DHHS Guidelines: Return of ‘Hit Hard, Hit Early’

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The U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents* has come nearly full circle—experts are now recommending that people with HIV start antiretroviral (ARV) therapy at CD4 cell counts higher than 350, with some even recommending treatment at more than 500 CD4 cells. The new guidelines, published today, December 1, also bumped the integrase inhibitor Isentress (raltegravir) up to “preferred” as a first-line regimen component in people new to HIV treatment.

The DHHS guidelines, constructed by a panel of top HIV researchers, clinicians and community activists, are regularly updated based on new results from clinical trials and other studies. When they vote to revise guidelines or add new recommendations, panelists may designate their recommendation as strong, moderate or optional, depending on how they interpret the strength of the data. Typically, two thirds of the panel must vote together in order to approve a new recommendation.

Perhaps the most significant change to the revised guidelines is the issue of when to start ARV therapy. While the first guidelines published following the debut of protease inhibitors suggested a “hit it hard, hit it early” approach for everyone, later guidelines pulled back sharply—recommending that treatment not be started until a person’s CD4s fell below 200—largely due to efficacy, dosing and safety concerns.

Since then, researchers have recognized the survival benefits of starting earlier, as well as the improved toxicity and ease of use of available treatments. A couple years ago, the guidelines were changed to recommend that people start treatment as soon as CD4 cells dropped below 350. More recently, however, some researchers have suggested that starting even earlier might be beneficial. Several studies have shown that even people with CD4 counts above 350 can experience a number of health consequences, including cardiovascular disease and a variety of cancers, at higher rates than would be expected if they were not HIV positive.

A Return to Earlier Treatment

Like the previous version of the guidelines, the panelists continue to assert that all HIV-positive people with CD4 counts below 350 be started on ARV therapy. The guidelines also continue the recommendation that treatment be started, regardless of the CD4 cell count, by HIV-positive people who are pregnant, have been diagnosed with HIV-associated nephropathy (kidney disease)

or require treatment for chronic hepatitis B virus (HBV) infection.

New to the guidelines is the recommendation that people with CD4 counts between 350 and 500 start ARV treatment.

According to the revised guidelines, “The standard procedure for the [panel] is to only make recommendations in agreement with two thirds of the [panel] members. This has not been possible for the When to Start recommendations in this updated version of the guidelines.” While there was universal agreement to start treatment between 350 and 500 CD4 cells, panelists were divided on the strength of the recommendation. Fifty-five percent of the panelists voted to make starting between 350 and 500 a strong recommendation, and 45 percent voted to make it a moderate recommendation.

Some panelists even recommend treatment in people with CD4 counts above 500, though it was an even split, with 50 percent favoring this approach and 50 percent saying it should be optional. Those recommending such early treatment cited a recent cohort study showing a survival benefit for people who started treatment at CD4 counts above 500. They also pointed out the growing awareness that untreated HIV is associated with increased rates of non-AIDS-defining diseases. And they mentioned that treatment has improved and is more tolerable—and that it may reduce the risk that people living with the virus will transmit it to others.

“The other 50 [percent] of the panel members,” say the new guidelines, “feel that current evidence does not definitively demonstrate clear benefit of antiretroviral therapy in all patients with [more than 500 CD4s]. They also feel that risks of short- or long-term drug-related complications, nonadherence to lifelong therapy in asymptomatic patients, and potential for development of drug resistance may offset possible benefits of earlier initiation of therapy.”

What to Use

The panelists also significantly changed the roster of treatments that are considered preferred when a person starts HIV treatment for the first time. The new preferred treatments are Sustiva (efavirenz), Reyataz (atazanavir) boosted by low-dose Norvir (ritonavir), Prezista (darunavir) boosted by low-dose Norvir, or Isentress. The revised guidelines recommend that all four treatments be combined with Viread (tenofovir) and Emtriva (emtricitabine)—typically used together in the fixed-dose combination tablet Truvada (Sustiva, Viread and Emtriva are often used together in the fixed-dose combination tablet Atripla).

Kaletra (lopinavir/ritonavir) has been downgraded to an alternative treatment option, except in pregnant women, where it is preferred, notably in combination with Combivir (zidovudine plus lamivudine).

The panel also made revisions to guidelines for managing treatment-experienced people, simplifying treatment, treating people with hepatitis C virus (HCV) coinfection and managing side effects and drug interactions. Additional guideline revisions detailed ARV drugs not to use.