Starting or Switching: Truvada Outpaces Combivir in Studies

July 26, 2007 By Tim Horn

Researchers have reported extended follow-up data from a clinical trial comparing two pairs of nucleoside reverse transcriptase inhibitors (NRTIs), both combined with Sustiva (efavirenz): once-daily Truvada (tenofovir plus emtricitabine) versus Combivir (zidovudine plus lamivudine). The 144-week data from Gilead Science's Study 934, presented by José Arribas, MD, of the University Hospital La Paz in Madrid, at the fourth IAS Conference on HIV Pathogenesis, Treatment and Prevention, in Sydney, indicate a few possible efficacy and safety advantages of Truvada over Combivir.

Also reported at the conference were 24-week data from a study that switched patients from Combivir to Truvada. Compared to those remaining on Sustiva plus Combivir, explained lead study author Graeme Moyle, MD, of Chelsea Westminster Hospital in London, patients in the Gilead-sponsored SWEET trial who changed over to Sustiva plus Truvada saw improvements in their hemoglobin levels (a marker for anemia) and lipid levels, without compromising their virologic response to treatment.

More than ten years after the introduction of combination drug treatment for HIV, we know that piecing together a safe and effective regimen requires doctors and patients to choose their meds carefully. Fortunately, much research has been done to help guide this selection process. Most studies have investigated key differences among the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). To control HIV, however, PIs or NNRTIs need to be matched up with a "backbone" of other drugs, usually two NRTIs.

Until recently, it was generally believed that the NRTIs were more alike than different. As a result, experts thought it safe to say that any two would do. But we now know that there are differences between NRTI options and that studies are needed to help guide their selection. In turn, results from clinical trials like Gilead Science's Study 934, comparing the dual NRTI-combo Combivir to Truvada, have been watched closely.

For the first two years of the study, patients in the Truvada group took Viread (tenofovir) and Emtriva (emtricitabine) separately. Truvada, a tablet containing both drugs, became commercially available after the study began. In turn, at the 96-week point in the study, these patients were

switched to Truvada.

Atripla, a fixed-dose combination tablet containing Sustiva, Viread, and Emtriva, is also commercially available, though it was not used in the study.

Study 934 enrolled 517 HIV-positive people starting HIV treatment for the first time. The 48-week data from the study, published in 2006 in the New England Journal of Medicine, found that 80 percent of people in the Truvada group had viral loads below 50 (undetectable), compared with 70 percent in the Combivir group.

After 144 weeks of treatment, 71 percent of Truvada/Sustiva patients compared to 58 percent of Combivir/Sustiva patients achieved and maintained viral loads of less than 400 copies. The difference between the two groups was statistically significant, meaning that it wasn't due to chance.

Using the more sensitive viral load assay, which measures levels down to 50 copies, 64 percent of patients taking Truvada ad 56 percent of patients taking Combivir had undetectable viral loads. This difference was just shy of statistical significance, meaning that both drugs remain comparable with respect to viral load reductions below 50.

Among patients who stopped responding to their assigned treatment regimen, fewer patients taking Truvada—compared to those taking Combivir—did so because of resistance to their emtricitabine (in Truvada) or lamivudine (in Combivir), both of which are hobbled by the M184V mutation in HIV's reverse transcriptase gene. In the Truvada group, two patients developed the mutation, compared to 10 patients in the Combivir group.

As for CD4 count increases, patients in the Truvada group had significantly higher levels at weeks 48 and 96 weeks of the study. By week 144, there was still a noticeable difference between the two groups—a 312-cell increase in the Truvada group versus a 271-cell increase in the Combivir group—but the comparison was no longer statistically significant.

The study authors also reported that, after 96 weeks of treatment, discontinuation of study medications due to side effects was significantly higher among Combivir patients (11 percent) than among those receiving Truvada (5 percent). The most common side-effect-related reasons for discontinuing treatment were anemia (14 percent in the Combivir group vs. 0 percent in the Truvada group) and rash (1 percent vs. 4 percent, respectively).

Total cholesterol levels after 144 weeks had increased by 36 mg/dL in the Combivir group, compared to a 24 mg/dL increase in the Truvada group. Triglyceride levels had risen by 36 and 4 mg/dL, respectively. These differences were also statistically significant.

Finally, study 934 also measured limb fat, the amount of fat in the legs, using DEXA scanning in some patients in both groups. The researchers included this measurement to determine if either regimen increases the risk of lipoatrophy (a decrease in subcutaneous fat in the legs, arms or

face).

Patients in the Viread/Emtriva group had significantly more limb fat (7.9 kg) at week 144 than patients in the Combivir group (5.4 kg). Since the beginning of the study, patients in the Combivir group experienced an average limb fat decrease of 1.1 kg, compared to a 0.9 kg increase in the Truvada group. This difference, as it was at early timepoints in the study, was statistically significant.

In the SWEET study, 234 patients who had undetectable viral loads while taking Sustiva plus Combivir were randomized to either continue on that regimen or substitute the Combivir with Truvada combo. Twenty-four weeks after switching—the midpoint of the study—89.7 percent in the Combivir group and 94 percent in the Truvada groups maintained viral loads below 50 copies, with no statistically significant difference between the two arms. There were, however, statistically significant improvements in hemoglobin, total cholesterol and triglyceride levels, all in favor of Truvada.

Source:

Arribas J, Pozniak A, Gallant J, et al. **Three-year safety and efficacy of emtricitabine (FT)/tenofovir DF (TDF) and efavirenz (EFV) compared to fixed dose zidovudine/lamivudine (CBV) in antiretroviral treatment-naïve patients** [Abstract WEPEB029]. Fourth IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, 2007.

Moyle G, Fisher M, Reilly G, et al. **A randomized comparison of continued zidovudine plus lamivudine BID (Combivir, CBV) versus switching to tenofovir DF plus emtricitabine (Truvada, TVD), each plus efavirenz (EFV), in stable HIV-infected persons: results of a planned 24-week analysis** [WEPEB028]. Fourth IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, 2007.

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