



HIV Medication Update of New Protease Inhibitors: Tipranavir (Aptivus®) and Darunavir (Prezista™)

Ivette Talavera, Pharm.D. Intern
Jaime P. Anaya, B.S., Pharm.D., CDE

Abstract

Antiretroviral therapy (ART) for the treatment of Human Immunodeficiency Virus type-1 (HIV-1) has improved since the beginning of the AIDS epidemic. The approval of new medications offers improved convenience, safety, and efficacy profiles versus earlier medications. Current data indicates that up to 80%-90% of naïve patients (no prior history of ART use) in clinical trials achieve a treatment goal of “no detectable virus” or “undetectable” using ART. Available studies report that 70% of patients in urban clinics achieve undetectable virus levels. For treatment failures secondary to multi-drug resistance, there are two new agents recently approved for this scenario. Tipranavir (Aptivus®) and Darunavir (Prezista™), both co-administered with ritonavir, have been approved for the treatment of HIV-1 infection in patients who are highly treatment-experienced or have HIV-1 strains resistant to multiple PIs.

Background

Antiretroviral therapy (ART) for the treatment of Human Immunodeficiency Virus type-1 (HIV-1) has improved since the beginning of the AIDS epidemic. The approval of new medications offers improved convenience, safety, and efficacy profiles versus earlier medications. There are currently over 20 approved antiretroviral agents that belong to four different classes of antiretroviral medications. These classes are the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and entry inhibitors (EIs)¹. EIs work by inhibiting the fusion of HIV-1 with CD4+ cells (type of white blood cell involved in the human body’s immune response). This process occurs by blocking the conformational change in gp41 (glycoprotein 41) required for membrane fusion and entry into CD4+ cells by HIV. Both NRTIs and NNRTIs work on the reverse transcriptase enzyme needed by HIV for the infectious process by interfering with HIV viral RNA-dependent DNA polymerase. PIs work by preventing the cleavage of essential protein precursors which cause HIV maturation by inhibiting protease enzyme and before viral assembly.²

According to the most recent edition of the “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents,” the preferred regimen(s) for treating naïve patients (no prior history of ART use), consists of two NRTIs and either an NNRTI or a ritonavir-boosted PI.¹ (Table 1)

Table 1#

Column A:		Column B:
Efavirenz or Atazanavir/Ritonavir	+	Tenofovir/Emtricitabine
*Fosamprenavir/Ritonavir		or
*Lopinavir/Ritonavir		Zidovudine/Lamivudine
*taken twice daily		

#one component from Column A and one from Column B

Current data indicates that up to 80%-90% of naïve patients in clinical trials achieve a treatment goal of “no detectable virus” or “undetectable” using ART. In contrast, available studies report that 70% of patients in urban clinics achieve undetectable virus levels.¹ ART failure, defined as “a suboptimal response to therapy,” is known to increase the risk of HIV disease progression and is often associated with virologic failure, immunologic failure, and/or clinical progression. Additionally, there is currently a reported pre-treatment resistance prevalence of 6% to 16% in naïve patients.¹

For treatment failure secondary to multi-drug resistance, there are two new agents approved for this scenario. Tipranavir (Aptivus®)³ and Darunavir (Prezista™)⁴, both co-administered with ritonavir, have been approved for the treatment of HIV-1 infection in patients who are highly treatment-experienced or have HIV-1 strains resistant to multiple PIs.(Table 2) Tipranavir and darunavir have shown to have an additive antiviral effect when combined with either NNRTIs or NRTIs, and to be synergistic when combined with EIs.³⁻⁴

Tipranavir (Aptivus®)

Clinical Efficacy/Clinical Trials^{3,5}: In the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies, patients (n=1483) were recruited from the United States, Canada, and Australia (RESIST-1). Additionally, patients from Europe and Latin America were included (RESIST-2), and the primary endpoint in both RESIST-1, and -2 was the proportion of patients with a confirmed viral load reduction of 1 log₁₀ copies per milliliter or greater (“treatment response”). Study participants received an optimized background regimen along with tipranavir/ritonavir (500mg/200mg twice daily; n=746), or an investigator chosen competitor PI/ritonavir (n=737). Combined results reported at 48 weeks from these two ongoing, randomized, open-label, multinational phase III clinical studies of tipranavir showed a treatment response in 251 (33.6%) tipranavir treated

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patients as compared to 113 (15.3%) in the comparison group ($p < 0.0001$). Also at week 48, 30.4% of the patients receiving tipranavir/ritonavir and 13.8% of the patients receiving the competitor-PI/ritonavir had HIV-1 RNA values of < 400 copies/mL. A greater proportion of patients achieved HIV-1 RNA values of < 400 copies/mL when they took tipranavir/ritonavir along with the EI enfuvirtide. At week 48, mean increase from baseline in CD4+ cell counts were greater in the tipranavir/ritonavir group than in the competitor-PI/ritonavir group (45 cells per μL vs. 21 cells per μL).

In vitro experiments showed that there are six protease mutations (I13V, V32I, L33F, K45I, V82L, I84V) which confer more than a 10-fold reduced susceptibility to tipranavir. Tipranavir shows less than a four-fold decrease in susceptibility against 90% of the HIV-1 isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir.

Precautions^{3,6}: Tipranavir should not be administered without ritonavir because co-administration with ritonavir is needed to assure appropriate tipranavir serum concentrations. Tipranavir should not be used in treatment-naïve patients because there are no current clinical trials documenting the safety and efficacy of tipranavir in these patients.

Tipranavir is classified as FDA pregnancy risk category C, and even though it is not known to be secreted in breast milk, mothers should be instructed not to breast-feed due to possible risk of postnatal transmission of HIV.

Tipranavir has black box warnings stating that caution be taken when administered in patients with hepatitis B/C or hepatic disease and has recently added a warning of fatal and nonfatal intracranial hemorrhage, seen in some patient taking tipranavir/ritonavir. Tipranavir also contains a sulfonamide moiety and should be used with caution in patients with known sulfonamide hypersensitivity.

Darunavir (Prezista™)

Clinical Efficacy/Clinical Trials⁴: In two controlled, randomized clinical trials, patients treated with darunavir experienced higher rates of reduction of their HIV viral load than in patients on other ritonavir-boosted PI combinations. Combined results from these two studies showed that at 24 weeks, 70% of patients taking darunavir achieved a virologic response (reduction in HIV RNA = $1 \log_{10}$ below baseline), compared to 21% of patients in the comparator groups. Mean increases from baseline in CD4+ cell counts were 92 cells per μL in the darunavir arm as compared to 17 cells per μL in the comparator arm.

Additional data from two non-randomized trials of treatment experienced patients ($n=246$) showed that at week 24, 65% had a virologic response, defined as reduction in HIV RNA = $1 \log_{10}$ versus baseline and 40% were less than 50 copies per milliliter.

In vitro and in vivo studies have shown that darunavir has at least eight protease mutations which exhibit a 50- to 641-fold decrease in darunavir susceptibility, some of which include V32I, I47V, or I54L or M. Clinical trials have shown that the amino acid substitution V32I developed with darunavir treatment in $> 30\%$ of virologic failure isolates. Amino acid substitution at

position I54 developed in $> 20\%$ of virologic failure isolates with darunavir treatment. Currently, there is no resistant profile characterized in treatment-naïve patients.

Darunavir has displayed less than a 10-fold decrease in susceptibility against 90% of HIV-1 isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir.

Precautions^{4,7}: Darunavir should not be administered without ritonavir because co-administration with ritonavir is needed to assure appropriate darunavir serum concentrations. Darunavir should not be used in treatment-naïve patients because the risks and benefits in these patients have not yet been established.

Darunavir is classified as FDA pregnancy risk category B, and it is not known to be secreted in breast milk, however mothers should be instructed not to breast-feed due to possible risk of postnatal transmission of HIV and potential serious adverse effects in nursing infants.

Caution should be used in patients with hepatic disease because darunavir is primarily metabolized by the liver. Darunavir also contains a sulfonamide moiety and should be used with caution in patients with known sulfonamide hypersensitivity.

Summary: Due to initial safety concerns, lack of long-term efficacy data, and in an effort to avoid or delay wide-spread resistance, the use of tipranavir and darunavir should be reserved as a salvage therapy for individuals who exhibit multiple PI viral mutations, have advanced disease, are treatment-experienced, and continue to show evidence of ongoing viral replication.

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Table 2: Comparisons of tipranavir and darunavir^{1,3,4,7,8}:

Parameters	Tipranavir (Aptivus®)	Darunavir (Prezista™)
Classification:	Non-peptidic protease inhibitor	Protease Inhibitor
Dose/Administration	<ul style="list-style-type: none"> o Adults: 500 mg (given with ritonavir 200 mg) po twice daily with food o Max dosage limit for adults and elderly patients: 1000 mg/day 	<ul style="list-style-type: none"> o Adults: 600 mg, given with ritonavir 100 mg, po twice daily with food o Max dosage limit for adults and elderly patients: 1200 mg/day
Pharmacokinetics:	<ul style="list-style-type: none"> o PB:>99% plasma protein bound o S.S concentration: attained after 7-10 days of twice daily dosing o Mainly metabolized by CYP3A4 but metabolism is minimal when given with ritonavir o Excretion in feces: about 80% of dose o Excretion in urine: about 4% of dose o Mean elimination T½: about 6 hours 	<ul style="list-style-type: none"> o PB: about 95% plasma protein bound o Metabolized to inactive metabolites primarily by CYP 3A o Excretion in feces: about 80% of dose o Excretion in urine: about 14% of dose o Terminal elimination T½: 15 hrs
Adverse Reactions:	<ul style="list-style-type: none"> o Most common: diarrhea, ALT and AST elevations of more that 10 the upper limit of normal o Unique: Intracranial hemorrhage and hepatotoxicity 	<ul style="list-style-type: none"> o Most common: nausea, increased amylase, neutropenia, and nasopharyngitis o Unique: Stevens-Johnson Syndrome (rare)
Drug Interactions:	<ul style="list-style-type: none"> o Should not be used with bepridil, amiodarone, flecainide, propafenone, quinidine, simvastatin, lovastatin, rifampin, rifapentine, astemizole, terfenadine, cisapride, pimozone, midazolam, triazolam, ergot alkaloids, St. John's wort, and fluticasone 	<ul style="list-style-type: none"> o Concomitant use with astemizole, cisapride, midazolam, pimozone, voriconazole, rifampin, lovastatin, simvastatin, carbamazepine, phenobarbital, or phenytoin should be avoided unless benefits outweigh the risks
How Supplied:	<ul style="list-style-type: none"> o 250 mg pink, oral capsule o Imprint of "TPV 250" on one side of capsule 	<ul style="list-style-type: none"> o 300 mg orange, oval-shaped, film-coated tablet o Imprint of "300" on one side and "TMC 114" on the other side
Cost:	120 caps = \$1090.68 (AWP)	120 caps = \$915 (AWP)

Ivette Talavera, Pharm.D. Intern, Cooperative Pharmacy Program University of Texas at El Paso/Austin, El Paso, Texas.

Jaime P. Anaya, B.S., Pharm.D., CDE, Clinical Assistant Professor of Pharmacy, Cooperative Pharmacy Program, University of Texas El Paso/Austin El Paso, Texas.