Original Article

Routine CD4 monitoring in HIV patients with viral suppression: Is it really necessary? A Portuguese cohort

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Raquel Duro*, Nuno Rocha-Pereira, Cristovão Figueiredo, Carmela Piñeiro, Cátia Caldas, Rosário Serrão, António Sarmento

Infectious Diseases Department, Centro Hospitalar de São João and Faculdade de Medicina da Universidade do Porto, Alameda Professor Hernâni Monteiro, 4200-319, Porto, Portugal

Abstract *Purpose:* CD4 cell-count has been regarded as the key surrogate marker for prognostic staging and therapeutic monitoring of HIV-infected individuals. Our purpose was to assess the probability of maintaining a CD4 count >200 cells/μL in patients with continuous viral suppression and CD4 cell counts >200 cells/μL.
Methods: Retrospective cohort study of HIV-infected patients, treatment naïve, who started antiretroviral therapy between 2007 and 2011. We estimated the probability of maintaining CD4 counts >200 cells/μL during continuous viral suppression using the Kaplan—Meier method. The hazard ratios of a CD4 count <200 cells/μL were estimated and compared using Cox proportional hazards regression.
Results: 401 patients were included: 70.1% men; median age 37 years; 98.8% HIV-1 infected. The median duration of continuous viral suppression with CD4 counts >200 cells/μL was 40.5 months. Ninety-three percent of patients maintained CD4 counts $\geq$200 cells/μL during the period of continuous viral suppression. Compared with those with an initial CD4 count $\geq$350 cells/μL, patients with initial CD4 count <300 cells/μL had a significantly higher risk of a CD4 count <200 cells/μL. Patients with viral suppression and CD4 counts $\geq$350 cells/μL had a 97.1% probability of maintaining CD4 cell counts $\geq$200 cells/μL for 48 months.
Conclusions: The probability of a CD4 count <200 cells/μL in an HIV-infected patient with viral suppression and CD4 $\geq$350 cells/μL was very low. These data suggests less frequent monitoring of CD4 counts in these patients.

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* Corresponding author. Rua Académico Futebol Clube, nº 81 2º Esq, 4200-602, Porto, Portugal.
E-mail address: raquel.duro@gmail.com (R. Duro).

Introduction

First described as a new clinical entity in 1981,[1] the Acquired Immune Deficiency Syndrome (AIDS) was later attributed to infection with the human immunodeficiency virus (HIV).[2]

Our understanding of this disease has expanded significantly over the last decades. Following its natural course, HIV infection leads to severe depletion of CD4 T cells in the gut-associated lymphoid tissue with subsequent reduced levels of circulating CD4 lymphocytes in the peripheral blood.[3] The CD4 cell count (which normally varies between 500 and 1400 cells/μL[4]) reflects the level of immune suppression. As the CD4 cell count falls below normal, and particularly once thresholds of 200 cells/μL or a CD4 percentage of 14% are reached, the risk of opportunistic infection rises.[5]

Hence, CD4 cell count has been regarded as the key surrogate marker for prognostic staging and therapeutic monitoring of HIV-infected individuals and has had considerable value for both clinicians and people living with HIV.[6,7] Currently, absolute CD4 cell counts are regularly used as a surrogate for the risk of developing opportunistic infections and as an endpoint in HIV randomized controlled trials. Current guidelines advocates the initiation of ART, regardless of CD4 cell count.[5,8,9]

However, viral load monitoring has become more accessible in many countries and a key instrument in monitoring therapeutic success; in this setting, the role of CD4 monitoring has been recently questioned. Current guidelines[5,9] recommend 3—6 month CD4 monitoring in HIV-infected patients, but advise to consider less frequent evaluation for clinically stable, virally suppressed patients with high CD4 cell counts.

Contrary to viral load monitoring, CD4 cell count has a low sensitivity and specificity to detect virological failure or the emergence of drug resistance during antiretroviral therapy.[10,11] Recent studies (including a meta-analysis) have debated whether there is a benefit of continued monitoring of CD4 cell counts in patients with both high CD4 cell counts and sustained viral suppression.[12—16] Cessation of CD4 monitoring would, on one hand, avoid misinterpretations of random fluctuations in CD4 cell counts and, on the other hand, allow substantial cost-savings.[17]

Our purpose with this study was to assess the probability of maintaining a CD4 cell count over 200 cells/μL in patients with continuous viral suppression and CD4 cell counts above 200 cells/μL.

Methods

We designed a retrospective cohort study of all HIV-infected patients, treatment naïve, who started antiretroviral therapy between 2007 and 2011 in the Department of Infectious Diseases at Centro Hospitalar de São João (Porto, Portugal).

Of these patients, we included those in which a period of continuous viral suppression (defined as at least two consecutive viral loads $\leq$200 copies/mL) and CD4 counts >200 cells/μL (at the time of the viral loads measurements) was identified. The date of the first measurement was set as the beginning of the period of continuous viral suppression. This period ended when: 1) the CD4 count was <200 cells/μL, 2) prior to a viral load >200 copies/mL or 3) at the end of the observation period (31st December 2013). A 'CD4 dip' was defined as a CD4 cell count <200 cells/μL occurring during the period of continuous viral suppression.

Patients were stratified by initial CD4 ranges of 200—249, 250—299, 300—349, and $\geq$350 cells/μL. For any patient who experienced a CD4 dip, we performed a chart review, focusing on known causes for non-HIV CD4 lymphopenia.

The protocol was submitted to the Ethics Committee for Health of our hospital and an approval was obtained (Ethics Reference No: 40/2016).

We estimated the probability (with corresponding 95% confidence intervals — CI) of maintaining a CD4 count $\geq$200 cells/μL during continuous viral suppression, stratified by initial CD4 ranges, using the Kaplan—Meier method. CD4 dip-related hazard (with corresponding 95% CI) were estimated and compared using Cox proportional hazards regression. Comparisons between continuous variables were performed with the Mann—Whitney U test.

Data were analyzed with SPSS®22.0 and GraphPad®5. The results were considered statistically significant when $p < 0.05$.

Results

Of the 544 patients that started antiretroviral therapy between 2007 and 2012, 401 met the criteria for inclusion in this analyses. The median age was 37 years (IQR 17.5) and 281 (70.1%) were male; 396 (98.8%) were infected with HIV-1. At the time of antiretroviral therapy prescription, 161 (40.2%) had a CD4 count <200 cells/μL and the median viral load was 104,000 copies/mL (IQR 271800). The median duration of continuous viral suppression (with CD4 counts $\geq$200 cells/μL) was 40.5 months (IQR 28).

Ninety-three percent (373/401) of patients maintained their CD4 counts $\geq$200 cells/μL during the period of continuous viral suppression. The occurrence of a CD4 dip was more frequent in patients with lower CD4 cell counts at the beginning of the period of continuous viral suppression: 15.7% of the patients with an initial CD4 count of 200—249 cells/μL had a CD4 dip, compared do 2.6% in those with $\geq$350 cells/μL (Table 1). Compared with patients that maintained CD4 counts $\geq$200 cells/μL, those with a CD4 dip presented with lower CD4 cell counts at diagnosis (146 cells/μL versus 232 cells/μL, p = 0.017) and at the beginning of the period of continuous viral suppression (249 cells/μL versus 349 cells/μL, p < 0.001). Compared with those with an initial CD4 count $\geq$350 cells/μL, patients with initial CD4 count <300 cells/μL had a significantly higher risk of a CD4 dip (CD4 200—249: HR 6.7, 95% CI 2.4—18.7, p < 0.001; CD4 250—300: HR 4.1. 95% CI 1.2—13.3, p = 0.02).

The majority of the events observed (71.4%) occurred in the within 24 months of follow-up. Of the 28 patients that presented a CD4 dip, 17 (60.7%) had a plausible alternative for non-HIV CD4 lymphopenia that occurred within one month of the observed dip. Chart reviews identified 5 interferon based hepatitis C treatment, 3 concomitant

Table 1 Distribution of patients during follow-up period, stratified by CD4 cell counts at the beginning of the sequence.

	CD4 Count Range at the beginning of the period of viral suppression [Cells/μL, n (%)]				
	Total	200—249	250—299	300—349	≥350
N	401	89	62	59	191
CD4 count maintained at ≥200 cells/μL	373 (93.0%)	75 (84.3%)	56 (90.3%)	56 (94.9%)	186 (97.4%)
CD4 dip occurred	28 (7.0%)	14 (15.7%)	6 (9.7%)	3 (5.1%)	5 (2.6%)
Without a cause other than HIV-infection	11	8	3	0	0
With a cause other than HIV related	17	6	3	3	5

severe infection, 2 intravenous drug use, 2 chemotherapy treatments, 2 radiotherapy treatments, 1 lymphoma, 1 renal transplantation and 1 treatment with infliximab. All patients that presented a CD4 dip with an initial CD4 count >300 cells/μL had a non HIV-related cause for the CD4 lymphopenia. In the follow-up of the 11 patients with a CD4 dip without a cause other than HIV-infection, only two maintained their CD4 count <200 cells/μL in the next measurement; both of them presented with an initial CD4 count <250 cells/μL.

Kaplan—Meier plots of the probability of maintaining CD4 counts ≥200 cells/μL during continuous viral suppression are shown in Fig. 1. For patients with an initial CD4 count of 300—349 cells/μL, the probability of maintaining CD4 counts ≥200 cells/μL at 48 months was 93.5% (95% CI, 81.3—97.9); when the initial count was ≥350 cells/μL, this probability was 97.1% (95%CI, 93.2—98.8) (Fig. 1A).

The same plots were performed after excluding data from the 17 patients with CD4 lymphopenia due to non-HIV causes (Fig. 1B). There was no CD4 dip observed in patients with an initial CD4 count ≥300 cells/μL. After 24 months of continuous viral suppression, no patient experienced a CD4 dip in any group.

Discussion

In accordance with current guidelines, both viral load and CD4 cell counts are monitored in patients with antiretroviral therapy in high-income settings, at least every 6—12 months.[9] Viral load monitoring is the preferred approach to access treatment efficacy and detect adherence problems.[7] The added value of CD4 cell count monitoring in patients with continuous viral suppression has been recently questioned.

In this study, we assessed the probability of maintaining a CD4 count over 200 cells/μL during continuous viral suppression. Our results are in agreement with recent published papers[12—16]: we have found that the probability of a CD4 count <200 cells/μL in an HIV-infected patient with continuous viral suppression and CD4 counts ≥300 cells/μL was very low. All patients with CD4 counts >300 cells/μL
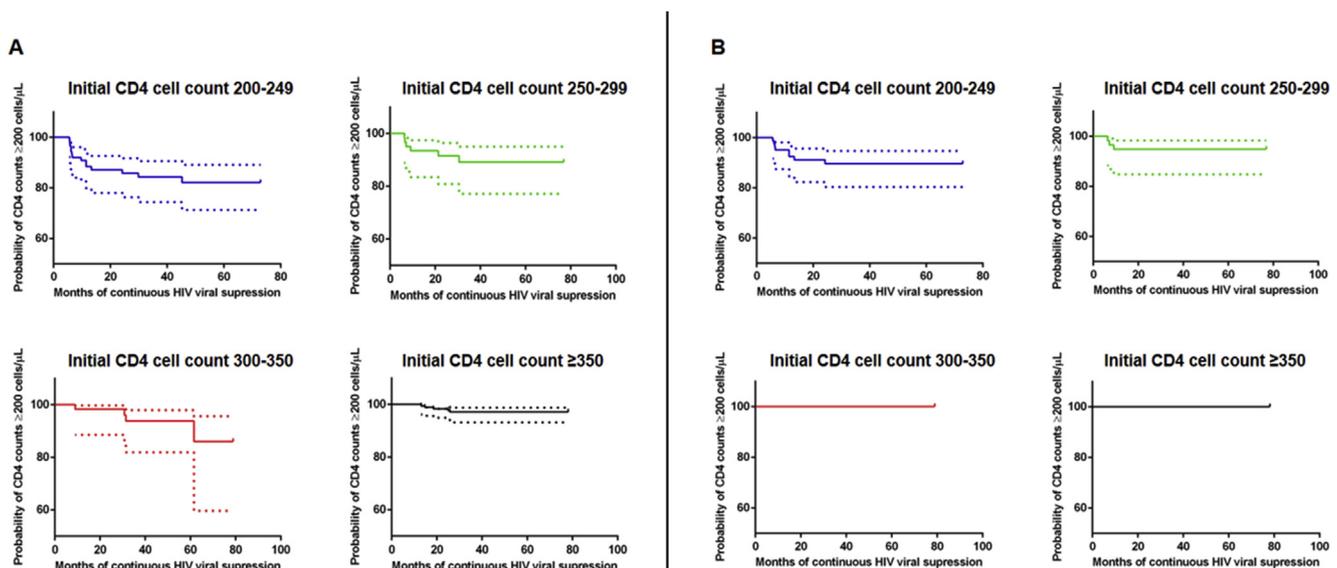
Figure 1. Kaplan—Meier estimates of the probability for maintaining CD4 counts ≥200 cells/μL during continuous HIV suppression (<200 copies/mL). Results are stratified by initial CD4 count in cells per microliter. **A** — All patients included in the analysis; **B** — Following exclusion of 17 patients with non-HIV causes for CD4 lymphopenia, 11 patients experienced CD4 dips. **Legend:** probability, solid line; 95% confidence limits, dashed lines.

and continuous viral suppression maintained CD4 count >200 cells/μL during the follow-up period (after exclusion of those with a non-HIV cause for CD4 lymphopenia).

A number of factors other than HIV infection influence CD4 cell counts.[4] Significant changes in the total white cell count can lead to marked changes in the absolute CD4 cell count. Certain medications or infections associated with leukopenia may result in depression of the absolute CD4 cell count. In contrast, specific medications or infections which lead to leucocytosis can result in elevated CD4 cell count. In our study, we found that 60.7% of patients that experienced a CD4 dip had an identifiable non-HIV cause for CD4 lymphopenia, making it predictable.

Of the 11 patients that presented a CD4 dip with no cause identified other than HIV-infection, 9 had CD4 counts >200 cells/μL in the next measurement and all experienced the event during the first 24 months of follow-up. Intra-laboratory measurements and individual patient physiologic factors also influence CD4 cell counts,[18] and probably explain the variability observed in these patients, hence the importance of considering CD4 percentage as well.

Our study has several limitations. It was a retrospective study of a single medical centre. Chart reviews were only performed in those that presented a CD4 dip (although review of the remaining charts is not expected to impact the results as these patients maintained CD4 counts >200 cells/μL). No assessment was made of the patient's antiretroviral therapy or adherence; the total white blood cell count and the proportion of CD4/CD8 cells were also not analyzed. Even so, it was a study performed in the real word context, outside of clinical trials, with a median time of follow-up over three years. The use of a CD4 count of <200 cells/μL as the Kaplan—Meier endpoint for an increase in clinical risk (opposed to an opportunistic infection) overestimates true clinical risk, as most opportunistic infections occur at much lower CD4 counts (≤100 cells/μL), particularly during viral suppression.[19,20]

Reduced CD4 monitoring would allow considerable cost savings and a broad impact on HIV clinical care,[21] with rational re-allocation of resources to areas in need. Another potential benefit would be the alleviation of patient's anxiety from fluctuations in serial CD4 counts due to laboratory and physiologic variability.[9] However, this represents a change in the paradigm of HIV-infection monitoring that needs to be properly addressed with patients in order to reduce unnecessary concern from not knowing CD4 cell counts.

Along with other published reports,[12–16] our data strongly supports less frequent CD4 monitoring in patients with viral suppression and high CD4 counts, and suggests that viral load monitoring is sufficient in these patients. In such patients, the risk of sustained CD4 count decline to lower levels was very low. This recent evidence may inform future guidelines. Continued viral suppression could be used as an alternative surrogate marker for adequate immunologic performance.

References

1. Centers for Disease Control. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. *MMWR : Morb Mortal Wkly Rep* 1981;**30**(25):305—8.

2. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983;**220**(4599):868—71.

3. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* 2004;**200**(6):749—59.

4. Laurence J. T-cell subsets in health, infectious disease, and idiopathic CD4+ T lymphocytopenia. *Ann Intern Med* 1993;**119**(1):55—62.

5. European AIDS Clinical Society. *Guidelines for the clinical management of HIV infected adults in Europe, version 8.0*. 2016. http://eacsociety.org [accessed 17.08.16].

6. Taylor JM, Fahey JL, Detels R, Giorgi JV. CD4 percentage, CD4 number, and CD4:CD8 ratio in HIV infection: which to choose and how to use. *J Acquir Immune Defic Syndr* 1989;**2**(2):114—24.

7. World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach*. 2nd ed. Switzerland: WHO Press; 2016.

8. Fahey JL, Taylor JM, Detels R, Hofmann B, Melmed R, Nishanian P, et al. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1. *N Engl J Med* 1990;**322**(3):166—72.

9. 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 Service; 2016.

10. Mee P, Fielding KL, Charalambous S, Churchyard GJ, Grant AD. Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa. *AIDS* 2008;**22**(15):1971—7.

11. Reynolds SJ, Nakigozi G, Newell K, Ndyanabo A, Galiwongo R, Boaz I, et al. Failure of immunologic criteria to appropriately identify antiretroviral treatment failure in Uganda. *AIDS* 2009;**23**(6):697—700.

12. Stephan C, Hill A, Xi N, van Delft Y, Moecklinghoff C. Research letter: is monitoring for CD4 counts still needed for the management of patients with long-term HIV RNA suppression? *J Acquir Immune Defic Syndr* 2012;**61**(5):e73—75.

13. Gale HB, Gitterman SR, Hoffman HJ, Gordin FM, Benator DA, Labriola AM, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts >=300 cells/muL and HIV-1 suppression? *Clin Infect Dis* 2013;**56**(9):1340—3.

14. Girard PM, Nelson M, Mohammed P, Hill A, van Delft Y, Moecklinghoff C. Can we stop CD4+ testing in patients with HIV-1 RNA suppression on antiretroviral treatment? *AIDS* 2013;**27**(17):2759—63.

15. Phillips AN, Youle M, Lampe F, Sabin CA, Hill A, Ransom D, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/ml on antiretroviral therapy. *AIDS* 2002;**16**(7):1073—5.

16. Ford N, Stinson K, Gale H, Mills EJ, Stevens W, Gonzalez MP, et al. CD4 changes among virologically suppressed patients on antiretroviral therapy: a systematic review and meta-analysis. *J Int AIDS Soc* 2015;**18**(1):20061.

17. Gazzard B, Moecklinghoff C, Hill A. New strategies for lowering the costs of antiretroviral treatment and care for people with HIV/AIDS in the United Kingdom. *Clin Outcomes Res* 2012;**4**:193—200.

18. 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**(Suppl 2):S67—73.

19. Mocroft A, Reiss P, Kirk O, Mussini C, Girardi E, Morlat P, et al. Is it safe to discontinue primary Pneumocystis jiroveci

pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis* 2010;**51**(5):611—9.

20. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.

21. Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. *JAMA Intern Med* 2013;**173**(18):1746—8.