

# TIPRANAVIR

## *the First Nonpeptidic Protease Inhibitor*

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Resistance to anti-HIV medications is an ongoing dilemma. A recent study in 16 European countries and Israel found primary drug resistance mutations in 10% of 1,633 people newly diagnosed with HIV disease who had never taken anti-HIV therapy. French clinicians have reported that 78% of viral samples taken between 1997 and 2002 from over 2,000 chronically infected people showed some resistance to at least one antiretroviral drug, and 25% had some resistance to three major drug classes (excluding fusion inhibitors). Similar findings have been reported in the U.S. and Britain. As a significant number of people with HIV find themselves with fewer treatment options, researchers struggle to develop medications that remain effective against genetically varied forms of the virus.

Tipranavir, the first in a new category of protease inhibitors (PIs), appears to be such a drug. Studies have shown that tipranavir (formerly known as PNU-140690) durably reduces viral load in some people whose dominant HIV strain is resistant to at least two other PIs. The quality of tipranavir resistance that does develop has also been examined, and the extent of this agent's usefulness in people needing salvage therapy is under investigation.

## Recent Data

Early *in vitro* (test-tube) studies of tipranavir were impressive. Brendan A. Larder, PhD, of Virco and colleagues reported in the September 8, 2000 edition of *AIDS* that 90% of 105 HIV isolates highly resistant (more than ten-fold) to approved PIs—in this case, indinavir (Crixivan), nelfinavir (Viracept), zidovudine (Retrovir), and saquinavir (Fortovase)—were highly sensitive to tipranavir. Only 2% were highly resistant to the experimental PI; the remaining 8% had moderate (four- to ten-fold) resistance.

This was an important finding, since the virological benefit of PIs (i.e., reduced viral load) is blunted by high levels of cross-resistance, as seen in these viral isolates. (Viral isolates refer to HIV taken from infected individuals. Cross-resistance refers to genetic mutations in HIV that render some or all agents in the same drug class less effective.) The challenge was to reproduce such robust activity in human clinical studies.

### BI 1182.2

Eighty-week data from a Phase II, randomized, open-label trial known as BI 1182.2 were reported this past October at the 9<sup>th</sup> European AIDS Conference in Warsaw. This study enrolled 41 subjects with unsuppressed viral load despite having used two or more PI-based regimens. None of the participants had used a non-nucleoside reverse transcriptase inhibitor (NNRTI). Median baseline viral load was 4.43 log (about 26,000) copies/mL and median baseline CD4 cell count was 273 cells/mm<sup>3</sup>. Subjects were randomized to take either 1,200 mg of tipranavir plus 100 mg of ritonavir twice daily, or 2,400 mg of tipranavir plus 200 mg of ritonavir twice daily. All subjects also received 600 mg once daily of the NNRTI efavirenz (Sustiva) and two nucleoside reverse transcriptase inhibitors (NRTIs).

A soft-gel formulation of tipranavir, known as SEDDS, was introduced during the study. A majority of participants subsequently switched from the original "hard-filled" tipranavir capsules to the SEDDS version by week 48 at doses of 500 mg and 1,000 mg, respectively, along with 100 mg of ritonavir, all twice daily. Soft-gel SEDDS used with low-dose ritonavir reduced overall pill burden and greatly enhanced tipranavir bioavailability (the degree to which it is absorbed and circulated in the body).

At 80 weeks, the median viral load reduction was 2.55 log copies/mL (greater than 99%) for those taking the lower dose of tipranavir and similar (2.43 log) for those in the high-dose arm. In an as-treated analysis (which is less rigorous and clinically useful than an intent-to-treat analysis), the study authors noted that 43% in the low-dose arm and 90% in the high-dose arm had viral loads below 50 copies/mL at week 80. Using a test unable to measure below 400 copies/mL, 64% in the low-dose group and 90% taking the higher dose had undetectable viral loads. The median CD4 cell count increases were 175 cells/mm<sup>3</sup> and 143 cells/mm<sup>3</sup>, respectively.

The most common adverse events reported in the low-dose arm were nausea (31%), diarrhea (26%), and increased levels of GGT (a bile duct enzyme; 26%) and triglycerides (a type of blood fat; 21%). In the high-dose arm, common side effects were diarrhea (72%), nausea (31%), increased levels of ALT (a liver enzyme; 27%), and vomiting (22%).

Encouragingly, this study showed a sustained virological response in some subjects with viral resistance to multiple PIs. Yet the original tipranavir formulation used during the beginning of the trial almost certainly affected some of the data and drop-out rates, particularly in the high-dose group, which had tolerability problems using the hard-filled capsules. Only 50% of subjects in the high-dose arm (compared with 74% in the low-dose arm) continued to week 80.

**BI 1182.52**

BI 1182.52 was a larger randomized, double-blind, international, Phase IIb trial designed to find the optimal dose of tipranavir/ritonavir for use in Phase III studies. Three tipranavir/ritonavir doses were given: 500/100 mg, 500/200 mg, and 750/200 mg, all twice daily. The 216 randomized subjects (15% female, 22% black) were followed for at least 24 weeks. All had used three classes of anti-HIV agents, and had detectable virus despite having used at least two PI-based regimens (excluding the most recently approved PIs, fosamprenavir [Lexiva] and atazanavir [Reyataz]). Median viral load was 4.5 log (about 32,000 copies/mL, and median CD4 cell count was 177 cells/mm<sup>3</sup>.

At 24 weeks, 23 subjects (31%) in the 500/100 mg arm, 29 (40%) in the 500/200 mg arm, and 32 (45%) in the 750/200 mg arm had at least a 1 log (90%) decrease in viral load. The study authors found no statistical difference across the three arms. CD4 cell counts increased by an average of 10 cells/mm<sup>3</sup> in the 500/100 mg arm, 18 cells/mm<sup>3</sup> in the 500/200 mg arm, and 46 cells/mm<sup>3</sup> in the 750/200 mg arm. These figures were based on an intent-to-treat analysis, which included data on all subjects according to the original randomization.

Diarrhea and nausea were common in all study arms (an overall incidence of about 31%). Grade 3 (severe) or 4 (life-threatening) laboratory abnormalities were also noted in all arms, with the lowest incidence seen in subjects taking 500/100 mg. Among those taking 500/200 mg and 750/200 mg, the following increases were reported: AST (a liver enzyme) in 6.9% and 7.0%, ALT in 11.1% and 21.1%, bilirubin (a byproduct of red blood cell destruction) in 0% and 2.8%, cholesterol in 2.8% and 5.6%, and triglycerides in 27% and 22%, respectively.

The study authors concluded that tipranavir-based therapy was effective in the 500/200 mg and 750/200 mg arms, and that an acceptable safety profile was observed in the 500/100 mg and 500/200 mg arms. As a result, tipranavir is currently being studied at the 500 mg dose with 200 mg of ritonavir twice daily (see “RESIST,” below).

Again, the ability of this experimental PI to suppress HIV in some heavily pretreated individuals has spurred continued research by the drug’s developer, Boehringer Ingelheim.

**Resistance Profile**

Tipranavir has a unique structure: it is a nonpeptidic—and therefore more flexible—molecule, which may account for its increased potency. All currently available PIs are derived from peptides (short chains of amino acids; peptides combine to form proteins). Peptide-based PIs theoretically are less able to adapt their shape and disable HIV protease with minor structural changes, a hallmark of mutated virus. The studies described above show that resistance to tipranavir does develop, although it appears to require a higher threshold of accumulated resistance mutations compared with other PIs.

Resistance mutations are detected using a genotypic test. Mutations are normally referred to by numbers, such as 10 or 36, that indicate their position on a particular HIV gene. Broad cross-resistance to PIs is often seen in HIV with mutations at positions 33, 82, 84, and 90 of the protease gene; these are known as universal protease inhibitor-associated mutations, or UPAMs. Mutations are also divided into primary and secondary categories. Anti-HIV drugs are each associated with at least one primary mutation that is a strong predictor of drug resistance. Secondary mutations may render HIV less sensitive to a specific drug, but do not normally lead to high-level resistance in the absence of a primary mutation. The risk of PI resistance increases as more mutations to the protease gene accumulate.

Researchers found a low rate of resistance to tipranavir in study BI 1182.2. High-level resistance to the drug was seen in only one (2%) and decreased susceptibility in only six (14%) of the 41 subjects, all of whom had detectable virus when using other PIs. Decreased susceptibility—which does not necessarily imply reduced virological response—was associated with an average of 16 mutations including two or three UPAMs. Notably, the number of baseline protease gene mutations did not predict reduction in viral load.

Resistance data from the larger BI 1182.52 study have also shown that susceptibility to tipranavir is maintained despite multiple protease mutations. In separate analyses, it appeared that at least three baseline UPAMs, and 16 to 20 total mutations, were required to impair virological response to the drug. In contrast, similarly reduced susceptibility to other PIs may be associated with only one or two UPAMs. (For more information on drug resistance, see “Genotypic and Phenotypic Resistance Testing,” *BETA*, Summer 1999.)

**Drug Interactions**

Interactions between tipranavir and other agents have been reported. Tipranavir can lower blood levels of the

NNRTI delavirdine (Rescriptor) by 95%, so the two drugs should not be used together. The antibiotic rifampicin (Rifadin, Rimactane) is also contraindicated. Enteric-coated ddi (didanosine, Videx EC) should be taken four hours before or after tipranavir. Blood levels of AZT (zidovudine, Retrovir) are reduced by 33–43% in the presence of tipranavir, though standard AZT doses are believed to be adequate. In addition, antacids reduce tipranavir blood levels by 30%.

## RESIST

A set of Phase III studies known as RESIST (Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients with Tipranavir) is currently underway. The RESIST 1 and 2 trials will study tipranavir in subjects who have used NRTIs, NNRTIs, and PIs, and have limited treatment options. These randomized, open-label studies will compare the safety and efficacy of 500/200 mg tipranavir/ritonavir against another ritonavir-boosted PI, which will be selected according to resistance testing and treatment history.

RESIST 1 recently completed enrollment of 500 participants in North America and Australia, while RESIST 2 aims to enroll at least 800 participants in Europe and South America. Some study sites are running companion trials (RESIST 3 and study 1182.51) for people with extensive treatment experience who do not qualify for the larger RESIST 1 or 2 studies.

RESIST should further reveal the utility of tipranavir and its side effect profile in a larger pool of individuals with antiretroviral resistance. Nevertheless, for people with more than two UPAMs, careful selection of drugs will remain essential.

**Nicholas Cheonis is editor of BETA.**

### Selected sources

Cooper, D. and others. Baseline phenotypic susceptibility to tipranavir/ritonavir (TPV/r) is retained in isolates from patients with multiple-protease inhibitor (PI) experience (BI 1182.52). 10<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI). Boston. February 10–14, 2003. Abstract 596.

Hall, D. and others. Characterization of treatment-emergent resistance mutations in two Phase II studies of tipranavir. XII International HIV Drug Resistance Workshop. Los Cabos. June 10–14, 2003. Abstract 13.

Kohlbrenner, V. and others. Tipranavir/ritonavir (TPV/r) demonstrates potent efficacy in multiple protease inhibitor (PI)-experienced patients at 24 weeks: BI 1182.52. 9<sup>th</sup> European AIDS Conference (EACS). Warsaw. October 26–29, 2003. Abstract 7.2/2.

Larder, B. and others. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. *AIDS* 14(13): 1943–1948. September 8, 2000.

Mayers, D.L. and others. The inhibitory quotient (IQ) of tipranavir/ritonavir (TPV/r) in triple class experienced HIV+ patients: results from BI 1182.52. 2<sup>nd</sup> International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment. Paris. July 14–17, 2003. Abstract 9.

Neubacher, D. and others. Long-term 80-week follow-up of highly treatment-experienced (HTE) patients on tipranavir-based antiretroviral therapy (BI 1182.2). 9<sup>th</sup> EACS. Abstract 7.2/3.

Rosko, P.J. and others. Standard doses of efavirenz (EFV), zidovudine (ZDV), tenofovir (TDF), and didanosine (ddI) may be given with tipranavir/ritonavir (TPV/r). 2<sup>nd</sup> IAS Conference. Abstract 865.

Schwartz, R. and others. Resistance to tipranavir is uncommon in a randomized trial of tipranavir/ritonavir (TPV/RTV) in multiple PI-failure patients (BI 1182.2). 9<sup>th</sup> CROI. Seattle. February 24–28, 2002. Abstract 562-T.

Squires, K. and others. Tipranavir/ritonavir (TPV/r) demonstrates a robust resistance profile in multiple protease inhibitor-experienced patients: correlation of baseline genotype and antiviral activity in BI 1182.52. 2<sup>nd</sup> IAS Conference. Abstract 812.

Tamalet, C. and others. Resistance of HIV-1 to multiple antiretroviral drugs in France: a 6-year survey (1997–2002) based on an analysis of over 7,000 genotypes. *AIDS* 17(16): 2383–2388. November 7, 2003.

Wensing, A.M.J. and others. Analysis from more than 1,600 newly diagnosed patients with HIV from 17 European countries shows that 10% of the patients carry primary drug resistance: the CATCH-study. 2<sup>nd</sup> IAS Conference. Abstract LB1.

**See page 46 for information on a trial of TMC114, a PI in Phase II development that also may be effective against PI-resistant HIV.**

## San Francisco AIDS Foundation Bilingual Hotline

(English/Spanish)

**415-863-AIDS**

Toll-Free in California

**800-367-AIDS**

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In California, call toll-free

**800-367-2437**

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