Kaletra Monotherapy Failure Predicted by HIV Levels in the Brain

August 31, 2010

Not only was Kaletra (lopinavir plus ritonavir) monotherapy inferior to standard three-drug treatment in people with HIV, but rising HIV levels in the cerebrospinal fluid (CSF) were tied to treatment failure. These results, published online August 26 in *AIDS*, also revealed that the people most likely to experience treatment failure while on monotherapy were those whose CD4 count had ever fallen below 200.

Monotherapy with a Norvir (ritonavir)–boosted protease inhibitor (PI) has the advantages of using fewer antiretroviral (ARV) drugs in a regimen, reducing the cost of treatment and potentially sparing people certain side effects.

Though many people participating in clinical trials have been able to maintain undetectable viral loads upon switching from a triple-drug regimen to boosted PI monotherapy, it is also true that a significant number of people who make the switch experience treatment failure. What these studies have not yet revealed, however, are the factors associated with success or failure upon switching to PI monotherapy.

To help answer this question, Christine Gutmann, MD, from the Cantonal Hospital St. Gallen in Switzerland and her colleagues designed at study that would randomize 100 people to either continue on their current suppressive ARV regimen, or switch to Kaletra monotherapy for 48 weeks. People randomized to remain on standard treatment would be allowed to switch to monotherapy later, after they'd completed 48 weeks of therapy.

An undetectable viral load for the previous six months was a requirement to enter the study. Gutmann's team monitored CD4 and HIV levels in the blood regularly throughout the study. Participants' HIV levels in the genital tract and CSF were also measured at study entry, after 48 weeks of treatment and at the point of treatment failure.

To protect the participants, the study was designed to terminate early if six of the first 30 people in the monotherapy arm experienced treatment failure. Treatment failure was defined as having more than 400 copies of virus in the blood on two consecutive viral load tests. As six of the first 30 people in the monotherapy arm did experience treatment failure, the study was halted early, after only 60 percent of the planned number of participants had been recruited. In turn, "the focus of investigations, therefore, shifted to explaining these failures and looking for predictive factors,"

the authors commented.

The average amount of time between switching to monotherapy and experiencing treatment failure was 12 weeks. CSF measures were taken upon confirmed treatment failure, usually within four weeks.

Gutmann and her colleagues found that detectable HIV levels in the CSF were associated with treatment failure. Given the study design, it isn't possible to determine that increased viral replication in the brain actually caused treatment failure. The authors point out, however, that none of the 15 people on standard therapy—who consented to have their CSF measured at that time point—had detectable virus in the brain upon study termination, while eight of 24 people on monotherapy did have detectable virus

What's more, the authors report that four of the six people in the monotherapy arm who experienced treatment failure also had neurological symptoms before failing treatment. Conversely, there were no neurological symptoms in those who did not experience treatment failure.

The other predictive factor of treatment failure on Kaletra monotherapy was having ever had a CD4 count below 200. In fact, there were no treatment failures in the monotherapy arm among those who'd always had CD4s over 200.

The authors acknowledge that monotherapy with other Norvir-boosted protease inhibitors might work better, provided that those drugs are better able to penetrate the brain. Moreover, though study staff asked participants about adherence at every visit—adherence levels appeared to be high among participants—the authors concede that adherence was not measured formally and could have been a factor in the very poor performance of monotherapy.

"At least in patients with low HIV RNA level replication in blood, and in patients with a low CD4 nadir, lumbar puncture to confirm virologic suppression in CSF needs to be considered," the authors concluded. "Further studies with long-term follow-up and evaluation of monotherapy efficacy in CNS are needed before monotherapy generally can be considered as an option for HIV therapy."

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