Global Trends in CD4 Measurement and Immunosuppression at ART Initiation Among Children With HIV

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Abstract: Eligibility for antiretroviral therapy is no longer based on immune criteria. In a global cohort of 97,453 children, between 2005 and 2021, we observed large declines in CD4 measurement, from 51% to 12% among <5 seconds, and from 74% to 20% among those 5–14 years of age. Lack of CD4 testing may negatively affect clinical care and surveillance of severe immune suppression.

Key Words: severe immune suppression, CD4 cell count, antiretroviral therapy, advanced HIV disease, pediatric HIV

(*Pediatr Infect Dis J* 2025;44:873–875)

Since the implementation of "treat all" policies, which recommend all people with HIV be eligible for treatment regardless of their level of immune suppression, there has been a substantial decline in CD4 measurement.[1] However, CD4 at antiretroviral therapy (ART) initiation remains an important surrogate measure of HIV disease. Lower baseline immunity in children is associated with slower immune recovery on ART,[2] and CD4 measurement at ART initiation and at reengagement in care is used to guide prevention of deadly opportunistic infections.[3] Assessing the prevalence of immune suppression at ART initiation is also important for ART programs to identify gaps in linking children to HIV care, delays in treatment initiation, and the overall burden of advanced HIV disease (AHD).

Despite considerable improvements in HIV prevention, treatment and outcomes for children, ART coverage remains significantly lower compared with adults and mortality remains high.[4] Even in the era of universal treatment, extremely high prevalence of severe immune suppression (SIS), up to 55%, have been observed among children starting ART.[5,6] However, an increasing proportion of children starting ART have unmeasured CD4% or cell counts, and more recent data are needed.[5]

We describe trends in CD4 measurements and immunosuppression among children <15 years old at ART initiation, using observational data from HIV clinics in 29 countries across 7 regional cohorts (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/G177) within the International epidemiology Database to Evaluate AIDS (IeDEA) collaboration.

Accepted for publication February 16, 2025

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The International epidemiology Databases to Evaluate AIDS (IeDEA) is supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Fogarty International Center: Asia-Pacific, U01AI069907; CCASAnet, U01AI069923; Central Africa, U01AI096299; East Africa, U01AI069911; Southern Africa, U01AI069924; and West Africa, U01AI069919. Informatics resources are supported by the Harmonist project, R24AI24872. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

The authors have no conflicts of interest to disclose.

G.P. designed the study, analyzed the data, and drafted the manuscript. N.A. contributed to the study design and analysis. All authors contributed to critically revising the manuscript, and read and approved the final version.

Data are not publicly available.

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).

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ISSN: 0891-3668/25/449-873875
DOI: 10.1097/INF.0000000000004819

METHODS

We included children <15 years old initiating ART between 2005 and 2021. Between 2008 and 2015, ART eligibility guidelines were revised several times (see Text, Supplemental Digital Content 2, http://links.lww.com/INF/G177). We excluded children with inconsistent data [n = 153 (0.16%)], and those who enrolled at IeDEA clinics after ART initiation. For each area and calendar year, we described the proportion of children with a CD4 measure at ART initiation, and among those with a CD4 measure, the proportion with SIS. We reported data from South Africa separately because CD4 measurement differed significantly from the rest of Southern Africa. We calculated 95% confidence intervals (CIs) using the Beta distribution. For children <5, we used CD4%, and for those 5–14 years of age, we used CD4% or cell counts. We used the CD4 measure taken closest to the ART initiation date, and considered measurements up to 6 months before and within 2 weeks after, and performed sensitivity analysis to include measurements taken up to 1 month after ART start (Table, Supplemental Digital Content 3, http://links.lww.com/INF/G177). We defined SIS according to WHO 2007 criteria: CD4% <25% for children <12 months old, CD4% <20% for children 12–35 months old, CD4% <15% for children 36–59 months of age, and CD4% <15% or CD4 count <200 cells/μL among children ≥5 years.[7] In sensitivity analyses, we aggregated country-level data to assess variability in the trends between countries within the same region. Local institutional review boards approved the use of routine clinical data for collaborative analyses.

RESULTS

We included 97,453 children from 7 areas: South Africa (19,694), Southern Africa excluding South Africa (45,299), East Africa (15,494), West Africa (6626), Central Africa (3563), the Asia-Pacific (5292) and Latin America (1485). In our study population, annual ART initiations varied over time, peaking at 7643 in 2009 and declining to 1940 by 2021. Results are disaggregated by age-group and area, with detailed characteristics provided in Tables, Supplemental Digital Contents 4 and 5, http://links.lww.com/INF/G177. Area-specific CD4 availability and SIS are illustrated in Figure 1.

Children <5 Years

Among 47,937 children, 50% were female, with a median age of 1.8 years [interquartile range (IQR): 0.8–3.1], which decreased from 2.2 (IQR: 1.1–3.5) in 2005 to 1.5 (IQR: 0.5–2.7) in 2021, and varied between areas from 1.0 (IQR: 0.3–2.3) in South Africa to 2.2 years (IQR: 1.2–3.6) in Central Africa.

Overall, 33% of children had a recorded CD4%, declining from 51% (95% CI: 49%–54%) in 2005 to 12% (95% CI: 10%–14%) in 2021. CD4% availability for the study duration varied between areas from 11% (95% CI: 11%–12%) (Southern Africa) to 73% (95% CI: 71%–74%) (Asia-Pacific). Most areas experienced declining trends in CD4% availability over the study period. In Southern Africa, CD4% availability increased from 0% (95% CI: 0%–2%) in 2005 to 31% (95% CI: 29%–34%) in 2014, then declined sharply to 1% (95% CI: 0%–2%) in 2021. This trend was driven by data from Zambia (not shown). Latin America experienced declines from 54% (95% CI: 39%–69%) in 2005 to 3% (95%

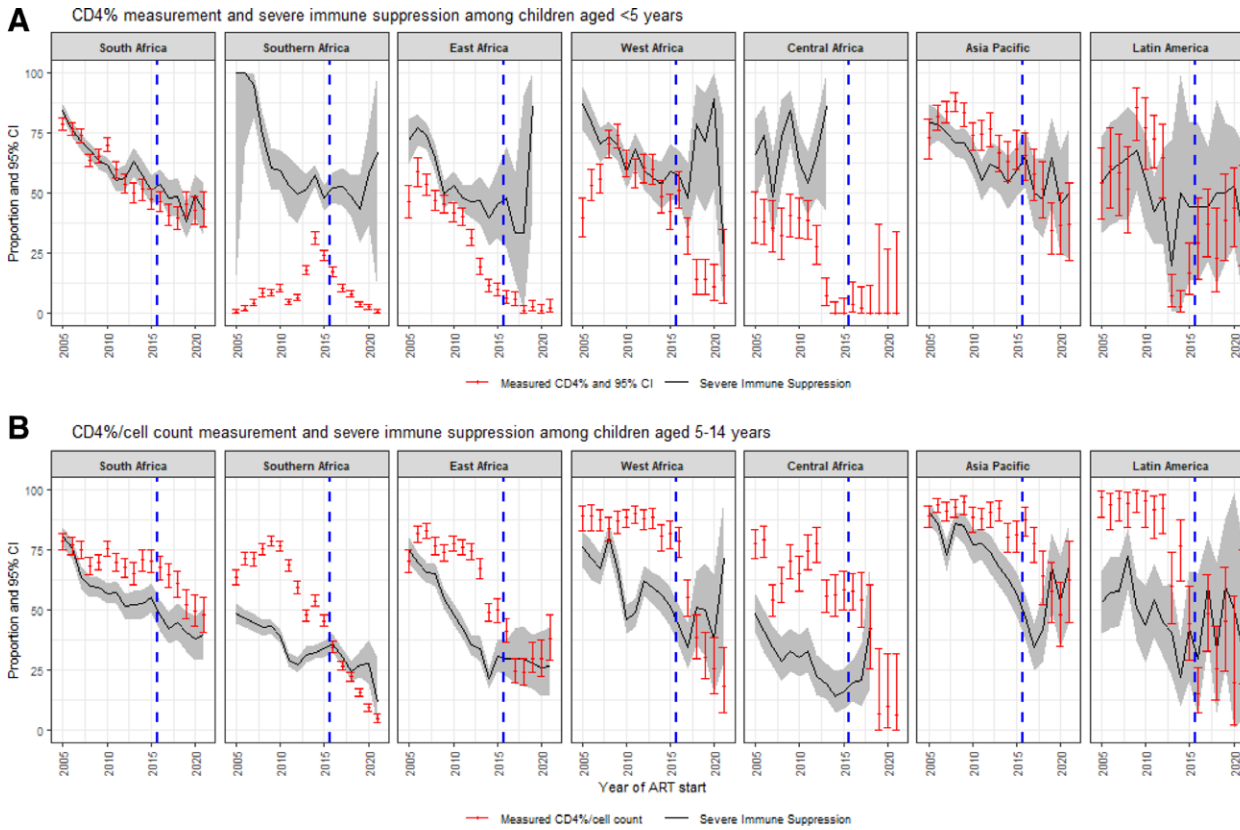

FIGURE 1. Proportion of children with HIV from IeDEA cohorts with measured CD4% or count and severe immune suppression at ART initiation by area and calendar year among children (A) <5 and (B) 5–14 years old. Red error bars represent CD4 availability estimates and their 95% confidence intervals (CIs). Black lines and gray shaded areas represent SIS prevalence and 95% CI. Blue dashed line represents September 2015 when WHO revised their guidelines to treat all. full color online

CI: 0%–10%) in 2014, followed by increased testing to 39% (95% CI: 20%–62%) by 2021. In African regions excluding South Africa, by 2021 CD4% testing ranged from 0% (95% CI: 0%–34%) to 15% (95% CI: 4%–35%).

Among those tested, the median CD4% increased from 12.2 (IQR: 7.9–17.6) in 2005 to 24.1 (IQR: 15.3–37.3) in 2021. SIS prevalence decreased from 82% (95% CI: 79%–84%) in 2005 to 42% (95% CI: 33%–51%) in 2021.

Children 5–14 Years of Age

Among 49,516 children, 53% were female, with a median age of 9.4 years (IQR: 7.1–12.0), which increased from 8.8 (IQR: 6.8–11.2) in 2005 to 10.2 (IQR: 7.3–12.8) in 2021, and varied between areas from 8.4 (IQR: 6.6–10.9) in the Asia-Pacific to 10.1 years (IQR: 7.7–12.4) in Latin America.

Overall, 59% of children had a CD4 measurement, declining from 74% (95% CI: 72%–75%) in 2005 to 20% (95% CI: 18%–23%) in 2021. CD4 availability over the study duration varied between areas from 48% (95% CI: 47%–48%) (Southern Africa) to 86% (95% CI: 85%–88%) (Asia-Pacific), with all areas experiencing declines. By 2021, CD4 availability in African regions excluding South Africa ranged between 5% (95% CI: 3%–7%) and 38% (95% CI: 29%–48%).

For those with a CD4 cell count, the median CD4 count rose from 200 (IQR: 70–368) in 2005 to 371 cells/μL (IQR: 159–668) in 2021. SIS prevalence decreased from 66% (95% CI: 64%–68%) in 2005 to 37% (95% CI: 30%–44%) in 2021.

DISCUSSION

In this cohort of over 90,000 children initiating ART across 29 countries, we observed large declines in CD4 measurement. CD4 measurement in children <5 years was lower than among older children, with particularly low rates in African regions outside of South Africa. Although our data show a persistent prevalence of SIS, the decreasing availability of CD4 testing makes it challenging to interpret these trends meaningfully.

This study updates previous global data on the prevalence of SIS and CD4 measurement in children, which demonstrated declines in SIS at ART initiation after the implementation of universal ART in 2015.[6] Previous estimates indicated that by 2013, 42%–46% of children in low- to middle-income countries started ART with SIS, with 40% having missing CD4 measures.[6] By comparison our study found that by 2021, only 16% of children had a CD4 measurement, and among those tested, 39% had SIS. This suggests that since 2013, declines in the prevalence of SIS have been limited, but SIS prevalence is increasingly unknown due to low CD4 testing.

Declines in CD4 measurement have been documented in adults with HIV,[1] but our findings reveal that CD4 measurement in children is considerably lower. Contributing factors include the discontinuation of laboratory platform manufacturing, limitations in point-of-care CD4 testing, increased focus on viral load testing, and shifts in funding allocation.[7] This reduction in CD4 testing likely adversely affects both clinical care and the surveillance of SIS and AHD in both children and adults.[8] WHO continues to recommend CD4 monitoring at ART initiation and at reengagement in care to diagnose AHD,[9,10] as well as interventions, for individuals >5 years with a CD4 count <200 cells/μL. Expanding access and improving tools for the prevention, diagnosis and treatment of life-threatening opportunistic infections, along with enhancing linkage and retention in ART care, is essential to further reducing AIDS-related mortality. This includes CD4 measurement to direct the administration of the AHD care package.

Our study focused on CD4 measurement at ART initiation, and not at reengagement in care following treatment interruption. Some children reengaging in care may have been misclassified as ART initiators. Sicker children may be more likely to receive CD4 testing, introducing bias into our SIS prevalence estimates, and possibly lowering our estimates for median CD4%/count. This is evident in some areas where declines in CD4 measurement coincided with increases in SIS prevalence.

Children account for a disproportionately high number of AIDS-related deaths, and ART coverage remains significantly lower compared to adults.[4] There are substantial differences in the clinical presentation of AHD and the prevalence of certain opportunistic infections among children, adolescents and adults. Identifying and appropriately managing children with SIS may be crucial to lowering AIDS-related mortality. While rapid tests to identify people with HIV with CD4 <200 cells/μL are in use in some contexts, similar tests are not available for children <5, since they require CD4 measurement in percentages. Evidence to guide the management of AHD has largely been from adult populations, but given the persistence of SIS in children, more pediatric-specific approaches for addressing SIS and lowering mortality in children are needed, including the development of risk-based CD4 monitoring tailored to children where CD4 testing is not feasible.

CONCLUSION

The declining frequency of CD4 measurement and the persistent prevalence of SIS at ART initiation are concerning. Improved access to CD4 testing at ART initiation is needed to better guide patient care and monitor ART programs.

ACKNOWLEDGMENTS

The authors are grateful to all children, caregivers and data managers involved in the participating cohorts and treatment programs.

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