Can We Break the Habit of Routine CD4 Monitoring in HIV Care?

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Every provider of treatment for human immunodeficiency virus (HIV) has experienced some version of the following exchange with at least 1 of his or her stable HIV outpatients:

Provider: Your blood tests look great—viral load undetectable, CD4 cell count 550, liver and kidney tests all fine.

Patient [worried]: CD4 550? It was 860 last time—that’s a drop of over 300 cells!

Provider [trying to be reassuring]: There’s a lot of variability in the CD4 count [1], especially when it’s normal like yours. Plus, the most important test for showing whether your treatment is working is the viral load.

Patient [unconvinced]: Okay. [A brief pause]: Hey, maybe it’s because I had a cold that day. Or because I did it too early in the morning—and without breakfast! And it’s always been lower when I do it on a Monday. Should we repeat the test?

The above dialogue typifies a strange paradox of contemporary HIV clinical practice—namely, that we continue to order routine monitoring of CD4 cell counts on stable patients despite not using the results for clinical decision making. The most recent version of Department of Health and Human Services guidelines [2] acknowledges but does not eliminate this paradox, writing:

In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 cell count provides limited information, and frequent testing may cause unnecessary anxiety in patients with clinically inconsequential fluctuations. Thus, for the patient on a suppressive regimen whose CD4 cell count has increased well above the threshold for opportunistic infection risk, the CD4 count can be measured less frequently than the viral load. In such patients, CD4 count may be monitored every 6 to 12 months.

I look at this “every 6 to 12 months” frequency as a gentle way of trying to wean us off a monitoring strategy we have had now since the 1980s. Both patients and providers are so accustomed to regular CD4 monitoring that it seems too difficult to stop doing it cold turkey. But if the data are looked at critically, one could easily make the argument that among these stable HIV patients on treatment, the CD4 cell count need not be measured at all.

The lack of clinical utility of CD4 cell count monitoring is nicely demonstrated in a paper published in this issue of Clinical Infectious Diseases [3]. Evaluating 1820 patients and 25,463 CD4 cell counts collected from 1998 to 2011, investigators from a single Veterans Affairs Medical Center described the likelihood that a patient with virologic suppression and a CD4 count of >200 cells/μL would experience decline in the CD4 cell count to <200 cells/μL despite HIV RNA of <200 copies/mL. This threshold was chosen because this is the value at which prophylaxis for Pneumocystis jirovecii pneumonia (PCP) is indicated.

The results are striking, in particular for patients with a CD4 count of >300 cells/μL who did not have an obvious cause of CD4 lymphopenia (eg, interferon treatment, chemotherapy, corticosteroids). For these individuals, the likelihood that the CD4 would remain >200 cells/μL was 99.2%. In those few who did experience this decline, it occurred relatively early during successful treatment—no patient experienced a CD4 decline to <200 cells/μL after 2 years of suppressive antiretroviral therapy.
The authors appropriately note that their assumption that the CD4 threshold of 200 cells/μL was clinically meaningful probably overestimated the importance of this value in the current treatment era. Indeed, data from a large cohort study showed that the incidence of PCP for patients’ not receiving prophylaxis with CD4 cell counts between 100–200 cells/μL and virologic suppression was 0 cases [95% confidence interval, 0–2.7] per 1000 person-years of follow-up [4]—a rate as low if not lower than those who received PCP prophylaxis in clinical trials.

The most important reason for not measuring CD4 counts routinely in a stable patient is that the results will not influence care, as patients with high CD4 cell counts so rarely dip below clinically meaningful thresholds. But what about for another group, those with poor immunologic response despite virologic suppression? Again, the utility of CD4 monitoring is questionable. Although this group of patients may have a worse prognosis compared to those with robust immunologic recovery [5], no antiretroviral or immune-based strategy has yet to demonstrate a clinically meaningful outcome with treatment modification [6–8]. As a result, treatment guidelines state that "no consensus exists on when or how to treat immunologic failure," and generally treatment should not be changed.

Ironically, laboratory monitoring of HIV treatment in many resource-limited settings typically includes CD4 cell counts and not HIV RNA. This situation arose out of the central role CD4 played—and still plays—in assessing the efficacy of current antiretroviral therapy among untreated patients. Provided that a CD4 cell count is at normal or near-normal levels, a significant proportion of asymptomatic patients with HIV can safely defer therapy in the short term, allowing those with more advanced immunosuppression to be treated. As a result, in locations with limited access to HIV therapy, incorporation of flow cytometry to measure CD4 cell counts enables clinicians to prioritize treatment for those who needed it the most.

Once treatment has begun, however, CD4 is a poor proxy for the effectiveness of treatment, with the high variability of the CD4 response providing unreliable evidence of virologic control [9, 10]. Patients may be erroneously classified as having treatment failure based on CD4 declines that are simply benign variations or, alternatively, be maintained on a failed regimen despite virologic failure as CD4 decreases are often delayed [11, 12]. One recent cost-effectiveness study found that monitoring with HIV RNA alone—and not CD4—was a cost-effective strategy, as this would avoid unnecessary switching to more expensive later lines of therapy [13].

Given that regular CD4 monitoring is so firmly embedded in HIV care, how can we break the habit of sending a test that has little or no clinical utility? I propose the following 3-step program to wean us from this wasteful addiction:

1. HIV treatment guidelines should remove the recommendation for regular CD4 monitoring in clinically stable patients, especially those who already have normal or near-normal CD4 cell counts. One way to soften the blow to providers and patients who are not ready to abandon this test is to consider CD4 cell counts “optional” for those with CD4 counts greater than a certain threshold, for example, 350 or 500 cells/μL.

2. Quality improvement and other programs should acknowledge the primacy of HIV RNA as the definitive (and only) marker of the efficacy of current antiretroviral therapy, no longer considering both CD4 and viral load tests part of a “bundle” of appropriate laboratory monitoring. Our state’s HIV drug assistance program, for example, still requires both tests on its renewal forms, even for those who have been on treatment for years.

3. We need to continue educating our patients about why we are changing our practice. The message should be simple—we no longer need this test to make decisions about your treatment.

On this last point, so far several of my patients have been willing at the very least to reduce their frequency of CD4 monitoring, especially once they hear that the results will have no influence on their management. In fact, many are happy to forego both the cost and the extra tubes of blood!

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