Trials challenging HIV drug doses could usher in huge cost cuts

When researchers say they are trying to do more with less in the fight against HIV, they mean it. At last month's International AIDS Society (IAS) conference in Kuala Lumpur, Malaysia, researchers presented preliminary results from a clinical trial that showed a lower dose of the commonly used antiretroviral drug efavirenz was just as effective as the approved higher dose and seemed to cause fewer side effects in study participants.

"It's going to have a big impact," Keith Crawford, assistant chief of public health research at the US Military HIV Research Program in Bethesda, Maryland, says of the study. "The fact that this very useful drug can be used in a reduced dose is a big deal. This is a money saver that will allow us to treat more patients."

Finding the right dose for an HIV drug is tricky. The virus mutates rapidly, so if patients take too low a dose the pathogen will quickly develop resistance. However, the drugs are so powerful that too high a dose causes toxic side effects in patients. "Infectious diseases are challenging because we want to give a dose that is efficacious and has a high enough barrier against resistance," Crawford explains. As a result, when drug companies run clinical trials with their drugs, they often do so with the highest tolerable dose, even if there is not a demonstrable difference in efficacy compared to a lower dose.

The dose optimization trial of efavirenz, known as the ENCORE1 trial, is taking place across 13 countries and includes 630 HIV-positive individuals who had never received treatment before. Over the course of 96 weeks, the participants receive either 600 milligrams of efavirenz each day, the standard dosage regimen currently approved by the US Food and Drug Administration (FDA), or 400 milligrams. All of the study subjects also take a fixed-dose pill containing two antiretrovirals—tenofovir and emtricitabine—which is often given in combination with efavirenz, a pill marketed by New York's Bristol-Myers Squibb as Sustiva.

Four months into the trial, the researchers found no statistical difference between the two groups in terms of the amount of circulating HIV in the blood. Moreover, 278 patients receiving the higher dose reported a drug-related adverse event compared to 203 receiving the lower dose, a statistically significant 10% difference. Further analyses over the entire two-year study period—set to conclude in July 2014—will analyze safety, tolerability and quality of life.

"The results are extremely positive," says Sean Emery, principal investigator of the ENCORE1 study, who is also head of the therapeutic and vaccine research program at the Kirby Institute, near Sydney, Australia. "The trial has really illustrated in a robust way that in terms of potency, 400 milligrams for all intents and purposes is identical to 600 milligrams."

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Think twice: Two 200-milligram pills of efavirenz might be just as effective as three.

Access agenda

According to UNAIDS, out of the 34 million people infected with HIV worldwide in 2012, only 10 million, or 29%, were receiving antiretroviral treatment. UNAIDS has set a goal of increasing that number to 15 million by 2015 and to add an additional million each subsequent year, a task that will be challenging under current financial conditions.

The ENCORE1 trial is only one of several dose optimization trials being pursued in an effort to increase access to drugs in a cost-effective manner while also reducing toxicity from the drugs. Another dose optimization trial is the LASA trial, which is comparing 200 milligrams of the antiretroviral drug atazanavir in combination with 100 milligrams of ritonavir to the standard 300/100 milligram combination dose. The lower dose of efavirenz envisioned by the ENCORE1 trial could save an estimated $16 per person, or $192 million per year, assuming 15 million people per year are treated, whereas a successful LASA trial could result in savings of $501 million per year (*Curr. Opin. HIV AIDS*, **8,** 34–40, 2013).

There's a precedent for this type of dose optimization. Zidovudine, a second-line HIV treatment, has already been reduced from its original dosage of 300 milligrams every four hours to between 250 milligrams and 300 mg twice daily after the reduced version as shown to be just as effective (*N. Engl. J. Med.* **322**, 941–949, 1990). Now, a phase 2 study is evaluating 200 milligrams versus 300 milligrams twice daily of zidovudine over 48 weeks in 136 treatment-naive patients. The primary goal of the study is to evaluate the reduction of anemia, not efficacy of the reduced dose. So, the trial will not provide enough evidence to gain regulatory approval, but it could act as a starting point for future investigations.

Additionally, there are several dose-optimization trials evaluating lower drug dosages in children, including a randomized study in 200 Thai children testing a lower dose of lopinavir/ritonavir. A poster presented at July's IAS meeting in Kuala Lumpur showed that compared to the approved dose, a lower dose demonstrated noninferiority over 96 weeks with less dyslipidemia, a side effect that results in an abnormal amount of fat cells in blood.

"HIV drugs work very well," says Andrew Hill, a pharmacologist at Liverpool University in the UK, who is not involved with the dose optimization trials, "but you have a spectra of all these problems."

With the verdict of the ENCORE1 trial now in, the study investigators plan to start working with the FDA on regulatory approval as well as with the drug manufacturers to create lower-dose pills, says Emery. He estimates that the lower-dose pills could be widely available within one year.

Dose-optimization strategies have not yet caught on for other diseases, but Crawford thinks that they will, given that other infectious diseases have similar challenges to HIV in terms of cost and access to treatment. "HIV is going to be the model," he says.

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