

## Invited Commentary

# Defining Success With Antiretroviral Therapy

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**Two critically important issues** in human immunodeficiency virus (HIV) therapeutics are when to start antiretroviral therapy and how well these medications restore immunity. In this issue of *JAMA Internal Medicine*, Okulicz et al<sup>1</sup>



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were monitored for this early in their infection, only 38.4% achieved a CD4<sup>+</sup> T-cell count of 900 cells/ $\mu$ L or greater, and in individuals waiting until after 12 months of the infection to start therapy, only 28.3% achieved a normal CD4<sup>+</sup> T-cell count. A higher level of CD4<sup>+</sup> T-cell recovery was associated with decreases in the frequency of an AIDS diagnosis, normalization of markers of immune activation, and better response to hepatitis B vaccination.

This is an important study because the investigators used as primary end points measures of immune function that should be the goal of antiretroviral therapy: full restoration of immune function. Historically, many of the sentinel studies used to make policy decisions on when and how to treat HIV infection used end points such as suppression of virus replication in peripheral blood, increases in peripheral blood CD4<sup>+</sup> T-cell count, or progression to a diagnosis of AIDS. Despite achieving these end points that have been labeled as indicators of therapeutic success, multiple studies documented that significant immunologic abnormalities remained in these patients and that they continued to have adverse outcomes.<sup>2</sup> The CD4<sup>+</sup> T cells continued to be dysfunctional, lymphoid tissues remained depleted of CD4<sup>+</sup> T cells,<sup>3</sup> markers of immune activation remained elevated,<sup>4</sup> the CD8<sup>+</sup> T-cell responses remained abnormal,<sup>5</sup> and responses to vaccine continued to be suboptimal.<sup>6</sup>

In acknowledging the failure of antiretroviral therapy to completely restore immune function, we should not discount the significant progress that has been made. Modern antiretrovirals are easier for patients to take and less toxic compared with the earlier agents and people with access and means to consistently adhere to therapy are living longer and are generally healthier, and there is no doubt that the burden of infection in the community is gradually decreasing. Antiretroviral therapy should be started as soon as possible. However, AIDS is still a leading cause of death and patients continue to have increased morbidity and mortality. If full restoration of immunologic and clinical health is our goal, then the present study tells us that the best chance we have is to start antiret-

roviral therapy within 12 months of infection. Even then, only approximately one-third of the patients will achieve "normal" levels of immune function, as defined in this study.<sup>1</sup> Even if we were to accept a score of only one-third of persons as a success, it is unrealistic to think that we will routinely identify patients within 12 months of infection, especially in the parts of the world where this disease is most prevalent.

This sobering observation underscores the need to better understand the pathogenesis of HIV infection and use that information to inform drug discovery and rational policies for treatment. Why is it that these drugs do not allow for full restoration of immunity? One fundamental problem is that despite suppression of viral RNA in their blood, patients continue to have elevated markers of immune activation from a variety of causes; this elevation directly contributes to decreased immune activation of HIV is the major cause of immune activation in untreated disease, but it remains an important cause in treated infection. Two studies<sup>7,8</sup> using a treatment-intensification strategy with an integrase inhibitor documented ongoing replication in some patients and, when the additional drug was given, markers of immune activation decreased. The likely reason for persistent replication of HIV in the tissues of some patients is that antiretroviral drugs do not penetrate into lymphoid tissues at a concentration that will fully contain viral replication.<sup>9</sup> Other causes of persistent immune activation in treated HIV infection are common coinfections, such as cytomegalovirus,<sup>4</sup> and tissue abnormalities in the gut that allow for microbial translocation.<sup>10</sup> Whatever the cause, the net result is a well-defined process of fibrosis (ie, accumulation of scar tissue) in lymph node- and gut-associated lymphoid tissues that directly inhibits full restoration of CD4<sup>+</sup> T-cell populations.

This important study reminds us that the goal of HIV therapy should be full restoration of immune function and not just suppression of viral replication. Okulicz and colleagues<sup>1</sup> have provided the clearest signal to date that we will not restore immunity with the drugs we have available. Under ideal conditions only approximately one-third of the patients who receive treatment could achieve this goal. Most of the 35 million people infected with HIV live in conditions where only a few will have the opportunity to start therapy within 12 months of seroconversion. We need better formulations of antiretroviral drugs that fully suppress virus replication in tissues. However, we also need adjunctive therapies that eliminate the causes of persistent immune activation and restore lymphoid tissues to their normal anatomy and function.

## ARTICLE INFORMATION

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