Reducing CD4 Monitoring in Children on Antiretroviral Therapy With Virologic Suppression

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Background: Ongoing CD4 monitoring in patients on antiretroviral therapy (ART) with viral suppression has been questioned. We evaluated the probability of CD4 decline in children with viral suppression and CD4 recovery after 1 year on ART.

Methods: We included children from 8 South African cohorts with routine HIV-RNA monitoring if (1) they were "responders" [HIV-RNA < 400 copies/mL and no severe immunosuppression after ≥1 year on ART (time 0)] and (2) ≥1 HIV-RNA and CD4 measurement within 15 months of time 0. We determined the probability of CD4 decline to World Health Organization–defined severe immunosuppression for 3 years after time 0 if viral suppression was maintained. Follow-up was censored at the earliest of the following dates: the day before first HIV-RNA measurement >400 copies/mL; day before a >15-month gap in testing and date of death, loss to follow-up, transfer out or database closure.

Results: Among 5984 children [median age at time 0: 5.8 years (interquartile range: 3.1–9.0)], 270 children experienced a single CD4 decline to severe immunosuppression within 3 years of time 0 with probability of 6.6% (95% CI: 5.8–7.4). A subsequent CD4 measurement within 15 months of the first low measurement was available for 63% of children with CD4 decline and 86% showed CD4 recovery. The probability of CD4 decline was lowest (2.8%) in children aged 2 years or older with no or mild immunosuppression and on ART for <18 months at time 0. This group comprised 40% of children.

Conclusions: This finding suggests that it may be safe to stop routine CD4 monitoring in children older than 2 years and rely on virologic monitoring alone.

Key Words: HIV-1, children, CD4, monitoring, viral load, sub-Saharan Africa, antiretroviral

(*Pediatr Infect Dis J* 2015;34:1361–1364)

For over 20 years, CD4 cell count measurements have been central to the management of patients with HIV to assess disease progression, guide decisions about antiretroviral therapy (ART) initiation and monitor treatment response.[1,2] Although CD4 measurement continues to play an important role as a marker of disease progression and to identify the risk of opportunistic infections, the value of CD4 measurements for monitoring treatment response and diagnosing failure in settings where virologic monitoring is also available have come into question.[3] Studies from the United States,[4] Europe,[5] Uganda[6] and South Africa[7] have shown that, among adult patients who are stable on ART and virologically suppressed, CD4 decline is rare, and when it does occur, decline is usually transient, suggesting that repeated CD4 monitoring after viral suppression on ART is not necessary. Further CD4 measurement in a virally suppressed patient rarely contributes to clinical decision making.[8] Studies among adult patients in the United States,[9] the United Kingdom,[10] Australia,[8] Kenya[11] and South Africa[12] have all estimated substantial programme cost savings if routine CD4 monitoring is reduced or stopped. Guidelines issued by the Southern African HIV Clinicians Society in 2013 recommend that for adult patients with routine viral load monitoring, there is no need to continue CD4 testing once CD4 is >200 cells/mm^3 and viral load is suppressed. CD4 testing is recommended if virologic or clinical failure occurs.[13] In 2014, the World Health Organization (WHO) issued a technical document based on expert consultation, which concluded that if viral load is available routinely, CD4 monitoring could be reduced or stopped altogether in virologically suppressed patients.[14] However, the absence of data for children was noted. We assessed CD4 changes in a cohort of virologically suppressed children on ART in South Africa.

MATERIALS AND METHODS

We conducted a retrospective analysis of data from 8 cohorts contributing to the International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration (www.iedea-sa.org). All cohorts have ethics approval from their respective local institutional review boards to contribute data to IeDEA-SA, and IeDEA-SA has been approved by the Human Research Ethics Committees of the Universities of Cape Town and Bern where the IeDEA-SA data centers are located.

Antiretroviral naïve children at sites with routine (at least annual) HIV-RNA and CD4 monitoring were included in the

Accepted for publication March 22, 2015.

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Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases (grant number 2U01AI069924-06; Egger, M.A.D.). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. H.R. has been paid by AbbVie for teaching activities unrelated to this manuscript. O.K. was supported by a PROSPER fellowship grant (nr 3233B_150934) from the Swiss National Science Foundation. The other authors have no conflicts of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/15/3412-1361
DOI: 10.1097/INF.0000000000000912

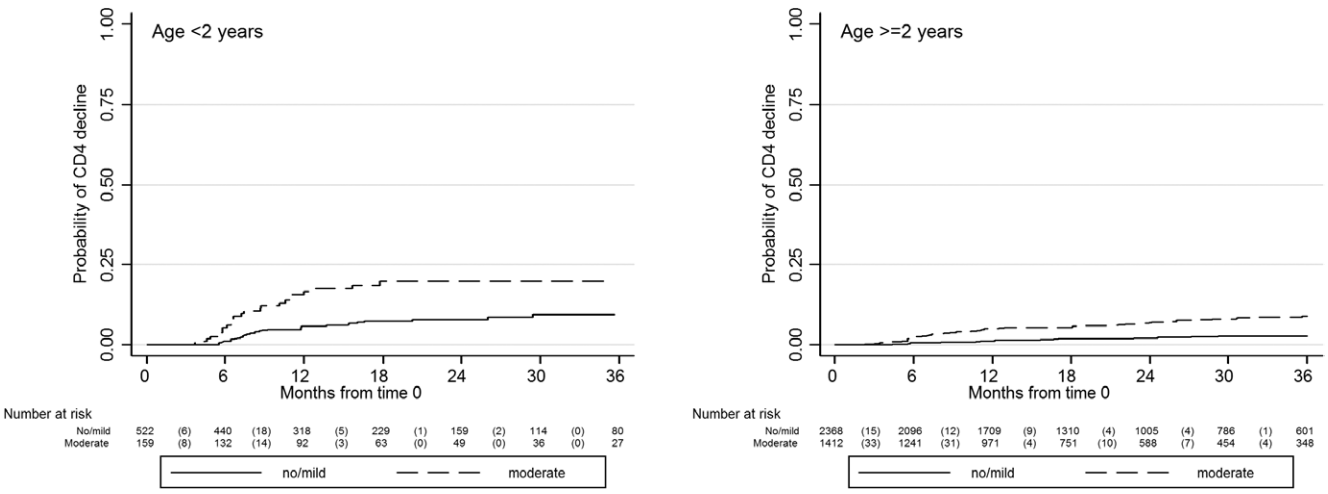

FIGURE 1. Probability of CD4 cell decline to severe immunosuppression for up to 3 years after time 0 according to degree of immunosuppression (no/mild vs. moderate) at time 0. All children on ART for <18 months at time 0.

analysis if they had ≥12 months follow-up on ART. Children entered the analysis on the first date that they met the criteria for an adequate response to treatment (defined as HIV-RNA <400 copies/mL and simultaneous CD4 with no severe immunosuppression after ≥9 months on ART). The time when a child first met these criteria was designated time 0. We evaluated all subsequent paired HIV-RNA and CD4 measures to determine the probability of a CD4 decline to severe immunosuppression after time 0 in children who remained virologically suppressed. Children who did not have at least 1 subsequent paired HIV-RNA and CD4 measurement within 15 months of time 0 were excluded. We used the WHO 2006 criteria to define severe immunosuppression: CD4 < 20%/750 cells/mm^3 (age: 12–35 months), CD4 < 15%/350 cells/mm^3 (age: 36–59 months) and CD4 < 15%/200 cells/mm^3 (age: ≥5 years).[15] Data were censored the day before the first HIV-RNA measurement >400 copies/mL, the first >15-month gap in testing or last date of follow-up because of death, loss to follow-up (LTFU) or transfer out. LTFU was defined as no visit for 9 months before database closure.

Associations between characteristics at time 0 and CD4 decline were assessed using Cox-proportional hazards models. Multivariable models included variables considered a priori to affect the probability of CD4 decline, including age and duration on ART at time 0 and degree of immunosuppression both at time 0 and at ART initiation. Severe immunosuppression was defined as mentioned earlier. The definition of no/mild immunosuppression was based on the WHO criteria: CD4 ≥ 25% and 1000 cells/mm^3 in a child younger than 5 years or ≥20% and 500 cells/mm^3 in a child aged 5 years or older.[15] Hazards proportionality was assessed by the analysis of scaled Schoenfeld residuals. All analyses were performed using Stata version 12.0 (College Station, TX).

RESULTS

Among 9503 children who had been on ART for ≥12 months, 5984 met the inclusion criteria for this analysis. The reasons for exclusion are shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/C263. The characteristics of included and excluded children are summarized in Table, Supplemental Digital Content 2, http://links.lww.com/INF/C264. Median (interquartile range) age at time 0 in children included in the analysis was 5.8 (3.1–9.0) years, and median (interquartile range) time on ART was 12.9 (11.3–18.0) months. First-line regimen information was recorded for 5696 (95.1%) children, of whom 31.9% initiated lopinavir-/ritonavir-based ART, whereas 61.6% and 3.5% initiated efavirenz (EFV)- and nevirapine-based regimens, respectively. During the following 3 years, 270 children experienced a CD4 decline to severe immunosuppression, with a probability of 6.6% (95% CI: 5.8–7.4). Most declines were not sustained: a subsequent CD4 measurement within 15 months of the first measurement was available for 169 (63%) of 270 children with a CD4 decline; the majority (n = 145, 86%) no longer had severe immunosuppression at the next measurement. Only 3 of these children underwent a treatment change between the first and subsequent CD4 measurement: 1 child switched to second line [change of both nucleoside reverse transcriptase inhibitors and change from EFV to lopinavir/ritonavir (LPV/r)]; 1 child had a single-drug change from LPV/r to EFV and in the third child, ritonavir superboosting was added to the LPV/r-based regimen as tuberculosis treatment was started. Among the 270 children with CD4 decline, outcomes in the following year were as follows: 85.2% remained in care, 1.1% had died, 1.9% were lost to follow-up and 11.9% had been transferred to another site. In children with CD4 decline who remained in care but did not have a repeat CD4 measurement for inclusion in the analysis (n = 84), the main reason (n = 47) was that there was <1 year of follow-up from the date of low CD4 measurement to the date of database closure. Hence, there was insufficient time for a repeat CD4 as national guidelines recommended annual CD4 monitoring. Other reasons were that the next CD4 measurement was >15 months after the date of decline (n = 23) or that the child was not virologically suppressed at the next CD4 measurement (n = 8). Six children had no subsequent CD4 measurement despite >365 days of follow-up before database closure.

The 3-year probability of CD4 decline to severe immunosuppression was lowest (2.8%; 95% CI: 2.1–3.8) in children with the following characteristics: ≥2 years old at time 0, met the criteria for an adequate response to ART within 18 months of starting treatment and good immunologic response (ie, had no/mild rather than severe immunosuppression at time 0). This subgroup comprised 40% (n = 2368) of all children included in the analysis (Fig. 1; see Table, Supplemental Digital Content 3, http://links.lww.com/INF/C265). The following characteristics at time 0 were associated with an increased risk of CD4 decline: age < 2 years [adjusted hazard ratio (aHR): 2.80; 95% CI: 1.95–4.01], moderate versus no/mild immunosuppression (aHR: 2.89; 95% CI: 2.14–3.89) and taking longer than 18 months to respond adequately to ART (aHR: 1.51;

95% CI: 1.08–2.12). In addition, severe immunosuppression at ART initiation was associated with an increased risk of CD4 decline (aHR: 1.96; 95% CI: 1.21–3.18). The groups with high (≥20%) risk of CD4 decline were those younger than 2 years at time 0 who either took >18 months to respond to ART or were still moderately immunosuppressed at time 0. These comprised only 3.3% (n = 195) of all children included in the study.

DISCUSSION

The value of continued CD4 monitoring for stable patients in settings where viral load is available has been questioned. The findings of our study carried out in a large pediatric population across several treatment sites in South Africa with both routine HIV-RNA and CD4 monitoring concur with reports among adult patients and suggest that the risk of CD4 decline in virologically suppressed children on ART is low, especially those aged >2 years who have attained no/mild immunosuppression. This finding indicates that it may be safe to reduce CD4 monitoring in virologically suppressed children aged >2 years on ART.

The risk of CD4 decline was higher in those aged <2 years at entry into the study, especially if their immune responses were slower and less robust. As children had to have at least 12 months of follow-up on ART at study entry, these children would all have been 1–2 years of age at study entry, and so would have been followed up during the period when there is a biologic age–related rapid decline in CD4 count.[16,17] This age-related decline may explain their increased risk of CD4 values falling to severe immunosuppression, especially if initial CD4 recovery was suboptimal. Further research needs to evaluate the clinical implications of CD4 decline at younger ages to determine whether there is a need for ongoing CD4 monitoring during this period of biologic rapid CD4 decline.

The current rationale for CD4 monitoring includes determining the need for ongoing co-trimoxazole prophylaxis; however, recent data have suggest that there is a benefit to continuing co-trimoxazole prophylaxis irrespective of CD4 count. A recent trial of co-trimoxazole prophylaxis in HIV-infected children on ART demonstrated substantial protection of prolonged co-trimoxazole against hospitalizations.[18] Revised WHO 2014 guidelines recommended lifelong co-trimoxazole for HIV-infected children in settings where malaria and/or severe bacterial infections are highly prevalent.[19]

CD4 monitoring could also have a role in identifying patients at risk of opportunistic infections. In the context of ongoing virological suppression this need is likely to be small and the importance of this role depends on the availability and cost-effectiveness of interventions to diagnose and treat such illnesses. As our study lacked detailed data on opportunistic infections, we could not examine whether CD4 declines were associated with increased opportunistic infection risk, or whether there were any clinical interventions in response to low CD4 values. However, it is reassuring that most declines were transient without treatment changes in the majority of children and that mortality and LTFU in the year after a CD4 decline were low. However, our study was limited to South African sites with capacity for electronic data collection, and findings may not be generalizable to other regions of the world with children of different genetic background,[16] different frequency of viral load measurement, antiretroviral regimens and opportunistic infection risk. Therefore, further research is encouraged to confirm these findings in other settings and over a longer duration.

The role of CD4 cell measurement in guiding treatment initiation for children may also be diminishing, given recent changes in guidelines for starting pediatric treatment. For programmatic reasons, WHO currently recommends that all adults, adolescents and children should be initiated on ART irrespective of CD4 cell count.[20] Several countries are already providing or considering immediate ART to all children <15 years of age.[21,22] However, although programmatically this may increase the current inadequate levels of pediatric treatment coverage, the current evidence regarding the individual clinical benefit of immediate ART initiation in children aged 5–14 years is limited, and a number of countries will likely continue to rely on CD4 to guide treatment initiation decisions for some years to come.

Thus, measurement of CD4 cell count will remain an important tool for assessing baseline health status, investigation for certain opportunistic infections and initiation of ART in older children. However, in settings where both CD4 and viral load testing are available and patients are stable on ART, this study suggests that ongoing routine monitoring of CD4 in children older than 2 years has limited additional value, and consideration should be given to reducing the frequency of CD4 monitoring or dropping its routine use altogether unless clinical deterioration or viral rebound occurs. This could simplify programmes allowing for increased treatment access and for resources to be directed at ensuring that routine viral load measurement is undertaken satisfactorily.

ACKNOWLEDGMENTS

The authors thank the children whose data were used in this analysis, as well as their caregivers. They also thank all staff at participating sites for providing patient care and preparation of data contributed to the IeDEA-SA collaboration. They thank the IeDEA-SA Data Centre teams at the Universities of Cape Town and Bern.

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