately 3 hours. Steady-state plasma concentrations were achieved within 3 days. At day 14, trough ($C_{\text{min}}$) values ranged from 4 to 142 ng/mL, while $C_{\text{max}}$ values ranged from 2168 to 8040 ng/mL.\textsuperscript{7}

Also, coadministration of low-dose ritonavir with darunavir has been studied at 200/100 mg daily, 400/100 mg daily, 300/100 mg twice daily, 600/200 mg daily or 1200/200 mg daily. The resultant $C_{\text{min}}$ values ranged from 480 to 1486 ng/mL, while the $C_{\text{max}}$ values ranged from 1569 to 5453 ng/mL.\textsuperscript{7}

The elimination half-life of darunavir is approximately 10 hours.\textsuperscript{34} The inhibitory quotient (IQ, defined as the ratio $C_{\text{min}}/EC_{50}$), driven by baseline darunavir fold-change, was recently shown to be a strong predictor of virological response to darunavir. The highest IQ was observed with the darunavir 600-mg dose when given twice daily with ritonavir 100 mg, confirming the appropriateness of this dosage for clinical use.\textsuperscript{35}

In a comparison of PEG-containing darunavir oral solution and compressed tablets, 15 healthy participants were given a single 400-mg dose of the different formulations with ritonavir under fasted and fed conditions. The darunavir AUC achieved with the compression tablet increased by 42\% with food intake, while food did not affect systemic exposure to the oral solution.\textsuperscript{36} Taken together, these studies demonstrate that the direct compression tablet of darunavir provides adequate and predictable systemic exposure if it is administered with low-dose ritonavir and with food.

**DRUG-DRUG INTERACTIONS**

Important drug interactions with darunavir have been described. Hoetelmans and colleagues\textsuperscript{36} demonstrated that coadministration of ritonavir-boosted darunavir and tenofovir disoproxil fumarate resulted in a 37\% increase in $C_{\text{min}}$ of tenofovir, while the $C_{\text{max}}$ and exposure (AUC) of tenofovir increased by 24\% and 22\%, respectively. Increases in the $C_{\text{min}}$, $C_{\text{max}}$, and AUC of darunavir were 24\%, 16\%, and 21\%, respectively. There was no increase in adverse events, leading the researchers to conclude that the drugs can be coadministered without dose change.\textsuperscript{37}

Also, the bioavailability of darunavir was not affected by coadministration of omeprazole 20 mg daily or ranitidine 150 mg twice daily.\textsuperscript{38} Ritonavir-boosted darunavir has been shown to increase the serum levels of atorvastatin: coadministration of darunavir with a 10-mg dose of atorvastatin resulted in atorvastatin exposure that was approximately 85\% of the exposure following 40 mg of atorvastatin alone. Thus, it was recommended that atorvastatin should be started at 10 mg if it is coadministered with boosted darunavir, followed by dose adjustment based on clinical response.\textsuperscript{39}

In a recent study, the coadministration of ritonavir-boosted darunavir and atazanavir resulted in an 87\% increase in atazanavir drug levels and an approximate 50\% increase in ritonavir exposure. There was no change in exposure to darunavir.\textsuperscript{40} There was no significant pharmacologic interaction when darunavir was coadministered with enfuvirtide\textsuperscript{41} or with TMC125 (etravirine), a second-generation NNRTI with activity against efavirenz- and nevirapine-resistant viral mutants.\textsuperscript{42}

In general, the clinician should be aware that additional drug interactions attributable to ritonavir are important considerations in patients receiving darunavir, which must be given with ritonavir. A prudent approach is to routinely consult the expanding list of drugs with which darunavir and ritonavir interact\textsuperscript{43} when first prescribing darunavir or when an existing regimen is changed.

**THE CLINICAL ROLE OF DARUNAVIR**

The clinical niche for ritonavir-boosted darunavir, based on clinical trials to date, is in the management of treatment-experienced patients with extensive resistance to currently licensed PIs. These patients invariably also have resistance to antiretroviral agents from other classes. Resistance testing is useful in forecasting a patient's response to darunavir. For best results, the background regimen should be crafted with the goal of optimizing the patient's phenotypic susceptibility score. This involves careful selection of NRTIs and typically the addition of enfuvirtide. Caution must be exercised when prescribing darunavir for patients with a history of sulfonamide allergy or abnormal liver function.

It is presumable that the benefits of darunavir can be enhanced if it is used in combination with novel drugs to which highly resistant virus remains susceptible. For example, in a 6-week study, a regimen of darunavir and TMC125 plus 1 or more NRTIs with or without enfuvirtide was shown to be effective against 3-class-resistant HIV, producing viral suppression to under 40 and 400 copies/mL in 5 of 10 and 8 of 10 patients, respectively.\textsuperscript{42} This type of regimen is being further evaluated in an ongoing phase 3 study that began enrollment in October 2005. Another ongoing study, the ARTEMIS
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Published on Patient Care Online (http://www.patientcareonline.com)

study, is an open-label comparison of ritonavir-boosted darunavir versus the lopinavir/ritonavir coformulation in treatment-naïve patients to evaluate the potential role of darunavir in earlier stages of HIV infection.

Darunavir and tipranavir overlap in their clinical niches, with both currently having indications for salvage treatment, but there are no comparative data available with which to differentiate them in this setting. As such, there is a need for a head-to-head clinical trial to compare their efficacy, safety/tolerability, and resistance profiles to better inform clinicians about the optimal PI for the highly treatment-experienced patient harboring numerous resistance mutations. Until these data are available, the results of a retrospective cross-study comparison of the darunavir POWER 1 and POWER 2 trials and the 2 large clinical studies of tipranavir—the RESIST 1 and RESIST 2 trials—are of interest. The results of this analysis indicated that at week 24, 71% of patients who received DRV/r 600/100 mg twice daily had more than a 1-log_{10} reduction in HIV RNA level, compared with 40% of tipranavir/ritonavir (TPV/r) 500/200 mg twice-daily recipients. In addition, the benefit of DRV/r over control PIs in the POWER trials was greater than the benefit of TPV/r over control PIs in the RESIST studies for the end points of achieving an HIV RNA level below 50 copies/mL, an HIV RNA level below 400 copies/mL, and a mean CD4 increase at 24 weeks. In a subgroup analysis of patients receiving enfuvirtide for the first time and those who did not receive enfuvirtide at all, better responses were found with darunavir than with tipranavir. There were some important similarities in the 4 studies included in this cross-study comparison. First, the patients in the 4 trials were well matched with respect to baseline characteristics (age, sex, race, baseline HIV RNA level, and PI mutations); second, there were similar virological responses among patients in the control arms across the 4 trials. Nonetheless, it is important to remember that the relevance of the findings from this study is limited by the flaws inherent in a cross-study analysis. Data on the comparative safety and tolerability of darunavir and tipranavir are slowly accumulating. In the RESIST trials, more patients treated with TPV/r developed grade 3 or 4 liver enzyme elevations than did those receiving a comparator PI. Further, a recent report described cases of fatal and nonfatal intracranial hemorrhage among patients taking tipranavir, although no causal relationship has been established. Finally, both darunavir and tipranavir carry the burden of numerous pharmacologic interactions with other drugs metabolized by the liver. In conclusion, teasing out the optimal salvage PI in a given scenario is a complex task that calls on the clinician to deliberately consider the patient's baseline resistance, comorbidities, and concomitant medications. Darunavir, like tipranavir, appears to be synergistic with enfuvirtide in enfuvirtide-susceptible patients. To make the best decision, the clinician should stay abreast of evolving data on the clinical and resistance profiles of darunavir, tipranavir, and other available PIs as well as those that are still in early development stages.

Dr Hicks reports having received research support as well as consulting fees and honoraria from Tibotec. No other potential conflict of interest relevant to this article was reported.

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