

# The Paradox of Incomplete CD4<sup>+</sup> Cell Count Restoration Despite Successful Antiretroviral Treatment and the Need to Start Highly Active Antiretroviral Therapy Early

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(See the article by Kelley et al. on pages 787–94)

The natural course of HIV infection is characterized by progressive and, ultimately, profound loss of CD4<sup>+</sup> T lymphocytes, the primary target of this virus that essentially infects the immune system. During peak viremia, in the acute phase of infection, CD4<sup>+</sup> cells are dramatically depleted in the gut, where the vast majority of them reside [1]. When the HIV load reaches a subsequent quasi-set point, circulating CD4<sup>+</sup> cells experience a transient recovery. However, over the course of infection, progressive CD4<sup>+</sup> cell loss leads to increasing immunodeficiency, resulting in opportunistic diseases and, finally, death [2]. CD4<sup>+</sup> cell counts, therefore, represent the principal surrogate marker for clinical symptoms and AIDS-defining illnesses.

With the advent of effective antiretroviral therapy, it became clear that decreases in CD4<sup>+</sup> cell counts can be drastically reversed. After treatment initiation, the fre-

quency of opportunistic infections dramatically decreases as the CD4<sup>+</sup> cell count increases, and the extent of CD4<sup>+</sup> cell count increase is associated with the degree of overall immune system recovery [3]. Therefore, CD4<sup>+</sup> cell count restoration has become a principal criteria for determining the efficacy of treatment strategies [4].

With some persons having now received effective antiretroviral therapy for more than a decade, marked heterogeneity in the course of treatment-associated CD4<sup>+</sup> cell count restoration has been noted. Typically, the CD4<sup>+</sup> cell count increases rapidly during the first 3–6 months after the initiation of treatment, which is comparable to what is seen in HIV-negative individuals after chemotherapy [5]. In a second phase, a more gradual increase is observed until a CD4<sup>+</sup> cell count >500 cells/mm<sup>3</sup> is reached [6, 7]; this is achieved by the majority of patients who have undetectable plasma HIV RNA levels while receiving antiretroviral therapy. Rates of CD4<sup>+</sup> cell count restoration have been described to be dependent on multiple factors, including age, baseline CD4<sup>+</sup> cell count, previous AIDS-defining events, coinfections, history of antiretroviral therapy, and duration of suppressive antiretroviral therapy [8–11]. However, a sub-

population of HIV-infected individuals do not recover CD4<sup>+</sup> cell counts to >500 cells/mm<sup>3</sup> [9]; this lack of increase in CD4<sup>+</sup> cell count has been associated with increased risk of both AIDS and non-AIDS-related events (e.g., cardiovascular disease, liver disease, and cancer) [12, 13]. Some of these patients appear to reach a “plateau” at a CD4<sup>+</sup> cell count <500 cells/mm<sup>3</sup> [7–10], but short follow-up periods in previous studies have limited the ability to define the extent of this phenomenon or the factors that predict this suboptimal response to treatment.

In this issue of *Clinical Infectious Diseases*, Kelley et al. [14] provide the most-extensive data to date on CD4<sup>+</sup> cell count restoration in antiretroviral-treated HIV-infected individuals. They examined 366 patients from 5 clinical cohorts who maintained plasma HIV RNA levels ≤1000 copies/mL for at least 4 years after therapy initiation. The authors show data for a median follow-up period of 7.5 years (interquartile range, 5.5–9.7 years). Almost one-quarter of these patients were followed up for >10 years. The good news is that nearly all patients (95%) who started therapy with CD4<sup>+</sup> cell counts >300 cells/mm<sup>3</sup> achieved a CD4<sup>+</sup> cell count >500 cells/mm<sup>3</sup>, which suggests strong immune reconstitution. In contrast, 44% of pa-

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tients who initiated antiretroviral therapy with a CD4<sup>+</sup> cell count <100 cells/mm<sup>3</sup> and 25% of patients who started therapy with a CD4<sup>+</sup> cell count of 100–200 cells/mm<sup>3</sup> were unable to achieve a CD4<sup>+</sup> cell count >500 cells/mm<sup>3</sup> over the same follow-up period; a large subset of patients had their CD4<sup>+</sup> cell count remain below this threshold for up to 10 years.

Of importance, these data show that a significant subset of individuals who did not achieve a CD4<sup>+</sup> cell count >500 cells/mm<sup>3</sup> at year 4 appeared to have their CD4<sup>+</sup> cell count plateau below normal levels. These individuals pose a major challenge in treatment, because current therapies appear to be unable to increase these patients' immunity to normal levels. Often, treatment is switched to a second-line therapy for these patients, with the assumption that the lack of CD4<sup>+</sup> cell count recovery is associated with direct cytotoxic effects of certain antiretroviral drugs [15, 16]. However, in a recent study published in *Clinical Infectious Diseases* [11], this presupposition was contradicted, because the data showed that the composition of antiretroviral drug regimens had no impact on immunological recovery in a cohort of >3000 patients.

In a study by Kelley et al. [14], the authors showed that lack of complete CD4<sup>+</sup> cell count restoration is more common among persons starting therapy with a low CD4<sup>+</sup> cell count, and the large size of this cohort allowed for analysis of factors modulating CD4<sup>+</sup> cell count recovery. Many theoretical mechanisms underlying poor immunological outcomes during therapy have been proposed, including insufficient thymic T cell output, reduced T cell proliferative capacity, higher rates of T cell apoptosis, and other potential unknown host factors. Interestingly and contrary to previous reports, Kelley et al. [14] demonstrated that age was the only factor evaluated in their study that was consistently associated with continued CD4<sup>+</sup> cell count increases after 4 years of treatment, whereas hepatitis C virus coinfection, sex, and pre-HAART nucleoside analogue ex-

posure were not significant predictors of CD4<sup>+</sup> cell count increases during this period.

A caveat in the study by Kelley et al. [14] relates to the remarkable improvements that have been achieved with regard to the ability to quantitate viral load, because the current highly sensitive assays were not available at the start of their study. Samples acquired early were detected with a lower HIV RNA cutoff level of 1000 copies/mL. Patients who maintained HIV RNA levels <1000 copies/mL were included in the study. Maintaining a viral load <1000 copies/mL would be expected to have a very different impact on disease than would maintaining a viral load <50 copies/mL. Additional long-term follow-up studies involving persons who maintain viral loads <50 copies/mL will be needed to know the effect of potentially more-profound viral containment on immunological recovery. Furthermore, it should be taken into consideration that approximately one-half (49%) of the cohort in the study was not treatment naive when their first HAART regimen was initiated. The true nadir CD4<sup>+</sup> cell count and the magnitude of increase in CD4<sup>+</sup> cell count in these individuals therefore remains unknown.

Despite these caveats, the important study by Kelley et al. [14] strongly supports the early initiation of HAART—a doctrine that is reflected in recent changes in the major US and European treatment guidelines. Both guidelines recommend initiation of antiretroviral therapy in patients with a history of an AIDS-defining illness or a CD4<sup>+</sup> cell count <350 cells/mm<sup>3</sup> [17, 18]. Unfortunately, these changes have yet to be implemented in many parts of the world, particularly in resource-constrained countries, where the epidemic of HIV infection continues to have the greatest impact. Changes in treatment guidelines globally would carry a large additional financial burden because of the increase in the numbers of patients needing HAART. However, adequate early therapy, leading to more-complete im-

mune reconstitution, may save resources because of the resulting lower incidence of opportunistic infections and reduced need for medical care. This will be an important issue to address as treatment access fortunately continues to expand.

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