The Modern ART of HIV Infection Management: Towards a Tailored Approach to Maximize CD4 T Cell Reconstitution

Sarah C. Sasson[1], Anthony D. Kelleher,[1,2] and David A. Cooper[1,2]

[1]National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, and [2]Centre for Immunology, St Vincent's Hospital, Sydney, Australia

(See the article by Kaufmann et al. on pages 361–72)

The great success during the 25-year history of HIV infection has been the introduction of combination antiretroviral therapy (ART). First introduced in the mid-1990s, ART greatly inhibits viral replication, often reducing viral loads to undetectable levels, allowing the homeostatic mechanisms of the immune system to at least partially restore the depleted CD4 T cell population [1]. The result has been clinically significant reductions in morbidity and mortality, converting the infection into a chronic condition in persons tolerant of prolonged ART [2]. However, the long-term outcomes of prolonged ART, both clinical and immunological, are not fully understood. Predictors of good response to ART are not fully elucidated. There is recurrent debate regarding the optimal time to commence ART, with current guidelines representing a compromise between maximizing immunological responses and minimizing long-term toxicities, resistance, and cost, while simultaneously judging the right time to intervene before the patient has developed life-threatening immunodeficiency. However, it is becoming increasingly clear that CD4 T cell responses are heterogeneous. Simple algorithms that allowed greater individual tailoring of therapy would be a significant clinical boon.

Studies of responses to ART have shown clinically significant numbers of discordant responders who, despite suppression of HIV load, do not regain expected proportions of CD4 T cells [3, 4]. Impeded CD4 T cell reconstitution in virally suppressed individuals has been related to low pretherapy CD4 T cell counts and to slow decreases in CD4 T cell counts before therapy [5]. Poor immunological response also correlates with markers of limited thymopoesis, including older age, decreased thymic mass, and decreased numbers of naive CD4 T cells [6, 7]. High baseline virus load and slower rates of viral decay have also been implicated [8]. However, because of the relatively recent introduction of ART, reports regarding predictors of immunological response to ART have been restricted by limited follow-up data.

In this issue of *Clinical Infectious Diseases,* Kaufmann et al. [9] build on previous work aimed at defining the predictors of CD4 T cell responses after ART. Kaufmann and colleagues have previously used the excellent follow-up program of the Swiss HIV Cohort to show that discordant responders have lower nadir CD4 cell counts and are older than nonresponders and that, for responders with consistent long-term increases in CD4 T cells, the vast majority of immune reconstitution is seen during the first year of therapy [10].

In their article, Kaufmann et al. [9] reported the extent of CD4 T cell reconstitution during the 5-year period after initiation of ART in a subset of the Swiss HIV Cohort restricted to patients with sustained virological responses (defined as viral loads consistently <1000 copies/mL). After excluding patients with missing baseline values or those who commenced ART with >500 CD4 T cells/μL, they identified 293 treatment-naive individuals who had been infected with HIV for a mean duration of 4.4 years.

The study group was divided on the basis of CD4 T cell count after 5 years of ART. Complete responders were defined as patients who attained a CD4 T cell count $\geqslant$500 cells/μL, and incomplete responders were defined as patients who achieved a CD4 T cell count <500 cells/μL. Pretherapy characteristics and clinical outcomes were compared between groups. Additionally, mathematical modeling was used to describe the kinetics of immune

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Reprints or correspondence: Dr. Sarah Sasson, HIV Research Lab, Centre for Immunology, St Vincent's Hospital, Corner of West St. and Boundary St., Darlinghurst, Sydney, NSW 2010, Australia (s.sasson@cfi.unsw.edu.au).

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reconstitution and to predict maximal CD4 T cell reconstitution.

Univariate analysis of pretherapy characteristics revealed that incomplete responders were older, had longer durations of HIV infection, had lower CD4 T cell counts, had higher HIV loads, and had progressed to CDC HIV disease category C more often, compared with complete responders. Incomplete responders had smaller increases in CD4 T cell counts after ART initiation, both during the first 3 months and at subsequent annual intervals. In multivariate analysis, age, baseline CD4 T cell count, and duration of HIV infection each independently predicted incomplete response after 5 years of ART.

Kaufmann et al. [9] described 2 patterns of immune reconstitution among incomplete responders. In nearly one-half of such patients, CD4 T cell counts reached a plateau, whereas the remaining incomplete responders continued to have small increases in CD4 T cell counts each year. No intergroup differences in the kinetics of T cell recovery could be distinguished within the first 3 years after initiation of ART.

Perhaps of greatest clinical relevance, Kaufmann et al. [9] developed a model that could predict long-term incomplete response with 80% sensitivity and 72% specificity on the basis of baseline age and CD4 T cell count and a CD4 T cell count increase of <99 cells/μL in the first 3 months of ART. The modeled data revealed that, after a mean ART duration of 4.25 years, nearly 90% of individuals fulfilling the given criteria will reach a CD4 cell count >350 cells/μL and nearly 70% will reach a CD4 cell count of $\geq$500 cells/μL.

This article contributes significantly to our understanding of long-term responses to ART. It provides a possible basis for an algorithm that could assist in predicting which patients are most likely to have optimal immunological responses if sustained virological suppression can be attained. This would allow for reassurance of patients who have a high likelihood of responding well and, for discordant responders, decreased costs and inconvenience associated with unnecessary drug regimen switching. This could be of particular significance in resource-limited settings where therapeutic decisions are usually made on the basis of CD4 T cell count alone. Moreover, this approach may allow for the individualization of the timing of treatment commencement.

However, a number of questions require answers before initiating this type of treatment algorithm. Despite the ability of the authors' model to predict with some certainty which patients will have a sustained CD4 T cell response, the observed differences in CD4 T cell response did not translate into differences in clinical outcomes. Although the number of AIDS-related events experienced by incomplete responders was higher than the number experienced by complete responders, these differences were not statistically significant. This may be related to sample size and the duration of the follow-up period, but it may also correspond to the selection of a CD4 T cell count of 500 cells/μL as the breakpoint. Although CD4 T cell counts are a good surrogate for immunocompetence, they are not a perfect indicator. Functional immune deficits may persist despite apparently adequate reconstitution of the T cell count. This finding may indicate that there is no absolute threshold at which immunocompetence is conferred during the process of immune reconstitution. The inclusion of AIDS-related events that are not directly linked to depressed CD4 T cell counts, such as non-Hodgkin lymphoma and tuberculosis, may explain the discrepancy, although their occurrence does not appear to be substantively different between the groups.

A further limitation of this model is its restriction to patients with sustained virological control. Despite the generous cutoff value (an HIV RNA load <1000 copies/mL), this study does not provide any information about the substantial group of patients for whom this level of control is not attainable. However, it provides insight into the upper limits of what is likely to be attainable. Furthermore, it reflects the degree of immune maintenance and reconstitution that can be expected for therapeutic strategies employing CD4 T cell count–driven structured treatment interruption, such as that being investigated in large trials with clinical end points (e.g., the Strategies for Management of Antiretroviral Therapy [SMART] study). Higher HIV loads during therapy are likely to have a negative impact on the degree of immune reconstitution.

Although beyond the scope of the article by Kaufmann et al. [9], the determinants of CD4 T cell response should be pursued, because they will improve understanding of the pathophysiology of the infection and may provide the basis for a simple measurement that, if performed at baseline or early during the reconstitution process, could add to the accuracy of their predictive model. Smaller pathophysiological studies have suggested that the determinants of effective reconstitution are multifactorial and include age, disease stage, intactness of the thymus, and intactness of peripheral lymphoid tissue. Relatively simple measures, such as quantitation of the naive CD4 T cell population, the degree of immune activation, or the levels of cytokines essential for immune regeneration (e.g., IL-7), may, when added to the model, improve its predictive value. Such a model would provide a useful clinical tool for optimizing the timing of treatment initiation, for minimizing the exposure to long-term metabolic toxicities of ART [11], and, perhaps, for identifying persons who are most likely to benefit from adjuvant immunotherapy, such as treatment with IL-2 or IL-7.

Of interest are factors that differentiate incomplete responders with a plateaued CD4 T cell response from those in whom the CD4 T cell count continues to increase. It is possible that the latter group may more closely resemble complete responders as they continue to respond to the homeostatic drivers of their immune systems, whereas incomplete responders

who have plateaued responses have lost either these critical drivers or the ability to respond to them. Such insights may guide both application and design of adjuvant immunotherapies aimed at improving immune reconstitution.

Early recognition of how patients will respond to ART may result in tailored drug regimens that improve outcome and quality of life and reduce unnecessary drug use and costs. The determinants of discordant response require further study, with the goal of developing new interventions. However, true advances in tailoring therapy will only be confirmed if they impact functional immunocompetence by not only increasing CD4 T cell counts but also decreasing HIV-associated morbidity and death.

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