Is Frequent CD4^{+} T-Lymphocyte Count Monitoring Necessary for Persons With Counts ≥300 Cells/µL and HIV-1 Suppression?

Howard B. Gale,[1] Steven R. Gitterman,[1] Heather J. Hoffman,[2] Fred M. Gordin,[1,3] Debra A. Benator,[1,3] Ann M. Labriola,[1,3] and Virginia L. Kan[1,3]

[1]Infectious Diseases Section, Medical Service, Veterans Affairs Medical Center, [2]Department of Epidemiology and Biostatistics, and [3]Division of Infectious Diseases, The George Washington University, Washington, District of Columbia

(See the Editorial Commentary by Sax on pages 1344–6.)

Among patients infected with human immunodeficiency virus (HIV), those with HIV-1 RNA <200 copies/mL and CD4 counts ≥300 cells/µL had a 97.1% probability of maintaining durable CD4 ≥200 cells/µL for 4 years. When non-HIV causes of CD4 lymphopenia were excluded, the probability rose to 99.2%. Our data support less frequent CD4 monitoring during viral suppression.

Keywords. CD4 count; %CD4; HIV-1 RNA; HIV load; HIV suppression.

CD4 counts (CD4) have proven essential for the clinical management of patients infected with human immunodeficiency virus (HIV) [1]. Current guidelines of the Department of Health and Human Services [2] recommend 6- to 12-month CD4 testing in clinically stable, virally suppressed patients with counts "well above the threshold for opportunistic infection risk" [3]. As this recommendation was based on expert opinion, our objective was to examine the incidence over time of CD4 counts <200 cells/µL among patients with viral suppression of <200 copies/mL and a CD4 count of ≥200 cells/µL.

Received 20 September 2012; accepted 19 November 2012; electronically published 11 January 2013.

Presented in part: XIX International AIDS Conference, Washington, DC, 22–27 July 2012. Abstract WEPDB0101.

Correspondence: Howard Gale, Infectious Diseases Laboratory (151B), Room GE 231, Veterans Affairs Medical Center, 50 Irving St NW, Washington, DC 20422 (howard.gale@va.gov).

Clinical Infectious Diseases 2013;56(9):1340–3
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2013.
DOI: 10.1093/cid/cit004

METHODS

We evaluated every paired HIV type 1 (HIV-1) viral load (VL) and CD4 count (n = 25 463) performed by the Infectious Diseases Laboratory for 1820 patients at the Washington, DC, Veterans Affairs Medical Center from September 1998 through December 2011 by adopting the following 2 definitions. First, a patient sequence *w*as defined as a period of continuous HIV-1 suppression. Sequence initiation required at least 2 consecutive VL/CD4 pairs with (1) VL <200 copies/mL, and (2) CD4 ≥200 cells/µL, and (3) CD4 percentage (%CD4) ≥14%, and (4) ≤390 days between the consecutive tests, and (5) a subsequent VL/CD4 pair within 390 days. Sequence termination and time of sequence termination occurred at the VL/CD4 pair (1) with a CD4 count <200 cells/µL, or (2) just prior to a VL ≥200 copies/mL, or (3) preceding a >390-day gap in testing or (4) preceding the end of the observation period. A patient could generate >1 sequence if the initiation criteria were met again following termination of the prior sequence. Secondly, a "CD4 dip" was defined as a CD4 count <200 cells/µL occurring during a period of continuous HIV-1 suppression of <200 copies/mL (ie, during a sequence).

Patients with 1 or more sequences were included in the analysis cohort, stratified by initial CD4 ranges of 200–249, 250–299, 300–349, and ≥350 cells/µL. The data was evaluated to characterize both the VL/CD4 results from individual sequences (sequence-based analyses) and from individual patients (patient-based analyses). For patient-based analyses, the initial CD4 was defined as the first value of each patient's first sequence. For any patient who experienced a CD4 dip, we performed a chart review, focusing on known causes for non-HIV CD4 lymphopenia [2, 4, 5] present since the patient's last VL/CD4 values were obtained prior to the CD4 dip.

We examined the probability of maintaining a CD4 ≥200 cells/µL during continuous viral suppression for the patient-based analysis using only the first sequence of each patient. Probabilities with corresponding 95% confidence intervals (CIs) stratified by initial CD4 ranges were estimated and plotted using the Kaplan-Meier method. CD4 dip-related hazard ratios with corresponding 95% confidence intervals were estimated and compared using Cox proportional hazards regression. As sequences were clustered by patients, CD4 dip times of sequences were analyzed using modified forms of the Kaplan-Meier [6] and Cox [7] methods that account for the intracluster dependence.

Downloaded from https://academic.oup.com/cid/article/56/9/1340/292905 by guest on 16 August 2022

Data were analyzed by SAS, version 9.2 (SAS Institute, Cary, North Carolina) and SAS-callable SUDAAN, version 10.0 (RTI International, Research Triangle Park, North Carolina). The SAS macro for determining sequences is provided in the Supplementary Data.

RESULTS

A total of 1358 patients had 3 or more paired VL/CD4 values with no more than 390 days between consecutive results over the 13-year observation period; 526 did not meet the criteria for a sequence to enter the analysis cohort. Of the remaining 832 individuals, 537 generated 1 sequence, and 295 generated 2–6 sequences for a total of 1294 sequences. For all 832 patients in the analysis cohort, the median period of VL/CD4 testing was 7.7 years (interquartile range [IQR], 3.9–11.9). The median of the total sequence time per patient was 2.5 years (IQR, 1.1–5.2), including those patients with multiple sequences. The median gap between each patient's VL/CD4 testing was 113 days (IQR, 96–138).

Ninety-three percent (771/832) of individuals with at least 1 sequence maintained their CD4 ≥200 cells/µL during periods of viral suppression; the remaining 61 patients experienced a total of 84 CD4 dips <200 cells/µL (1–4 dips per patient) with 52 occurring during their first sequence. Twenty-four of the 61 patients had a cause for non-HIV CD4 lymphopenia [2, 4, 5] that occurred in conjunction with their earliest CD4 dip. Chart reviews identified 9 radiation/chemotherapy, 7 interferon treatment, 3 postsurgery, 3 concomitant severe infection, 1 viral pneumonia, and 1 steroid treatment. All were documented within 1 month prior to the CD4 dip event.

As shown in Supplementary Tables 1 and 2, CD4 characteristics were similar between patient-based and sequence-based analyses. When analyzed by patient, 25% of individuals with an initial CD4 count of 200–249 cells/µL had a CD4 dip to <200 cells/µL, and the numbers decreased successively to 16% at 250–299 cells/µL, 5% at 300–349 cells/µL, and only 2% at ≥350 cells/µL (Supplementary Table 1). The higher the initial CD4, the greater the likelihood that a patient with a CD4 dip would also have a non-HIV cause for CD4 lymphopenia identified. In addition, when the initial CD4 was ≥300 cells/µL, the risk of a dip was significantly lower ($P < .05$ by Cox proportional hazards regression, Supplementary Table 3). An analysis using the %CD4 threshold of 14% provided similar results (Supplementary Table 2).

The Kaplan-Meier probabilities of maintaining a CD4 count ≥200 cells/µL during continuous HIV-1 suppression were similar whether analyzed by patient (Figure 1*A* and Supplementary Figure 1*A*) or by sequence (Supplementary Figure 2). For patients with an initial CD4 count of 300–349 cells/µL, the probability of a durable CD4 ≥200 cells/µL at year 4 was 95.3% (95% CI, 86.1–98.5; Figure 1*A*, Supplementary Figure 1*A*). When the initial CD4 was ≥350 cells/µL, the probability at year 4 was 97.5% (95% CI, 94.7–98.8). Combining the Kaplan-Meier data for 300–349 and ≥350 cells/µL, when the initial CD4 was ≥300 cells/µL, the probability at year 4 was 97.1% (95% CI, 94.6–98.5). In addition, no patient experienced an event (CD4 dip) after year 4 in any group.

In Figure 1*B* and Supplementary Figure 1*B*, the probabilities and 95% CIs shown are upper bounds because chart reviews for non-HIV causes of CD4 lymphopenia were performed only for patients with CD4 dips. When data from 18 patients with CD4 lymphopenia due to non-HIV causes were excluded, patients with an initial CD4 ≥300 cells/µL had a probability of a durable CD4 ≥200 cells/µL at year 5 of 99.2% (95% CI, 97.4–99.7). No patient experienced an event (CD4 dip) after year 2 in any group.

DISCUSSION

Multiple sources of CD4 count variability have been described, including intralaboratory measurements and individual patient physiologic factors [8, 9]. We found that 24% (201/832) of patients in the initial range of 200–299 cells/µL accounted for a disproportionate 70% (43/61) of all patients with CD4 dips. A subsequent examination of individual regression curves for patients who had a dip but remained virally suppressed (data not shown) confirmed that some patients had steady CD4 count increases after the dip endpoint was reached, suggesting CD4 variability as the primary cause for the dip. Importantly, there have been many reports regarding the undulating rise of CD4 in response to effective treatment [10, 11], and this rise may explain why no patient experienced a CD4 dip after year 2 of continuous viral suppression without a non-HIV cause for CD4 lymphopenia.

Our study had several limitations. This was a retrospective evaluation from a single, urban medical center. Chart reviews were restricted to the 61 patients with CD4 dips and were not performed for patients whose CD4 remained ≥200 cells/µL. No assessment was made of a patient's antiretroviral therapy or adherence.

Despite these limitations, we believe our conclusions to be robust. This study included our entire clinic population without any patients excluded. Although chart reviews were limited to the 61 patients with CD4 dips, the findings from other patients without CD4 dips would not have impacted our conclusions as CD4 counts for these patients remained ≥200 cells/µL. Finally, the use of a CD4 count of <200 cells/µL as the Kaplan-Meier endpoint for an increase in clinical risk rather than an actual opportunistic infection overestimated true clinical risk, as most opportunistic infections occur at much lower CD4, particularly

Downloaded from https://academic.oup.com/cid/article/56/9/1340/292905 by guest on 16 August 2022

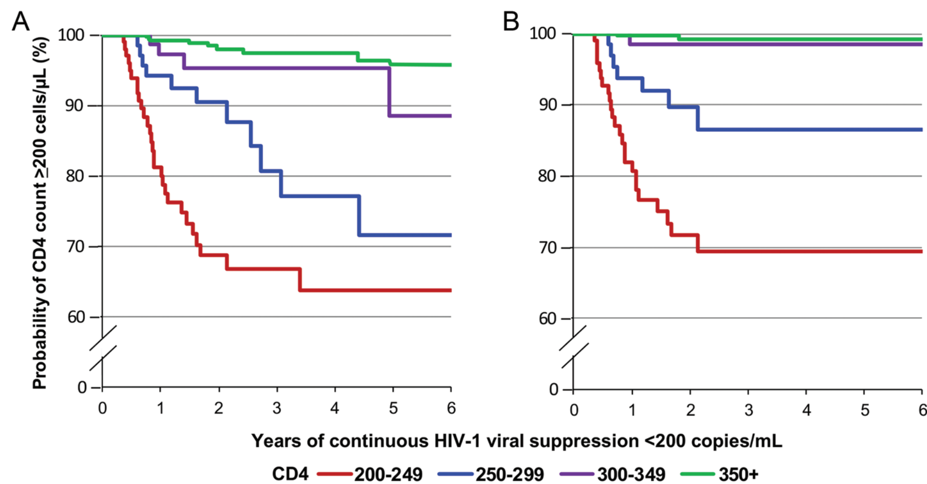

Figure 1. Patient-based Kaplan-Meier estimates (SAS, version 9.2) of probability for maintaining CD4 counts ≥200 cells/µL during continuous human immunodeficiency virus (HIV) type 1 suppression of <200 copies/mL. Results are stratified by initial CD4 count in cells per microliter. Analysis restricted to first sequence of each patient with 9 patients excluded because they only experienced CD4 counts <200 cells/µL during later sequences. *A*, Fifty-two patients experienced events or CD4 dips, defined as CD4 counts <200 cells/µL occurring during viral suppression. Median first sequence duration, 1.5 years (interquartile range; 0.7–3.2). Data right-censored 326 times when viral load rebounded to ≥200 copies/mL, 165 times when repeat testing not performed within 390 days, and 280 times when observation period ended 31 December 2011. *B*, Following exclusion of 18 patients with causes for non-HIV CD4 lymphopenia, 34 patients experienced CD4 dips. Probabilities are upper bounds because only patients who experienced CD4 dips had chart reviews. Abbreviation: HIV-1, human immunodeficiency virus type 1.

during viral suppression [12]. Therefore, we believe that our results can be generalized to most HIV care settings.

Reduced CD4 monitoring would provide a substantial cost savings and a broad impact on HIV clinical care. For example, 55% (approximately 550) of our patients had both viral suppression <200 copies/mL and CD4 ≥ 300 cells/µL at the end of our observation period. If these patients were monitored only annually, >$41 000 would be saved by eliminating 1100 CD4 counts at $37.92 per test based on the 2012 Medicare fee schedule. Another benefit would be the alleviation of patient anxiety from fluctuations in serial CD4 [2] due to laboratory and physiologic variability [8, 9]. We have found broad acceptance from patients when recommending reduced CD4 testing, allowing resources currently used for CD4 monitoring to be redirected to other clinical needs.

In conclusion, HIV-infected patients who maintained viral suppression <200 copies/mL and had CD4 counts ≥300 cells/µL were highly unlikely to experience a CD4 count <200 cells/µL. Our data support less frequent CD4 monitoring in clinically stable, virally suppressed patients and suggest that routine CD4 monitoring for this population may be unnecessary.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank the staff of the Infectious Diseases Clinic and our clinicians for their dedication to the human immunodeficiency virus (HIV) care of our patients, and Karen Rexroth and Rebecca Shinol for their performance of CD4 counts and HIV-1 RNA in the Infectious Diseases Laboratory.

This work was exempt from institutional review board approval and was reviewed by the research and development committee at this VA Medical Center. The views expressed are those of the authors and do not reflect the views or policies of the Department of Veterans Affairs.

Financial support. Statistical support for our work was provided by the District of Columbia Developmental Center for AIDS Research (P30AI087714/NIAID/NIH).

Potential conflicts of interest. All authors: No potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Egger M, May M, Chêne G, et al. ART Cohort Collaboration. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet **2002**; 360:119–29.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services **2012**. Available at: http://www.aidsinfo.nih.gov/guidelines/. Accessed 13 September 2012.
3. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases

Downloaded from https://academic.oup.com/cid/article/56/9/1340/292905 by guest on 16 August 2022

Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep **2009**; 58(RR-4):1–207.

4. Leukocyte differential count: diagnostic information and inferences. Lymphocytic series. In: Wu A, ed. Tietz clinical guide to laboratory tests. Philadelphia: W. B. Saunders Company, **2006**: 1194–5.
5. Feeney C, Bryzman S, Kong L, Brazil H, Deutsch R, Fritz LC. T-lymphocyte subsets in acute illness. Crit Care Med **1995**; 23:1680–5.
6. Williams RL. Product-limit survival functions with correlated survival times. Lifetime Data Anal **1995**; 1: 171–86.
7. Lee EW, Wei LJ, Amato DA. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein JP, Goel PK, ed. Survival analysis: state of the art. Dordrecht: Kluwer Academic Publishers, **1992**: 237–47.
8. Raboud JM, Haley L, Montaner JS, Murphy C, Januszewska M, Schechter MT. Quantification of the variation due to laboratory and physiologic sources in CD4 lymphocyte counts of clinically stable HIV-infected individuals. J Acquir Immune Defic Syndr Hum Retrovirol **1995**; 10:S67–73.
9. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr **1990**; 3:144–51.
10. Trotta MP, Cozzi-Lepri A, Ammassari A, et al; ICONA Foundation Study. Rate of CD4+ cell count increase over periods of viral load suppression: relationship with the number of previous virological failures. Clin Infect Dis **2010**; 51:456–64.
11. Maggiolo F, Leone S. CD4+ T lymphocyte recovery in individuals with type 1 human immunodeficiency virus infection. Clin Infect Dis **2010**; 51:465–7.
12. The Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE). Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/μL? Clin Infect Dis **2010**; 51: 611–9.

Downloaded from https://academic.oup.com/cid/article/56/9/1340/292905 by guest on 16 August 2022