Is CD4 Monitoring Needed Among Ugandan Clients Achieving a Virologic and Immunologic Response to Treatment?

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Abstract

It is unclear whether ongoing CD4 monitoring is needed following immunologic and virologic response to antiretroviral therapy (ART). We investigated the proportion of clients who achieved a virologic and immunologic response and then had a subsequent CD4 count < 200 cells/ μ L despite continued virologic suppression. Included in this analysis were clients receiving ART through the Rakai Health Sciences Program between June 2004–May 2013 who achieved a CD4 ≥ 200 cells/ μ L and VL ≤ 400 copies/mL and who had three sets of CD4 and VL measurements (defined as a *sequence*) within a 390 day period. A CD4 decline was defined as any drop in CD4 count to < 200 cells/ μ L during a period of viral suppression. A total of 1553 clients were included, 68% females, mean age of 35.5 years (SD 8.3), median baseline CD4 count 183 cells/ μ L (IQR 106–224). 43 (2.8%) clients developed CD4 declines, the majority, 32/43 (74%), among individuals whose initial CD4 was < 300 cells/ μ L. Of the 43 clients with CD4 declines, 24 had an additional CD4 measurement and 20/24 (83%) achieved a CD4 ≥ 200 cell/ μ L on their next measurement (median 285 cells/ μ L; IQR 220–365). CD4 declines were significantly greater among those with lower CD4 at sequence initiation [adjusted hazard ratio (AHR) 4.3 (95% CI 2.1, 9.0) CD4 200–249 versus ≥ 350 cells/ μ L]. Clients who achieved an immunologic and virologic response to ART were unlikely to experience a subsequent CD4 count decline to < 200 cells/ μ L, and among those experiencing a decline, the majority were transient in nature. Thus, ongoing CD4 monitoring could be omitted.

Introduction

ROUTINE VIRAL LOAD (VL) MONITORING has been shown to facilitate early identification of treatment failure, reducing the risk of genotypic resistance and of morbidity associated with advanced immune suppression.^{1,2} VL is also a tool to improve adherence to ART, thereby providing an additional benefit to treatment programs.³ Most programs in resource limited settings continue to monitor individuals either clinically, or clinical plus immunologic monitoring due

to logistical and cost constraints limiting access to VL testing. Several observational studies have revealed limitations of immunologic monitoring, including the poor sensitivity for identification of virologic failure and the potential for inappropriate switching to second line regimen due to poor specificity of the current immunologic monitoring guidelines.^{3–8} The recent 2013 WHO guidelines recommend implementation of VL monitoring where facilities are available, and several countries, including Uganda, are in the planning stages of scaling up VL monitoring.⁹

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The utility of routine CD4 monitoring in the setting of an immunologic and virologic response to ART is unclear and has not been evaluated in resource-limited settings. Reducing CD4 monitoring represents a cost saving option for programs faced with funding constraints.¹⁰ We evaluated the necessity of routine CD4 monitoring among rural Uganda patients receiving free ART who had achieved both an immunologic and virologic response to first line ART.

Methods

Rakai Health Sciences Program (RHSP) located in southwestern Uganda began offering free ART in 2004, eligibility criteria were CD4 <250 cells/ μ L or a WHO stage IV illness. Clients were monitored both clinically and with CD4 and HIV VL testing every 6 months until January 2011 when VL monitoring was performed annually after the first year on ART. Clients receiving ART through the program between June 2004 and May 2013 were eligible for inclusion in this analysis. We defined an immunologic response to treatment as achieving a CD4 cell count ≥ 200 cells/ μ L, and a virologic response as achieving an HIV VL <400 copies/mL after treatment initiation. We evaluated clients who had three sets of CD4 and VL measurements performed within a 390-

day period, defined as a *sequence*. A CD4 count decline was defined as a drop in CD4 count to <200 cells/ μ L during a period of viral suppression.

CD4 cell counts were measured by FACSCalibur (Becton Dickinson, New Jersey, USA). HIV VL was measured using Roche Amplicore Monitor 1.5 assay (Roche Diagnostics, Indiana, USA) until September 2010 and then Abbott Realtime HIV assay. (Abbott Laboratories, Illinois, USA).

Statistical methods

Descriptive statistics were used to describe the study population. Kaplan Meier survival curves were generated to compare the probability of maintaining a CD4 ≥ 200 cells/ μ L, within a single sequence within different CD4 count strata at initiation of a sequence (i.e., 200–249, 250–299, 300–349, and ≥ 350 cells/ μ L). Survival analysis was used to estimate time to first CD4 sequence and CD4 decline. A Cox proportional hazards model was used to identify factors associated with a CD4 decline.

Ethics statement

The study was approved by the Johns Hopkins School of Medicine IRB, the Uganda Virus Institute Science and Ethics

FIG. 1. Kaplan Meier curves showing per-patient analysis of probability of maintaining a CD4 ≥ 200 cells/ μ L within a single sequence. The *dotted lines* show the confidence interval bands around the survivor function, which is the *full line*.

TABLE 1. DISTRIBUTION BY PATIENT AND SEQUENCE ANALYSIS BASED ON INITIAL CD4 WHILE UNDER CONTINUOUS VIRAL SUPPRESSION

<i>Initial CD4 in sequence^a</i>	<i>All</i>	<i>200–249</i>	<i>250–299</i>	<i>300–349</i>	<i>≥ 350</i>
Per-client analysis	1553	294	299	254	706
CD4 count maintained at ≥200 cells/ μ L during viral suppression (%)	1510 (97.2)	275 (93.5)	286 (95.7)	245 (96.5)	704 (99.7)
CD4 count declines (%)	43 (2.8)	19 (6.5)	13 (4.3)	9 (3.5)	2 (0.3)

^aSequence defined as ≥3 sequential CD4 and VL measurements occurring within 390 days.

Committee, and the Uganda National Council for Science and Technology.

Results

Of the 1873 clients receiving first-line ART through RHSP with CD4/VL data to define a sequence, 167/2873 (5.8%) did not achieve a virologic response (HIV VL <400 copies/mL) and 153/2873 (5.3%) did not achieve an immunologic response (CD4 >200 cells/ μ L) to treatment. The remaining 1553 clients were included in this analysis (Fig. 1). The majority (68%) were females, mean age of 35.5 years (SD 8.3), median baseline CD4 count 183 cells/ μ L (IQR 106–224). Most (972/1553, 62.6%) were receiving a nevirapine-based regimen, while a minority (581/1553, 37.4%) received an efavirenz-based regimen. A total of 1482 (95.4%) clients had at least one sequence of CD4/VL measurements, while 71 (4.6%) had more than one sequence. On average, clients acquired a sequence after a median 8.3 months on ART (IQR 6.9–14.2). The median (IQR) duration between each paired CD4 and VL tests was 169 days (IQR 168–183). In a per-client analysis, 43 (2.8%) developed CD4 declines <200 cells/ μ L, the majority occurring among individuals whose initial CD4 was <300 cells/ μ L (Table 1). Of the 43 clients who developed CD4 declines, 24 had an additional CD4 measurement at a later follow-up visit and 20/24 (83%) of these individuals achieved a CD4 ≥200 cells/ μ L on the next measurement (median 285 cells/ μ L; IQR 220–365). None of the 43 clients who developed CD4 declines had a documented opportunistic infection during the time of the measured decline.

In a multivariate analysis examining predictors of CD4 declines among virologically suppressed clients, CD4 declines were significantly greater among those with lower CD4 counts at sequence initiation, adjusted hazard ratio (AHR) 4.3 (95% CI 2.1, 9.0) CD4 200–249 versus ≥350. A 50-cell/ μ L increase in the baseline CD4 count was associated with a reduced hazard of subsequent CD4 count decline, AHR 0.8 (95% CI 0.71, 0.96). Older clients had a slightly higher risk of experiencing a CD4 decline, AHR 1.2 (95% CI 1.02, 1.33) for each 5-year age increase. Baseline regimen and gender were not associated with CD4 declines.

Discussion

This is the first study from a resource-limited setting examining the utility of CD4 monitoring in the presence of virologic suppression and an immunologic response to ART. We found the risk of experiencing a CD4 decline <200 cells/ μ L to be very low among individuals who had achieved an immunologic and virologic response to treatment. We also did not find any new opportunistic infections at the time when

a CD4 decline was detected. In addition, the majority of clients who had a subsequent CD4 measured following a decline returned to a CD4 count ≥200 cells/ μ L. These results are consistent with those from North America where the necessity of CD4 monitoring in the presence of viral suppression has recently been questioned.^{11,12}

Our study has several limitations due to the retrospective design. Clinical outcome ascertainment was reliant on our clinical database, which may have under-reported the true rate of opportunistic infection. This is also a single site, which may limit the generalizability of our findings to other settings. We did not examine the outcomes among clients with virologic suppression but a poor immunologic response (CD4 <200 cells/ μ L) as numbers in this subgroup were very small, and other groups have shown that these individuals are at increased risk of mortality.^{13–17}

Despite these limitations, our findings add to the growing literature suggesting that a reduction in CD4 testing frequency may be safe among clients achieving a virologic and immunologic response to first line ART. The limited clinical benefit of frequent CD4 monitoring may be offset by the potential cost savings to programs where routine VL monitoring is available. Access to CD4 testing remains essential for treatment initiation decisions but it may be more efficient to consider less frequent or demand driven CD4 testing if a patient presents with a clinical syndrome where the CD4 could be helpful to determine the presence of an opportunistic infection. As the global scale up of ART continues and greater access to VL testing becomes a reality, it is imperative that guidelines are reviewed and the limited resources be spent efficiently.

In conclusion, HIV-infected clients on first line ART who achieved CD4 counts ≥200 cells/ μ L and maintained virologic suppression (HIV VL ≤400 copies/mL) were unlikely to experience a subsequent CD4 decline below 200 cells/ μ L. Among the few clients with CD4 declines, most regained a CD4 above 200 cells/ μ L at a subsequent measurement and none experienced an opportunistic infection during the period of CD4 decline. Thus, ongoing CD4 monitoring in virologically suppressed individuals with a CD4 above 200 cells/ μ L could be omitted without risking patient health, and would result in cost savings.

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Author Disclosure Statement

The authors declare no financial conflicts of interest.

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