The Pharmacist Activist

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Editorial

# September 11

That date brings to mind just one thing—it is not even necessary to add the year. It is one of a very small number of dates when all of us remember where we were and what we were doing when we heard the news of the terrorist attacks. The world changed after September 11.

The world changed in the worst possible way for pharmacist Jennifer Trebino Sands. Her husband Jim died in the collapse of Tower One of the World Trade Center. Understandably, Jennifer was initially overwhelmed with grief and anger. However, her anger was not directed against Osama bin Laden, of whom she had never heard, but rather was directed against God to whom she would pray for Jim's traveling safety when he would leave their home in Brick, New Jersey each weekday morning for New York City.

Jennifer believed in God prior to September 11, but had not been inclined to explore any further religious interests beyond that point. It was not until many months after Jim's death, when she could bring herself to go through his personal belongings, that she discovered that he had a Bible when, to her knowledge, there had not been a Bible in their home.

Five years after September 11, as a result of the encouragement and support of family members and friends, Jennifer is now a Christian author and speaker, as well as continuing as a part-time pharmacist at the Briarmill Pharmacy. She has experienced a spiritual transformation that has enabled her to move beyond Jim's and her tragedy to a point at which she has been a source of encouragement, inspiration, and hope to thousands who have heard her speak or have read her books.

Jennifer has written two books: *A Tempered Faith — Rediscovering Hope in the Ashes of Loss*, and *A Teachable Faith — Learning from God in Everyday Life*. My wife and I have greatly benefited from our friendship with Jennifer and from reading her books. The challenges that we and many others face are small in comparison to what Jennifer has experienced, and the open and gracious manner in which she shares her experiences, emotions, and faith is uplifting.

Additional information may be obtained at www.jennifersands.com.

Daniel A. Hussar

Editor's note: The two pages of commentary in this issue of *The Pharmacist Activist* do not address a pharmacy issue. This is not because I have run out of issues; indeed, it is not possible to cover all of the important issues our profession faces in a newsletter that is published just once a month. Rather, it is because I have come to recognize the value of setting some time aside to think about the things that are more important than the pharmacy issues.

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# New Drug Review

## Darunavir (Prezista)

**New Drug Comparison Rating (NDCR) = 4**
*(significant advantage[s])*
in a scale of 1 to 5, with 5 being the highest rating

### Indications:

Co-administered with 100 mg ritonavir, and with other antiretroviral agents, for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

### Comparative drugs:

Tipranavir (Aptivus)

### Advantages:

- May be active against HIV-1 strains that are resistant to other antiretroviral agents;
- Less risk of intracranial hemorrhage (which is the subject of a black box warning in the labeling for tipranavir);
- Less risk of clinical hepatitis and hepatic decompensation (which are the subject of a black box warning in the labeling for tipranavir);
- Is classified in Pregnancy Category B (tipranavir is in Category C);
- Dosage of ritonavir that is co-administered is lower (100 mg compared with 200 mg with tipranavir) and may be less likely to interact with certain medications;
- Does not need to be stored in a refrigerator.

### Disadvantages:

- May be more likely to interact with certain medications (e.g., certain anticonvulsants [e.g., carbamazepine, phenobarbital, phenytoin]); both darunavir and tipranavir may interact with anticonvulsant agents, but the concurrent use of darunavir should be avoided.

### Conclusions:

Darunavir is an HIV-1 protease inhibitor that has demonstrated activity against HIV strains that are resistant to other protease inhibitors. Like tipranavir and lopinavir, it must be co-administered with ritonavir in a regimen that also includes other antiretroviral agents. It was significantly more effective than comparator regimens in reducing viral load. Darunavir and tipranavir have not been directly compared in clinical studies. Because both darunavir and tipranavir may be of great benefit in patients for whom initial antiretroviral regimens have not been effective or resistance developed to their use, they should not be used in regimens for the initial treatment of HIV infection/AIDS.

Although darunavir shares the risks (e.g., hyperglycemia) experienced with all of the HIV protease inhibitors, it appears unlikely to cause other serious events. In contrast, there have been reports of clinical hepatitis and intracranial hemorrhage with the use of tipranavir, and these risks are the subjects of black box warnings in the labeling for this agent. All of the protease inhibitors interact with many other medications.

Both darunavir and tipranavir are co-administered with ritonavir twice a day with food. Darunavir tablets may be stored at room temperature whereas tipranavir capsules should be stored in a refrigerator prior to opening the bottle.

If the use of darunavir or tipranavir is being considered for the treatment of a patient with HIV infection/AIDS, darunavir is the best choice because of its apparently lower risk of serious adverse events.

## Discussion

Darunavir (Prezista-Tibotec) is the tenth HIV-1 protease inhibitor marketed in the United States, joining amprenavir (Agenerase), fosamprenavir (Lexiva, a prodrug of amprenavir), atazanavir (Reyataz), indinavir (Crixivan), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir), saquinavir (Invirase), and tipranavir (Aptivus). Like tipranavir and lopinavir, the new drug must be co-administered with ritonavir, which inhibits its metabolism and markedly increases its concentration and activity (i.e., "ritonavir-boosted" activity).

Both darunavir and tipranavir have demonstrated activity against HIV strains that are resistant to other protease inhibitors. Because these agents, as well as the fusion inhibitor enfuvirtide (Fuzeon), may be of great benefit in patients for whom initial antiretroviral regimens were not effective or resistance developed to their use, they should not be used in regimens for the initial treatment of HIV infection/AIDS. The specific indication for darunavir is essentially the same as that for tipranavir. It is co-administered with ritonavir in a regimen that also includes other antiretroviral agents, for the treatment of HIV infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor. The doses of ritonavir administered with each dose of darunavir and tipranavir are 100 mg and 200 mg, respectively.

Darunavir was approved under the provisions of the FDA's accelerated approval program based on a reduction in HIV-1 RNA (viral load) and an increase in CD4+ cell counts. The new drug was evaluated in patients who had prior treatment with protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs), and who met other study

parameters. A regimen of darunavir/ritonavir plus an "optimized background regimen (OBR)" of antiretroviral agents was significantly more effective in reducing viral load than comparator regimens containing other PIs plus OBR. Seventy percent of the patients treated with the darunavir regimen achieved a virologic response compared with 21% of those receiving other regimens. Darunavir and tipranavir have not been directly compared in clinical studies.

Although cross-resistance has been observed among many of the PIs, clinical isolates that are resistant to the other agents in this class, including tipranavir, are often susceptible to darunavir. There apparently is only limited cross-resistance between darunavir and tipranavir. Of the viruses isolated from patients experiencing virologic failure while being treated with a darunavir/ritonavir regimen, more than 50% were still susceptible to tipranavir while less than 5% were susceptible to the other PIs.

The adverse events experienced most often in the clinical studies with darunavir (and their incidence in the darunavir and comparator regimens, respectively) include diarrhea (20%, 28%), nausea (18%, 13%), and headache (15%, 20%). Seven percent of the patients treated with darunavir developed skin rash, and severe rash, including Stevens-Johnson syndrome, has been reported. Treatment with darunavir should be discontinued if a severe rash develops. The rates of discontinuation of treatment because of adverse events were 9% and 5% in patients receiving the darunavir and comparator regimens, respectively.

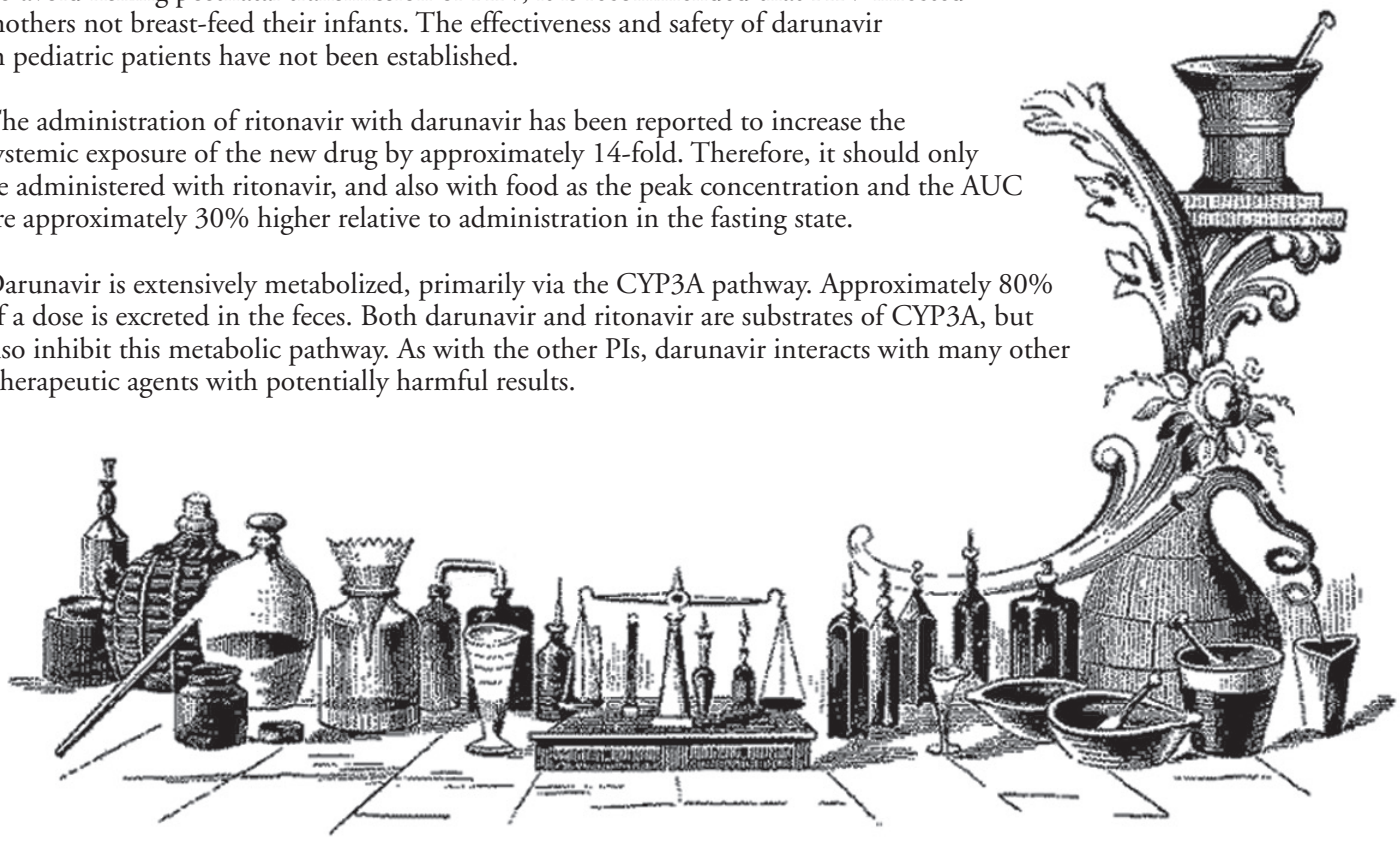
Like amprenavir, fosamprenavir, and tipranavir, the structure of darunavir contains a sulfonamide moiety. The potential for cross-sensitivity has not been evaluated, but caution must be exercised in patients who have a history of sulfonamide allergy.

All of the protease inhibitors, including darunavir, may cause hyperglycemia/diabetes mellitus, redistribution/accumulation of body fat (e.g., central obesity, "buffalo hump," peripheral and facial wasting, breast enlargement, cushingoid appearance), immune reconstitution syndrome (during the initial phase of treatment), and, in patients with hemophilia, an increased risk of bleeding.

Darunavir is classified in Pregnancy Category B, whereas tipranavir is in Category C. Prescribers are encouraged to register women who are pregnant and are to be treated with these drugs in the Antiretroviral Pregnancy Registry (800-258-4263). To avoid risking postnatal transmission of HIV, it is recommended that HIV-infected mothers not breast-feed their infants. The effectiveness and safety of darunavir in pediatric patients have not been established.

The administration of ritonavir with darunavir has been reported to increase the systemic exposure of the new drug by approximately 14-fold. Therefore, it should only be administered with ritonavir, and also with food as the peak concentration and the AUC are approximately 30% higher relative to administration in the fasting state.

Darunavir is extensively metabolized, primarily via the CYP3A pathway. Approximately 80% of a dose is excreted in the feces. Both darunavir and ritonavir are substrates of CYP3A, but also inhibit this metabolic pathway. As with the other PIs, darunavir interacts with many other therapeutic agents with potentially harmful results.



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Many medications are substrates for CYP3A and their plasma concentrations and activity may be increased by concurrent use with darunavir/ritonavir. The use of darunavir/ritonavir is contraindicated with midazolam (e.g., Versed), triazolam (e.g., Halcion), ergot derivatives (e.g., dihydroergotamine [e.g., Migranal]), pimozide (e.g., Orap), certain antiarrhythmic agents (amiodarone [e.g., Pacerone], bepridil [Vascor], flecainide [e.g., Tambocor], propafenone [Rythmol], quinidine), and cisapride (withdrawn from the market but available on a special-need basis). For the same reason, it is recommended that lovastatin (e.g., Mevacor) and simvastatin (e.g., Zocor) not be used in patients treated with darunavir/ritonavir.

Rifampin (e.g., Rifadin), carbamazepine (e.g., Tegretol), phenobarbital, phenytoin (e.g., Dilantin), and St. John's wort induce the CYP3A pathway and may reduce the action of darunavir, possibly resulting in the loss of virologic response and resistance to the new drug. Concurrent use of these agents with tipranavir is therefore not recommended.

Darunavir/ritonavir may increase the action of other medications including atorvastatin (Lipitor), clarithromycin (e.g., Biaxin), rifabutin (e.g., Mycobutin), trazodone (e.g., Desyrel), certain calcium channel blocking agents (e.g., felodipine [e.g., Plendil], nifedipine [e.g., Procardia]), certain azole antifungal agents (e.g., itraconazole [e.g., Sporanox]), certain immunosuppressants (e.g., cyclosporine [e.g., Neoral]), and the phosphodiesterase type 5 inhibitors (sildenafil [Viagra], tadalafil [Cialis], vardenafil [Levitra]). The dosage of some of these agents should be reduced when darunavir/ritonavir is used concurrently and the product labeling should be consulted for the specific recommendations.

Darunavir/ritonavir may decrease the action of methadone, warfarin (e.g., Coumadin), certain selective serotonin reuptake inhibitors (e.g., paroxetine [e.g., Paxil], sertraline [e.g., Zoloft]), and estrogen-containing oral contraceptives. It is recommended that women taking estrogen contraceptives who are to be treated with darunavir/ritonavir be advised to use alternative or additional contraceptive measures.

Potential drug interactions must also be considered in selecting other antiretroviral agents to be used with darunavir/ritonavir. Concurrent use with lopinavir/ritonavir or saquinavir has been reported to decrease the concentration of darunavir and the concomitant use of these agents is not recommended. The use of indinavir with darunavir has resulted in increased concentrations of both agents, and an appropriate dosage of indinavir for use in combination with darunavir has not been determined. The concurrent use of darunavir with efavirenz (Sustiva) has resulted in a decreased concentration of the new drug and an increased concentration of efavirenz. Caution should be exercised when the two agents are used together.

Darunavir tablets are supplied in a 300 mg potency. The recommended dosage is 600 mg (two tablets), with 100 mg of ritonavir, twice daily with food.

Daniel A. Hussar