Explaining, Predicting, and Treating HIV-Associated CD4 Cell Loss: After 25 Years Still a Puzzle

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occurring using intensive surveillance techniques and prevention schemes. These tools also are making genetic testing decisions and management of hereditary cancer syndromes even more complicated, underscoring the necessity for dedicated cancer genetic counselors and cancer risk assessment clinics that can best use these evolving tools to provide appropriate and evidence-based health care consultation.

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After 25 Years Still a Puzzle

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The clinical syndrome of AIDS is due to infection with the human immunodeficiency virus (HIV), which causes a progressive immunodeficiency characterized by the loss of CD4 T lymphocytes coupled with an immunosuppression related to global activation of the immune system. Since the seminal article by Mellors et al in 1996,[1] it has been known that as a group, individuals with a higher HIV RNA viral load tend to progress to AIDS and death at a more rapid rate than those with lower viral loads, and that different prognostic information can be derived from the CD4 cell count and the viral load. The conventional wisdom is that the CD4 cell count represents the current state of immune deficiency, whereas the viral load reflects the rate at which the immune system will further deteriorate.[2]

The report by Rodríguez and colleagues[3] in this issue of *JAMA* challenges the notion that, at the individual level, a limited number of HIV measurements over a short period of time provide meaningful prognostic information regarding the rate of CD4 cell decline and by extension the risk of opportunistic infections. Clinicians treating patients with HIV encounter some patients with low plasma viral levels who experience rapid progression. What mechanism is responsible for their profound and quick CD4 cell loss? On the other end of the spectrum are those patients with high-level HIV viremia who respond clinically like sooty mangabeys infected with simian immunodeficiency virus (SIV),[4]

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which can tolerate high levels of SIV replication without disease progression. Are such patients statistical extremes in an otherwise simple and uncontested paradigm, or are clinicians and researchers missing something?

Rodríguez et al have taken the perspective of the individual patient in attempting to quantify how much of the variability of the individual CD4 cell loss is explained by the baseline plasma HIV RNA viral load.[3] They used 3 clinical cohorts from several academic medical centers and confirmed their findings using the Multicenter AIDS Cohort Study (MACS) public data set, the same cohort that was used originally by Mellors et al.[1] Although the selection of patients who did not receive treatment immediately and the relatively short follow-up might have introduced some bias, the validation in a different well-characterized cohort is reassuring. The provocative main finding from their study was that the presenting plasma HIV RNA load predicted no more than 10% of the observed CD4 cell loss in patients with chronic untreated HIV infection.

What factor(s) explain the other 90%? Twenty-five years into the HIV epidemic, a complete understanding of what drives the decay of CD4 cells—the essential event of HIV disease—is still lacking. Direct and indirect effects of HIV infection, not fully measured by plasma HIV RNA levels, reverberate through a host's unique genetic and immunologic environment. HIV persists in tissues throughout the body and likely sets off chain reactions of acute and chronic immune disturbances.[5] Some of the mechanisms involved in this process most likely have been identified, but it is uncertain whether these factors are independent of one another, driven directly by the virus (or indirectly by the state of chronic immune activation associated with HIV infection), or a combination of both. In many cases it is difficult to elucidate what is cause and what is effect in these observations.

The importance of the host's genetic background in HIV pathogenesis has been increasingly recognized and appreciated. For instance, it has been known that some HLA patterns are associated with slower disease progression[6] and that individuals heterozygous for the Δ32 mutation in the CC chemokine receptor 5 (CCR5) tend to progress more slowly.[7] Moreover, proteins like TRIM5 α make some primate species resistant to HIV disease,[8] and polymorphisms in APOBEC3G[9] may play a role in disease progression. Other recently reported likely important genetic factors potentially influencing HIV progression include *CCL3L1* gene duplications[10] and polymorphisms in genes participating in postentry steps of the HIV-1 life cycle (*PML*, *TSG101*, and *PPIA*).[11]

The acute phase of HIV infection may cause profound damage to the immune system that may not be clearly linked to ongoing levels of HIV viremia observed during the chronic phase. Events that occur during acute HIV infection in the resting memory CD4 cells in intestinal mucosa might herald risk for subsequent disease progression, yet the degree of massive tissue CD4 cell depletion is not reflected by the level of peripheral CD4 cells.[12] Furthermore, residual disturbance of the lymph node architecture[13] and the amount of functional thymic tissue persisting after aging and HIV-related damage also may influence CD4 cell restoration.[14] Immune activation during the chronic phase of infection is also important and may be a better predictor of disease progression than HIV RNA viral load.[15] Many previously disparate processes may ultimately be shown to significantly interact and affect CD4 function and homeostasis in the setting of HIV infection. For example, very recent reports describe the critical role that the up-regulation of the programmed cell death protein PD-1 in CD4 and CD8 T-cells might have in the pathogenesis of HIV disease,[16] and how blockage of this protein can reverse immune dysfunction and improve control of viremia in vitro.[17] The puzzle of HIV pathogenesis keeps getting more pieces added to it.

The findings presented by Rodríguez et al[3] provide support to those who favor nonvirological mechanisms as the predominant cause of CD4 cell loss; however, these data should be interpreted with caution, and the issue of a single viral load as a prognostic marker should be separated from the role of viral replication in HIV pathogenesis. Measurements of a limited number of viral load levels may not provide a full picture regarding the overall impact of viral replication on the patient over the course of disease. To provide such a picture would require examination of a time-dose relationship for viral load and comparison with changes in CD4 T cells over an extended period of time. In addition, censoring patients who initiated antiretroviral therapy within 6 months of study may have eliminated a cohort of patients with the most rapid declines in CD4 cell counts from the analysis.

The study by Rodríguez et al may have several important clinical implications. The first and more straightforward is that baseline measurements of viral load alone should have less of a role in driving decisions on when to start antiretroviral therapy for an individual patient; these initial viral load levels cannot predict how rapidly the disease will progress. Current treatment guidelines[18,19] in the developed world progressively have recognized the limited role that HIV-RNA level plays in this decision and have increasingly stressed the importance of the baseline CD4 cell count. Interestingly, guidelines in the developing world[20] have reached the same conclusions, but have been based more on economic arguments. The secondary importance of baseline plasma HIV RNA levels does not diminish its critical importance in monitoring viral load responses after the initiation of antiretroviral therapy to document complete viral suppression and prevent the development of resistance. However, the seemingly useful practice of combining a CD4 cell count and plasma HIV RNA levels to assess an individual patient's prognosis for AIDS progression[21] or response to highly active antiretroviral therapy[22] needs reexamination.

The second and potentially more exciting implication of the findings of Rodríguez et al is that future improvements in the treatment of HIV infection and AIDS may result from

improved understanding of the 90% of CD4 cell depletion that remains enigmatic. The current paradigm of HIV treatment is the continuous use of antiretroviral combinations (targeting the widespread effects of ongoing HIV replication) for long periods of time, which now could approximate a normal life span. This approach has led to the most dramatic change in the prognosis of any disease in the last 2 decades, from usually lethal to regularly manageable. However, the sustainability of the current paradigm for the more than 40 million HIV-infected individuals and the more than 4 million new HIV infections per year is at best questionable.[23]

Unfortunately, treatment strategies that do not directly target HIV have not proven successful. Only 2 immunomodulators have been approved for the treatment of HIV-related disease: (1) interleukin 2, a cytokine used in some European countries to increase the CD4 cell count[24]; and (2) thalidomide, a tumor necrosis factor α antagonist for aphthous ulcers associated with HIV infection.[25] This is a meager list when compared with the 24 currently approved antiretroviral drugs, all of which directly inhibit stages of HIV replication.

As in the treatment of cardiovascular disease, developing therapeutic strategies for HIV that target both the etiology and the end organ damage may be more effective than either alone. Therapies focused on some of the nonviral factors (discussed above) may start to address the bulk of the "iceberg" below the tip of the measureable plasma HIV level. A better understanding of the immunologic and genetic factors that drive HIV-associated CD4 cell loss may translate to novel therapeutic approaches that could favorably shift the pathogen-host balance. In that direction, the first drugs that target a cellular factor (the chemokine receptor CCR5) have reached the clinical arena and are currently in phase 3 trials.[26,27] Discovering and developing therapies that target key nonviral factors has the potential over the decades ahead to build on the success of antiretroviral therapy and expand access to sustainable effective therapy.

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