

Monday, February 26, 2001

AIDS: "Hit Hard, Hit Early" Taking Hits (Part 1)

By Pat French

The panel that issues treatment guidelines for people infected with human immunodeficiency virus (HIV) or who suffer from acquired immune deficiency syndrome (AIDS) has changed its mind about when some people should start antiviral treatment.

The most recent update to the guidelines, issued February 5, now recommends that HIV-infected people who have no symptoms wait to begin highly active antiretroviral therapy (HAART) until the number of CD4+ T lymphocytes, the white blood cells most affected by HIV infection, fall below 350 per mm³ of blood (the normal number of CD4+ T cells is 800-1300 per mm³).

The updated guidelines do continue to recommend that all people with acute HIV syndrome, those who are in the first 6 months of being HIV-positive, and those who have symptoms from HIV infection receive HAART.

The guidelines, first issued 5 years ago by the Panel on Clinical Practices for the Treatment of HIV Infection, had called for HAART (also known as various "AIDS cocktails") if someone's CD4+ count fell to <500 cells per mm³ of blood or if there were more than 10,000-20,000 copies of the HIV nuclear material (ribonucleic acid, or RNA) per milliliter of plasma. This "hit hard, hit early" approach was encouraged even though no clinical data existed to support early versus delayed treatment.

Over time, the drawbacks of this approach started to emerge: patients were expected to comply with a regimen that required up to 12 pills a day at various times, cost up to \$20,000 a year in 1997 (that's \$55 a day), encouraged the development of HIV resistance, and increased their risk of severe bone-marrow toxicity, anemia, diabetes, drug interactions, and liver, kidney, digestive system, and nerve damage.

"We are now being a little more conservative in treatment," said Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), on abcnews.com. "Although the therapy is beneficial, it is better later in the course of infection."

In fact, no one knows the best time to begin HAART after HIV infection, as the updated guidelines themselves state, although early studies of monotherapy have shown that delaying treatment does not affect survival.

A group of investigators from the Adult AIDS Clinical Trials Group (AACTG) recently proposed the START study, to address this question in the era of HAART. The study would have started patients on antiretroviral therapy at different stages of their disease, which meant that patients randomized to receive drugs later would not receive any medication for some time. This was considered unacceptable (unethical) by reviewers.

When asked why no other study was planned to address the issue, Fauci said that he believes such a study would be "logistically impossible," because of how complex the different treatments are in the U.S.

"This is one of the most important questions in AIDS research," noted Michael Harrington on abcnews.com, senior policy director for the Treatment Action Group, which advocates for larger and more efficient AIDS investigations. "I am angry and disappointed they didn't do such a study. They are more interested in a high tech treatment or a new drug, not in answering questions important to the public and to people with HIV."

Another important question is: How should the effect of treatment (or nontreatment) be measured? For people with HIV, the answer might be longer survival, fewer illnesses, or more days at work. The guidelines, however, state that "results of therapy are evaluated primarily with plasma HIV RNA levels." They go on to define failure of therapy as having >50 copies of HIV-RNA per mL of blood after 4 to 6 months of HAART. How relevant this surrogate measure is to the day-to-day lives and ultimate outcomes of HIV-infected people is unclear.

Further, under this definition, one of the combination drugs specifically recommended by the guidelines, Kaletra, would have a 35% failure rate after less than 6 months of treatment, according to results of the largest trial leading to Kaletra's fast-track approval in September 2000. The longest treatment period with this drug in any controlled trial has been 72 weeks, at which time the failure rate was 42% among the small number of patients (n=36) given the recommended dose.

A third unanswered question is when to change treatment(s). Clearly this question can't be answered until a standard measure of treatment effect is defined. In the meantime, the guidelines urge HIV-positive people already taking the cocktail to check with their doctors about whether they should stop or change their medicines. The guidelines, a joint effort between the U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation, are continuously updated on the Internet as information becomes available.

Part 2 of this series will describe the efforts of one DCRI researcher to address some these questions.

For the most recent guidelines, click [here](#). For the previous version of the guidelines, click [here](#).
