DECISIONS

CD4 measurement in a 54-year-old man with sustained HIV-1 viral suppression

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The clinical scenario is fictional.

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A 54-year-old man with chronic HIV infection returns for a regularly scheduled visit. After his HIV diagnosis six years earlier, he started receiving highly active antiretroviral therapy and rapidly achieved sustained virologic suppression (HIV-1 viral load < 40 copies/mL). For the past four years, his CD4 measurements have been greater than 500 cells/μL. His current CD4 count is 592 cells/μL, reduced from a measurement of 634 cells/μL three months earlier. When informed about the decline in CD4 count, he voices concern and asks about its implications for his health.

What are possible explanations for the decline in this patient's CD4 count?

In stable patients, short-term random variability of CD4 counts is about 14% and is caused by both physiologic and laboratory factors.[1] Beyond random variability, declines in CD4 count may be HIV-related or non–HIV-related. HIV-related causes include virologic failure of antiretroviral therapy, as a result of antiretroviral resistance, nonadherence to therapy or both, resulting in a selective loss of CD4 cells.[2]

Non–HIV-related causes of decline in CD4 count include malignant disease; treatment with chemotherapy, corticosteroids or α-interferon; and acute viral and bacterial infections.[3] The latter causes are usually associated with a reduction in absolute lymphocyte count without a change in CD4:CD8 ratio.[3]

Box 1: Choosing Wisely Canada recommendation by the Association of Medical Microbiology and Infectious Disease Canada[7,8]

Don't routinely repeat CD4 measurements in patients with HIV infection with HIV-1 RNA suppression for > 2 years and CD4 counts > 500/μL, unless virologic failure occurs or intercurrent opportunistic infection develops.

- The 2014 recommendations of the International Antiviral Society — US Panel state that measurement of CD4 count is optional among patients with suppressed viral loads for > 2 years and CD4 counts > 500/μL. CD4 measurement in these patients is of low-value and may create unnecessary patient concern in response to normal variation of CD4 counts. In prospective studies of patients who have responded to antiretroviral therapy with HIV-1 RNA suppression and rises in CD4 cell count > 200 cells/μL, there was little clinical benefit from continued routine measurement of CD4 counts.

Is the decline in this patient's CD4 count clinically important?

A recent meta-analysis of 12 published studies and one unpublished study that included 20 297 virologically suppressed patients with HIV infection showed that only 0.4% (95% confidence interval 0.2%–0.6%) of patients experienced a decline in CD4 count to less than 200 cells/μL over durations of follow-up that ranged from 8 to 120 months.[2] This is the threshold below which prophylaxis against *Pneumocystis jiroveci* pneumonia would be indicated.[4]

Additionally, a retrospective cohort study involving 1820 patients with 25 463 paired viral load–CD4 measurements showed that patients who maintained virologic suppression (< 200 copies/mL) had a 97.1% probability of maintaining a CD4 count of 200 cells/μL or greater for four years.[5] When non–HIV-related causes of decline in CD4 count were excluded, this probability increased to 99.2%.[5] Therefore, the decline in this patient's CD4 count is likely of no immediate or long-term clinical importance.

What monitoring is required for this patient?

The International Antiviral Society — USA Panel and the US Department of Health and Human Services state that repeat measurement of CD4 count is optional in patients with virologic suppression and CD4 counts greater than 500 cells/μL for more than two years, unless intercurrent opportunistic infection develops or the patient starts receiving medications that may result in a reduction in CD4 count.[3,6] These recommendations and their supporting evidence led to the adoption of a Choosing Wisely Canada statement by the Association of Medical Microbiology and Infectious Disease Canada in favour of not routinely ordering CD4 counts in patients with suppressed viral loads and CD4 counts

greater than 500 cells/μL for more than two years (Box 1).[7,8]

In virologically suppressed patients with CD4 counts of 300–500 cells/μL for two years or more, the US Department of Health and Human Services recommends CD4 monitoring every 12 months.[3] For patients with virologic suppression and CD4 counts of less than 300 cells/μL, monitoring should occur every three to six months to determine the need for initiation or discontinuation of prophylactic therapies.[3,6] In all patients, laboratory monitoring for antiretroviral toxicity should be performed every three to six months and should be guided by the presence of comorbidities and the specific components of the antiretroviral regimen.[6]

What is the impact of discontinuing routine CD4 measurement for this patient?

At the level of the individual patient, a reduction in frequency or cessation of routine CD4 monitoring may reduce anxiety arising from random fluctuations in CD4 count that rarely result in changes in clinical management. Even a small reduction in CD4 count often requires substantial reassurance of the patient on the part of the physician.[9] Given the low probability of clinical events in patients with sustained virologic suppression and CD4 counts greater than 500 cells/μL, frequent monitoring of CD4 counts represents low-value care.[9] At a health-systems level, reduction in CD4 measurement from every 6 to 12 months in these patients in the United States was predicted to result in annual savings of more than $10 million.[10] In practices where CD4 counts are measured every three months, even greater savings could be realized.

Motivation to adhere to antiretroviral therapy for some patients may be derived from the positive reinforcement gained from knowledge of their CD4 counts. In implementing this Choosing Wisely Canada recommendation, physicians should redirect patients to the importance of sustained virologic suppression with antiretroviral therapy, which is associated with improvements in survival and quality of life.[3]

The case revisited

The patient and his provider had a discussion about the decline in his CD4 count. His physician reassured him that the most likely cause of the decline is random variation and that it would likely be of no clinical importance to him.[1] They also discussed the recommendation that routine CD4 measurement was no longer needed to make decisions about his HIV care. They agreed to stop routine CD4 measurement[3,6–8] and to focus on the importance of sustained virologic suppression.[3] Follow-up was arranged for ongoing clinical assessment and measurement of his HIV-1 viral load in six months.

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