Gradual Efavirenz Dosing Shows Promise

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Starting efavirenz (found in Sustiva and Atripla) at a lower dose and steadily increasing it over two weeks might help decrease the risk or severe dizziness, hallucinations and trouble concentrating—common central nervous system (CNS) side effects of the drug—according to a study published in the August 4 issue of the *Annals of Internal Medicine*.

Efavirenz has long been considered a "preferred" component of first-line antiretroviral (ARV) therapy by the U.S. Department of Health and Human Services (DHHS). Unfortunately, up to half of all those who take it experience a CNS side effect soon after starting the drug. While CNS-related problems generally decrease over time in the majority of people, their initial intensity can cause some to stop taking the drug.

A team of researchers in Spain, headed by Alicia Gutiérrez-Valencia, PharmD, from the Instituto de Biomedicina de Sevilla set out to determine whether gradual dose increases over a two-week period might limit the number of people experiencing these side effects, or at least lower their intensity.

The 114 patients enrolled received efavirenz plus either Truvada (tenofovir and emtricitabine), Epzicom (abacavir and lamivudine) or a combination of two other nucleoside reverse transcriptase inhibitors (NRTIs). Ultimately 50 people started on full dose efavirenz—600 mg, once-daily—while 58 started with 200 mg once-daily for the first 6 days, increased the dose to 400mg once-daily for the next 7 days and then starting taking the full dose on day 14.

The step-wise dose escalation significantly reduced the number of people experiencing side effects for the first six days of treatment. According to surveys conducted by the researchers, 50 percent fewer patients in the gradual dosing group, compared with those in the full-dose efavirenz group, reported feeling dizzy or hungover, or having impaired concentration or hallucinations.

After people in the step-wise dosing group increased their dose to 400 mg, however, the number of people experiencing side effects in both groups was roughly the same. However, the researchers noted that CNS side effects were less severe among those receiving 400 mg efavirenz before switching to the 600 mg dose.

Ultimately, the authors concede that their study was not large enough to detect a significant

difference in the incidence of side effects between the two treatment groups by the second and third week of treatment.

The numbers were also too small to determine whether step-wise dosing controlled HIV as well as full-dose efavirenz. By week 24, 96 percent of people in the full-dose arm had an undetectable viral load, compared with 87 percent in the step-wise dosing arm. This difference, however, was small enough to have occurred by chance.

Gutiérrez-Valencia and her colleagues conclude that because efavirenz side effects are most severe in the first few days of therapy—and because of the encouraging signals in their study—further research on step-wise introduction of efavirenz is warranted.
