Tipranavir (Aptivus™) Criteria for Use

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are dynamic and will be revised as new clinical data become available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist providers in making the best clinical decisions that result in high quality, consistent, cost-effective care. For a complete review of tipranavir, please refer to the full Drug Monograph on the PBMSHG website.

I. Overview

Tipranavir (TPV) was developed to fill a need for HIV-1 infected patients with multiple PI failures and resistance mutations. Although tipranavir is still affected by many of the common PI mutations, a greater number of mutations are required to observe a negative impact on activity compared to other PIs. Furthermore its virologic efficacy in the salvage setting has been shown to be superior to that of other approved PIs, however, the toxicity of TPV may be greater.

Tipranavir was approved for use, co-administered with 200 mg of ritonavir, in June 2005, for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. This indication was based upon virologic (HIV viral load) and immunologic (CD4 lymphocyte count) responses during controlled clinical trials in highly ARV-experienced patients. Tipranavir joins 8 other antiviral agents in the PI class on the VHA National Formulary. The efficacy of tipranavir in combination with low-dose ritonavir has been studied in two randomized, controlled, open-label, Phase III clinical trials, RESIST-1(conducted in North America and Australia), and RESIST-2 (conducted in Europe and Latin America). Both trials were designed to determine the potential benefit of using tipranavir in combination with other antiretrovirals (ARV) in highly treatment-experienced HIV-infected subjects with triple antiretroviral class (NRTI, NNRTI, and PI) experience and with at least two failed PI-based regimens. Patients had received a median of 12 prior antiretroviral agents and a median of 4 prior PIs. TPV/r 500mg/200mg was compared to other ritonavir boosted PI regimens (comparator PI/r) which were genotypically determined, along with an optimized background regimen (OBR). Median baseline CD4+ lymphocyte counts were $\leq$ 200 in all treatment arms and median baseline viral loads were 4.81-4.84 log 10 copies/mL. Patients were randomized (1:1) to receive TPV/r or CPI/r for 24 weeks of a planned 96 week analysis. Patients receiving CPI/r who did not show an initial virologic response by week 8 were allowed to rollover to another study where all patients received TPV/r. The intent-to-treat response at Study week 24 for the two studies is shown below.

Outcome	RESIST-1		RESIST-2	
	TPV/r	CPI/r	TPV/r	CPI/r
2 consecutive $\geq$ 1 log decrease from baseline *	41.5%	22.3%	41.0%	14.9%
Median change in VL (log10 copies/mL) at 24wks*	-0.88	-0.28	-0.72	-0.22
HIV RNA < 50 copies/ml*	25.1%	10.0%	22.5%	8.6%
Median CD4 change (cells/mm^3)*	36	6	31	1

* All differences were statistically significant and measured at Week 24

Change in viral load from baseline was greatest in those subjects receiving TPV/r and who had less than 5 baseline PI mutations. Subjects who had five or more baseline PI mutations and who received TPV/r without enfuvirtide began to lose antiviral activity between Weeks 4 and 8 with their HIV RNA trending back toward baseline by week 24. When evaluating the proportion of responders by baseline phenotype, there was a 45% response with a 3-fold or less change in TPV IC50 at baseline compared to a 21% when the TPV baseline phenotype values were >3 to 10-fold and 0% when TPV baseline phenotype values were >10-fold.

Tolerance and Side Effects

The most serious side effect associated with TPV in Phase II and III trials was hepatotoxicity which has led to a black box warning on the labeling. There have been reports of clinical hepatitis and hepatic

decompensation, including some fatalities with TPV/r co administration. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity. In clinical trials, 10% of patients receiving TPV/r compared to 5% of patients in the CPI/r arm discontinued therapy due to adverse effects. The most common side effects in the TPV/r and CPI/r arms were diarrhea (23% vs. 18%), nausea (14% vs. 7%), headache (9% vs. 6%), pyrexia (9% vs. 7%), and rash (11% vs. 10%). Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving TPV/r. In Phase 2 and 3 trials rash was observed in 14% of females and in 8-10% of males. Most common laboratory abnormalities included Grade 3-4 AST/ALT elevations (9.8% vs. 3.6%) and Grade 3-4 triglyceride elevations (21% vs. 11%).

II. Patient Selection for Tipranavir Treatment

VA clinicians considering the use of tipranavir/ritonavir are requested to apply a series of drug use criteria to each patient considered as a candidate for therapy. The criteria were designed from the clinical information available to date for tipranavir/ritonavir including safety, tolerability, and efficacy.

□ 1) Patients should be highly treatment-experienced including at least 2 prior failed PI regimens.

The studies presented to date on tipranavir/ritonavir have been in heavily pre-treated patients with triple antiretroviral class (NRTI, NNRTI, and PI) experience and relatively low CD4 lymphocyte counts. Patients included in these studies had failed at least 2 PI-based regimens. The exact placement of TPV/r in a progression of regimens (i.e. as the second or fifth regimen) has not been determined in clinical trials. TPV/r has not been studied in drug naïve patients or in those who have multiple regimen options remaining and the VHA cannot currently recommend the use of TPV/r in these patient populations given the lack of clinical efficacy data.

and

□ 2) Have evidence of virologic failure (documented by a viral load > 1,000 copies/ml) and evidence of genotypic or phenotypic resistance on their current PI regimen.

In Phase III studies, patients were infected with a high level of resistant virus at baseline (97% of the isolates were resistant to at least one PI, 95% to at least one NRTI, and >75% to at least one NNRTI). It is important to note, that while the treatment response for patients receiving TPV/r was superior to the treatment response of those receiving LPV/r, SQV/r, or APV/r, the comparator PI being used was not always "new" and was not always considered "genotypically available" on the baseline resistance report. In the LPV/r stratum, for example, if the LPV/r was "new" the treatment response was 45.3% in the TPV/r arm and 36.1% in the CPI/r arm (p=NS). Alternatively, in the LPV/r stratum, if the LPV/r was "ongoing" the treatment response was 35.2% in the TPV/r arm and 10.7% in the CPI/r arm, a statistically significant result. Treatment responses in patients who had a genotypically available and "new" pre-selected CPI/r were 46% and 33%, respectively.

and

□ 3) Not have more than two mutations at codons L33V/I/F, V82T, I84V or L90M or a phenotypic cutoff greater that 4 (using the PhenoSense assay) before initiating TPV/r as the presence of theses mutations and this cutoff is associated with decreased efficacy and makes it highly unlikely that TPV will have any activity. Genotypic or phenotypic testing and/or treatment history should guide the use of TPV/r.

The standard of care in the drug experienced population includes the use of HIV resistance testing to determine the likelihood of a treatment success and to evaluate possible treatment options in a given patient. Response rates were reduced if five or more protease inhibitor associated mutations were present at baseline and subjects did not receive concomitant enfuvirtide with TPV/ritonavir. The most common amino acid substitutions that developed on TPV/r in greater than 20% of TPV/r virologic failure isolates were L33V/I/F, V82T, and I84V. Both the type and number of baseline protease inhibitor mutations as well as use of additional active agents (e.g., enfuvirtide) affected TPV/ritonavir virologic response rates in Phase 3 studies. For phenotypic testing,

demonstration of a three-fold increase in the concentration of drug needed to inhibit viral replication by 50% (the IC_{50}) indicates a likely decreased response to tipranavir. The PhenoSense assay cutoff for TPV is 4. The only exception to using tipranavir in drug experienced patients with such significant resistance would be in cases of salvage and the goal of therapy is to decrease viral replication and to evolve viral strain less fit for growth in the presence of drug exposure.

and

☐ 4) Have the ability to construct a multi-drug regimen that includes preferably two other active anti-retroviral drugs in addition to TPV/r. Resistance testing is to be used in determining a reasonable ARV backbone regimen to be combined with TPV/r and should be assessed prior to initiating treatment with TPV/r. Consideration should be given to using enfuvirtide as part of an active antiretroviral regimen when initiating TPV/r treatment, as there was a higher treatment response for those who also used enfuvirtide than for those who did not use it. TPV/r should be added to an existing, failing regimen only if there is evidence that one or more drugs in that regimen may retain activity, and no other active drugs are available.

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In the RESIST trials, a treatment response was achieved with TPV/r in more than 40% of patients when used with 2 or more background ARV drugs that were considered genotypically available at baseline to the patient. TPV/r had potent early antiviral responses despite high-level protease inhibitor resistance, but to obtain a durable response with TPV/r additional active background drugs are needed. These clinical trials also provided evidence that the virologic impact of TPV/r is significantly greater when combined with enfuvirtide as part of the OBR in those patients with higher baseline viral loads (>5.0 log 10 copies/ml), lower CD4 counts (<75 cells/mm3), more prior ARV drugs use (>13 agents), and more baseline drug resistance (>2 mutations at codons 33,82,84, or 90). Subjects taking TPV/r with ENF were able to achieve >1.5 log10 reductions in viral load from baseline out to 24 weeks even if they had 5 or more baseline PI mutations.

and

☐ 5) Patient must be able to tolerate low dose ritonavir (200mg) twice a day. Tipranavir MUST be administered with low dose ritonavir to achieve its desired efficacy.

III. Contraindications of Tipranavir Therapy

☐ Patients with moderate and severe (Child-Pugh Class B and C, respectively) hepatic insufficiency. The tipranavir label includes a Black Box warning regarding hepatoxicity. Co-administration of TPV with low dose ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. The warning states that extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

Tipranavir undergoes cytochrome p450 metabolism and is known to inhibit isoenzymes 3A4, and 2D6. The following medications are contraindicated with TPV and ritonavir co-administration:

☐ antiarrhythmics (amiodarone, bepredil, flecanide, propafenone, quinidine) ☐ cisapride
☐ astemizole, terfenadine ☐ ergot derivatives ☐ pimozide ☐ midazolam, triazolam,

IV. Clinical Response Follow up

Clinical follow up of virologic response to a TPV/r -containing regimen should be tailored for each patient. This includes monitoring CD4+ lymphocyte counts, HIV viral load, and performing the appropriate safety laboratory tests relative to the ARV backbone, co-morbid disease, and co-administered medications prescribed to the patient.

☐ Liver function tests should be performed at initiation of therapy with TPV/ritonavir and monitored frequently throughout the duration of treatment. Consider discontinuing treatment for AST/ALT elevations >5 x ULN

☐ Use caution when prescribing TPV/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection or other underlying hepatic impairment. *Patients with chronic hepatitis B or hepatitis C co-infection or elevations in transaminases are at approximately 2.5-fold risk for developing further transaminase elevations or hepatic decompensation.*

- ☐ The clinician and patient should make the decision of when TPV/r therapy should be stopped secondary to intolerance, adverse events, clinical or virologic failure. Patients should be assessed for virologic response 4 weeks (1 month) following initiation of the TPV/r-containing regimen. Response should be > 1 $\log_{10}$ decline in HIV viral load from pre-TPV/r levels. Patients who do not reach this level of response should be reassessed for possible therapeutic changes. The new regimen may or may not continue to include TPV/r. Improvements in immunologic status (increased CD4 lymphocyte counts) despite suboptimal virologic response may be considered in decisions regarding continued use of TPV/r. If there is neither virologic nor immunologic improvement after six months of therapy, discontinuation of treatment with TPV/r should be considered.

V. Summary Advice on Addition of Tipranavir to an ARV Regimen.

To date, VHA has placed all FDA-approved ARVs on the national formulary. VHA's HIV clinicians are able to choose the best-available ARV regimen for an individual patient based on the patient's clinical status, their past experience with ARVs, the risks of side effects, and an expectation of tolerance and a potential for benefit. TPV/r has serious safety considerations and great caution should be used in prescribing this medication to highly treatment-experienced individuals with underlying liver impairment. Because of this, VA HIV clinicians must carefully weigh the potential risks and benefits of this particular medication when considering adding or changing to a TPV/r-containing regimen. Tipranavir/ritonavir was more effective in lowering viral load when compared to various comparator PI/ritonavir regimens in the highly treatment experienced population. Given the price difference between tipranavir/ritonavir as compared to other PI agents, VHA HIV clinicians should be aware of the impact of prescribing tipranavir on VHA pharmaceutical budget. VHA clinicians are asked to follow the above Criteria for use when prescribing tipranavir/ritonavir.

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References

DHHS Guidelines - http://www.aidsinfo.nih.gov/guidelines/

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