Predicting Responses to Aptivus or Prezista

September 28, 2006 By Tim Horn

For drug resistance testing to provide useful results, the companies that maintain the available assays frequently update the information that accompanies test results so that HIV-positive people and their healthcare providers can make important treatment decisions. On Thursday at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), two companies offering phenotypic drug resistance testing provided new data that will ultimately help treatment-experienced patients determine if Norvir® (ritonavir)-boosted Aptivus® (tipranavir) or Norvir-boosted Prezista™ (darunavir) are useful options to them.

Unlike genotypic testing, which looks for particular genetic mutations in HIV that causes drug resistance, phenotypic testing directly measures the sensitivity – or phenotype – of a patient's HIV in response to particular anti-HIV drugs.

Phenotypic testing is performed by placing samples of a patient's HIV in test tubes with each HIV drug to observe how the virus reacts. The ability of the virus to grow in the presence of each drug is evaluated. The virus is exposed to varying strengths, or concentrations, of each drug. The ability of the patient's virus to grow in the presence of the drugs is compared to some wild-type virus that is known to be 100% susceptible to all drugs being tested.

This process determines the concentration of a particular drug that is needed to stop HIV from reproducing. If four times as much drug is needed to achieve this, the virus being tested is considered to be four-fold resistant to the drug being tested. These fold changes translate into the results of the test.

In order for fold changes to make sense to healthcare providers, the companies conducting phenotypic testing also need to provide what are known as "clinical cutoffs." These come from actual clinical trials of specific HIV drugs. In these studies, researchers monitor patients to see what happens to their viral loads while on a specific drug (in combination with other drugs) and use phenotypic testing to determine both lower clinical cutoffs and upper clinical cutoffs.

The lower clinical cutoff reflects the point at which the drug's effect on the virus begins to decline (i.e., the virus is partially resistance). The upper clinical cutoff reflects the point at which the drug has little or no affect on the virus (i.e., the virus is highly resistant). If the fold change determined for a drug is below the lower clinical cutoff, the drug is considered to be fully effective against HIV.

If the fold change for a drug is between the lower clinical cutoff and the upper clinical cutoff, the drug may not be fully effective against the virus, but possibly effective enough to be used. If the fold change for a drug is above the upper clinical cutoff, the drug won't likely have much of an effect on the virus.

Two of the newest protease inhibitors (PIs), Aptivus and Prezista, are approved specifically for HIV-positive people who have tried and failed other PIs in the past. They are both combined with low doses of Norvir to boost their concentrations in the body, allowing them to challenge HIV resistant to other PIs. However, there is no guarantee of this, which is where drug-resistance testing comes in. The two reports at ICAAC indicate that the clinical cutoffs for these two important medications have been defined, which should help provide guidance to healthcare providers wanting to prescribe either of these PIs for their treatment-experienced patients.

The first report, presented by researchers at Monogram Biosciences (developer of the PhenoSense HIV drug-resistance assay), evaluated viral load responses in treatment-experienced patients participating in Boehringer Ingelheim's phase III RESIST studies. In these clinical trials, which led to the approval of Aptivus, patients received either Norvir-boosted Aptivus or a Norvir-boosted comparator PI, all in combination with an optimized background regimen (OBR) consisting of available HIV drugs.

Not only did the available RESIST data help Monogram determine the PhenoSense clinical cutoffs for Norvir-boosted Aptivus, the results also allowed for the clinical cutoffs for other widely used Norvir-boosted PIs – including Kaletra® (lopinavir) and Invirase® (saquinavir) – to be calculated.

To determine the clinical cutoffs, the researchers looked at viral load reductions documented after four weeks of therapy in the patients. After making data adjustments to account for the the effects of OBR on viral loads, the fold changes for Norvir-boosted Aptivus and the comparator PIs seen in patients responding well to therapy were averaged to determine the lower clinical cutoff, whereas the fold changes seen in patients responding very poorly to treatment were averaged to determine the upper clinical cutoff.

The RESIST data established that the lower clinical cutoff of Norvir-boosted Aptivus is a two-fold increase in the amount of drug needed to suppress HIV; the upper clinical cutoff is an eight-fold increase. As for Norvir-boosted Invirase, the lower clinical cutoff has been determined to be a 2.3-fold increase and the upper clinical cutoff has been determined to be a 12-fold increase. With Kaletra, the lower clinical cutoff was found to be a nine-fold increase and the upper clinical cutoff was determined to be a 55-fold increase.

Monogram Biosciences has since added these clinical cutoffs to the lab report it sends out to healthcare providers containing each patient's test results.

Based on these new cutoff determinations, the Monogram researchers looked at the fold changes seen in patients at the start of the RESIST studies to determine who had virus that was sensitive or highly resistant to any of these Norvir-boosted PIs. Approximately 53% of patients who entered

RESIST after failing at least one PI-based regimen in the past had virus that was sensitive to Norvir-boosted Aptivus, whereas 12% had virus that was highly resistant to it. Approximately 18% of patients entering RESIST had virus that was sensitive to Kaletra, compared to 55% with high-level resistance to the drug. As for Norvir-boosted Invirase, 17% had virus considered to be sensitive to this PI option at the start of RESIST, compared to 56% of patients with virus that was unlikely to respond to it.

In another ICAAC report, researchers from Virco in Belgium announced that they have determined clinical cutoffs for Norvir-boosted Prezista using its VircoType phenotypic assay. For this, Virco turned to data from the phase III POWER studies comparing Norvir-boosted Prezista to comparator PIs in patients with HIV resistant to other available therapies.

The lower cutoff was determined to be a 3.4-fold increase. The upper clinical cutoff was concluded to be a 96.9-fold increase. In all three POWER studies, approximately 91% of patients who entered the study with HIV that was less than 3.4-fold resistant to Norvir-boosted Prezista saw their viral loads decrease by at least 1 log after eight weeks of treatment. For those with a 96.6-fold increase or greater increase, 36% experienced a 1 log reduction in viral load after eight weeks. Responses in patients with fold changes between 3.4 and 96.6 varied accordingly.

These cutoffs have been included in the VircoType lab report from Virco. The Norvir-boosted Prezista cutoffs, using Monogram Bioscience's assay, were previously determined and are listed in its lab report: the lower cutoff is a ten-fold increase and the upper cutoff is a 40-fold increase.

Because of the technological differences between PhenoSense HIV and VircoType, the cutoffs are different for each assay.

Sources:

Bacheler L, Winters B, Vermeiren H, et al. VircoTYPE clinical cutoffs for TMC114 [Abstract H-997]. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 2006.

Coakley EP, Chappey C, Flandre P, et al. Defining lower (L) and upper (U) phenotypic clinical cutoffs (CCOs) for tipranavir/r (TPV), lopinavir/r (LPV), saquinavir/r (SQV) and amprenavir/r (APV) co-administration with ritonavir ® within the RESIST dataset by the PhenoSense assay [Abstract H-995]. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 2006.

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