Leading through Guidance

How can we harmonize the differences between HIV treatment guidelines in wealthy and resource-limited countries?

By Edwin J. Bernard

BY THE END of 2008, HIV treatment guidelines in wealthy countries were harmonized in their recommendation to begin antiretroviral therapy no later than when an individual's CD4 count reaches 350, with consideration to start earlier under many certain circumstances, such as pregnancy, hepatitis co-infection and underlying risks for cardiovascular diseases, or in individuals in a sero-discordant relationship.[1]

AS EVIDENCE ACCRUES from clinical trials suggesting that earlier treatment initiation may further reduce the risk of non-AIDS cancers and heart, liver or kidney disease, and with a number of more potent, less toxic, and easier-to-take-and-tolerate antiretrovirals available, the pendulum is swinging towards treating earlier and earlier.[2]

YET, THE WORLD Health Organization (WHO) treatment guidelines for low- and middle-income countries on when to start therapy have remained relatively unchanged since 2006. WHO recommends treatment with standardized first- and second-line antiretroviral regimens when people show serious symptoms of HIV infection and/or before CD4 counts fall below 200, with consideration given to treating patients with a CD4 count below 350. In practice, though, due to a lack of CD4 cell–counting machines in many settings, people tend to be treated only when they show signs of serious illness.[3]

SINCE TREATMENT GUIDELINES are based on a public health model, WHO must balance changing its guidelines to call for earlier treatment – which would make many millions more eligible for antiretroviral therapy – with the reality that most countries will not meet the goal of universal access by 2010 based on the current, lower thresholds of initiating treatment. Earlier treatment with newer drugs also has significant resource implications at a time when the Global Fund to Fight AIDS, Tuberculosis and Malaria indicates a U.S. $4 billion funding gap in 2010[4], and the World Bank estimates that up to 1.7 million people are at risk of antiretroviral treatment interruption due to the global financial downturn.[5]

MANY LOW-INCOME COUNTRIES already face an unenviable dilemma: attempting to treat more people by using cheaper drugs such as d4T (which is now all but rejected in wealthier countries due to high rates of toxicity) rather than using newer, better-tolerated ones like tenofovir, which is more expensive to manufacture. Drug costs aside, there are also concerns about the availability and cost of CD4 counts[6], as well as the additional personnel required to deliver treatment.

An HIV-positive beneficiary receives antiretroviral medications during a regular home visit by a Ugandan NGO worker in Kampala, Uganda. Photo: © 2005 David Snyder, Courtesy of Photoshare

EVEN AFTER A May 2007 update to WHO guidelines recommended either lowering the d4T dose or switching to AZT, only half of 15 PEPFAR focus countries had implemented these changes in their national treatment guidelines by January 2008.[7] Even when changes had been made, much time and many resources were required to implement them. For example, Zambia needed a year to organize stock management systems and train healthcare workers before patients could switch to tenofovir.[8]

TREATMENT GUIDELINES MAY set the standard for HIV care, but even in wealthy countries many people are not being diagnosed with HIV until their CD4 counts have fallen well below 200,[9] making the debate about whether to start earlier something of a moot point. A recent nine-country, 18-cohort review examining the outcome of public antiretroviral therapy access schemes throughout sub-Saharan Africa found a shockingly high rate of mortality, with many of the deaths occurring in the first three months of treatment.[10] In this cohort, average CD4 counts at treatment initiation ranged between 43 to 147.

SOME WOULD ARGUE that harmonizing treatment guidelines on when to start ART is unnecessary when the real issues are late diagnosis, suboptimal, toxic therapy and, in many settings, difficulty accessing *any* kind of treatment and care. However, even in those settings, guidelines on when to start are essential for clarifying how to optimize the benefit of treatment for the individual and the community, and they provide the impetus to work towards what some might see as unattainable goals. Guidelines tell politicians, funders and people living with and at risk of HIV that there is hope, not just for universal access, but also for universal, *equitable* access.

IN THIS SPIRIT, the Southern African HIV Clinicians' Society updated their treatment guidelines in January 2008 to recommend starting treatment at CD4 counts of 350, [11] not just to influence the private sector, but in order to lobby for changes to public-sector guidelines.

IN 2006, IAS President Julio Montaner introduced the additional public health benefits of treatment as prevention in a

study published in *The Lancet*. Late last year, WHO officials further explored the concept in a paper that modelled the potential impact on the epidemic of immediate treatment upon diagnosis in the context of universal routine testing.[12] WHO has now set in motion a process that will examine the technical, operational, cost and ethical implications of treating everyone regardless of CD4 count, potentially revolutionising the when-to-start-treatment paradigm.[13] Those are the types of arguments that are important for policymakers to hear.

WHILST PEOPLE ARE still needlessly dying of AIDS-related illnesses, guidelines must set out, in no uncertain terms, the quantifiable individual and public health advantages of treating earlier in order to help achieve universal access goals, even if universal equitable access remains a pipe dream. ■

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Clinical News

Better Quality of CD8+T Cells in the Mucosa of Long-term Non-progressors

"LONG-TERM NON-PROGRESSORS" (LTNP) refers to HIV-infected individuals whose disease progresses slowly because their bodies naturally control their HIV infection. These individuals may retain a high level of CD4+ T cells and maintain a low viral load (known as "viremic controllers") or an undetectable viral load ("elite controllers") for years in the absence of antiretroviral therapy. Scientists are trying to better understand the biological mechanisms underlying the ability of their immune systems to control the virus.

RESEARCHERS HAVE FOUND previously that the levels of CD8+ T cells in controllers are markedly elevated in comparison to non-controllers. Furthermore, investigators have shown that the characteristics and quality of these cells, rather than the frequency of HIV-specific CD8+ T cells, may partly explain natural viral resistance. However, in HIV-infected individuals, the HIV-specific CD8+ T cells are believed to be partially impaired and have shown to be ineffective in successfully controlling HIV infection.

CD8+ T CELLS, also called cytotoxic T cells, are a subset of the immune system that identifies and destroys host cells infected with foreign pathogens. The CD8+ T cells usually contain an artillery of molecular ammunition to protect the body against foreign organisms. The competency (also known as "polyfunctionality") of these cells is often defined as their ability to use several of these molecular ammunitions to defend the host cells from pathogens.

INFORMATION ABOUT THE response of mucosal CD8+ T cells can provide valuable knowledge about immune responses in the gastrointestinal tract and potential correlates to disease protection because this area of the body is known to be a reservoir for HIV replication due to the large number of lymphocytes located there.

IN A RECENT study, scientists looked at immune responses in mucosa and compared the CD8+ T cells in different groups of patients. One group was the elite controllers – defined in the study as individuals with a viral load below 75 copies per ml of blood in the absence of treatment. Viremic controllers were identified as untreated individuals with viral loads between 75 and 2,000 copies per ml. The non-controllers were patients with viral loads above 10,000 copies per ml in the absence of treatment. Control groups included patients with successful treatment suppressing viral load to below 75 copies per ml and people who were not infected with HIV.

RESEARCHERS COLLECTED THE HIV-specific CD8+ T cells from the blood and rectal mucosa of the study participants and then analyzed the characteristics and the quality of the samples, comparing them within and among the patient groups.

THE RESULTS OF the study revealed that the response of CD8+ T cells in the mucosa of elite controllers was significantly stronger and more complex than in HIV patients whose viral loads were suppressed by antiretroviral therapy. In both elite and viremic controllers, the polyfunctional response of the CD8+ cells in the mucosa was significantly higher than in non-controllers and patients on treatment. Additionally, the study found that strong mucosal CD8+ T cell responses were more often associated with controllers than blood CD8+ T cell responses.

DESPITE THESE ILLUMINATING findings, it is uncertain if the strong polyfunctional mucosal CD8+ T cell responses observed are the cause of effective viral suppression or a consequence of it. In controllers where viral replication is naturally suppressed, the host immune system may be intact, more potent and not damaged, as is the case of patients with high viral loads.

ALTHOUGH THE STRONG, more complex CD8+ T cell responses play an important role, it is likely that other immune mechanisms and other factors also influence viral control. As has previously been shown, the current study confirms that host genetics play a role in the host's immune response. The results of the study indicate that certain host genes are more strongly associated with long-term viral suppression.

THE STUDY RESULTS shed additional light on the factors associated with LTNP and their ability to naturally suppress viral replication. Better understanding of the underlying mechanism for long-term viral suppression will have significant implications for development of an effective HIV vaccine. ■

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