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# CD4 Trends with Evolving Treatment Initiation Policies among Children Living with HIV in Zambézia Province, Mozambique, 2012–2018

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## Abstract

**Background:** Historically, antiretroviral therapy (ART) initiation was based on CD4 criteria, but this has been replaced with “Test-and-Start” (T&S) wherein all people living with HIV are offered ART. We describe the baseline immunologic status among children relative to evolving ART policies in Mozambique.

**Methods:** This retrospective evaluation was performed using routinely collected data. Children living with HIV (CLHIV; 5–14 years) with CD4 data in the period of 2012–2018 were included. ART initiation “policy periods” corresponded to implementation of evolving guidelines: in Period 1 (2012–2016), ART was recommended for CD4<350; during Period 2 (2016–2017), the CD4 threshold increased to <500; T&S was implemented in Period 3 (2017–2018). We described temporal trends in the proportion of children with severe immunodeficiency (CD4<200) at enrollment and at ART initiation. Multivariable regression models were used to estimate associations with severe immunodeficiency.

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**Results:** The cohort included 1,815 children with CD4 data at enrollment and 1,922 at ART initiation. The proportion of children with severe immunodeficiency decreased over time: 20% at enrollment into care in Period 1 vs. 16% in Period 3 (p=0.113), and 21% at ART start in Period 1 vs. 15% in Period 3 (p=0.004). Children initiating ART in Period 3 had lower odds of severe immunodeficiency at ART start compared to those in Period 1 (aOR=0.67; 95%CI:0.51–0.88). Older age was associated with severe immunodeficiency at enrollment (aOR=1.13; 95%CI:1.06–1.20) and at ART initiation (aOR=1.14; 95%CI:1.08–1.21).

**Conclusions:** The proportion of children with severe immunodeficiency at ART initiation decreased alongside more inclusive ART initiation guidelines. Earlier treatment of CLHIV is imperative.

### Keywords

HIV; CD4 cell count; children; antiretroviral therapy; Mozambique

## INTRODUCTION

As of 2019, there were nearly 2 million children living with HIV (CLHIV) globally.[1] Greater than two-thirds of those living with HIV were in sub-Saharan Africa.[1] In Mozambique, the pediatric HIV prevalence is approximately 1 to 2%, and the vertical transmission rate is estimated to range from 5 to 14%.[1–4] Despite significant investments and widespread implementation of prevention of mother-to-child transmission (PMTCT) services, there are still 160,000 new pediatric HIV infections, worldwide, every year.[1] As is the case for adults living with HIV, early initiation of antiretroviral therapy (ART) – well before progression to severe immunodeficiency/AIDS – is essential to ensure optimal health outcomes for CLHIV.[5–15]

Pediatric ART initiation guidelines have evolved over time in response to emerging evidence for improved outcomes with earlier ART initiation. Historically, decisions to initiate ART were based on clinical (e.g., World Health Organization [WHO] Stage 3 or 4 conditions) or immunologic (i.e., CD4+ T-cell count [CD4] cutoffs) criteria. In 2008, WHO updated guidelines to recommend ART initiation for all CLHIV under 1 year of age, regardless of clinical or immunologic criteria.[16] In 2010, WHO expanded their age-based criteria to recommend ART initiation for all CLHIV less than 2 years of age,[17] and in 2013 they began recommending universal ART initiation for those less 5 years of age.[18] Aligned with adult guidelines, ART initiation for children 5 years or older continued to be based on clinical and immunologic criteria until 2016.[19] Since 2016, WHO has recommended ART initiation for all people living with HIV (including children), regardless of clinical, immunologic, or age criteria, a strategy referred to as “Test and Start”.[20] In Mozambique implementation of Test and Start began in a phased approach staring in July 2016, and the policy was not fully implemented across the entirety of Zambézia Province Mozambique until November 2017.[1–4]

With support from the United States Centers for Disease Control and Prevention (CDC) and the President’s Emergency Plan for AIDS Relief (PEPFAR), Vanderbilt University Medical Center (VUMC), through its subsidiary Friends in Global Health (FGH), has provided technical assistance in Zambézia Province, Mozambique since 2006. The Test and Start strategy commenced in Zambézia Province, starting first in the provincial capital of Quelimane in August 2016, followed by other large districts in April 2017, smaller districts as of November 2017, and all VUMC/FGH-supported districts as of February 2018.

Under older ART initiation policies, which delayed treatment until there were HIV-related declines in CD4 counts or the development of opportunistic conditions, it was expected that CLHIV would start treatment with a more advanced degree of HIV-related immunodeficiency. In contrast, it is expected that HIV-related immunodeficiency should be less severe among CLHIV initiating ART in the Test and Start era, wherein universal and immediate treatment is recommended, regardless of immunologic or clinical status. However, prior studies of HIV-related immunodeficiency among children relative to ART program maturation only included children starting ART prior to 2013,[21,22] and more recent studies focused solely on adults,[23,24] so less is known about CLHIV receiving HIV care and treatment in Mozambique in recent years. Therefore, the objectives of this evaluation were to describe the degree of immunodeficiency and to identify risk factors for enrolling in HIV care and starting ART with severe immunodeficiency among children during the period of evolving ART initiation policies in Zambézia Province, Mozambique.

# METHODS

## Data Sources and Ethical Considerations

An electronic Open Medical Record System (OpenMRS)™ is utilized at VUMC/FGH-supported health facilities to facilitate patient care and program monitoring and evaluation activities. De-identified data were extracted from the OpenMRS database for this secondary analysis. This data use and evaluation plan were approved by the VUMC Institutional Review Board (170970) and the Institutional Research Ethics Committee for Health of Zambézia Province (*Comité Institucional de Bioética para Saúde – Zambézia*; 16-CIBS-Z-18). This project was reviewed in accordance with CDC human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes.

## Study Settings

This evaluation took place in Zambézia Province, Mozambique, which is a relatively underserved region of Mozambique with an HIV prevalence of 15% (compared to 13% nationally).[1–4] Children receiving HIV care and treatment at 107 public health facilities in nine districts (86% of all health facilities in these districts) of Zambézia Province were included in this evaluation. Fifteen of the health facilities included in this evaluation were in Quelimane, the urban capital district of Zambézia Province, while the remaining health facilities were in rural districts. Each health facility offers comprehensive HIV services, including clinical care, laboratory testing, and pharmacy services. Each district-level health system consists of one large health facility/referral center located in the district capital (offering primary and sometimes secondary health care) and smaller peripherally located health facilities and/or health posts (providing only primary care).

## Study Design, Variables, and Definitions

This was a retrospective cohort study using routinely collected patient data. The objectives of this evaluation were to: i) describe CD4 count trends among CLHIV over time, relative to ART initiation policies; and, ii) identify risk factors for enrolling in HIV care and starting ART with severe immunodeficiency.

All ART-naïve CLHIV (≥5 to <15 years of age) enrolled in HIV care at a VUMC/FGH-supported health facility from September 30, 2012 through September 30, 2018 were eligible for inclusion in this study. Those with known enrollment and ART initiation dates and documented absolute CD4 count data were included. ART initiation date was defined as the first ART pick-up at a health facility. Children less than 5 years of age were excluded due to a paucity of CD4 percentage data (71% missing), the standard by which immune status is assessed in this younger age group. Data for included children were captured from their date of enrollment to December 31, 2018.

*CD4 count at enrollment* was defined as the CD4 count nearest the date of enrollment into HIV care, within the range from 2 months before or after the enrollment date. *CD4 count at ART initiation* was defined as the CD4 count nearest the ART initiation date, within the range from 6 months prior to 2 months after ART initiation. These definitions were not mutually exclusive; CD4 count at enrollment and at ART initiation could be the same. *Severe immunodeficiency* was defined as a CD4 count <200 cells/mm$^3$.[25] CD4 counts documented as ≤0 (0.2%) or >3,500 cells/mm$^3$ (1.1%) were considered invalid and were deleted from the dataset.[26]

ART initiation "policy periods" correspond to implementation of evolving pediatric ART initiation guidelines. In Period 1 (September 30, 2012 – July 31, 2016), ART was recommended for children ≥5 years of age who had a CD4 count <350 cells/mm$^3$ or a WHO clinical stage 3 or 4 defining condition. In Period 2 (August 1, 2016 – October 31, 2017), the CD4 count threshold increased to <500 cells/mm$^3$, and implementation of Test and Start began in Quelimane and Namacurra districts. In Period 3 (November 1, 2017 – September 30, 2018), Test and Start was implemented province-wide (Table 1).

Child, caregiver, and health facility variables were extracted from the OpenMRS database. Child characteristics included: age, sex, and CD4 counts. Caregiver characteristics included: mother's age, father's age, and parents' vital status (alive vs. deceased). Health facility characteristics included: district, setting (urban vs. rural), and health facility type (referral center vs. peripheral health facility).

## Statistical Analyses

Descriptive statistics were used to summarize child, caregiver, and program characteristics. Temporal trends in CD4 counts and the proportion of children with severe immunodeficiency at enrollment in HIV care and at the time of ART initiation were also described and stratified by policy period and patient, caregiver, and program characteristics. We did not investigate whether there were cases where children were started on ART despite not meeting the criteria for ART initiation in effect during the policy period in which they were started on ART; rather, we were interested in aggregate outcomes during the respective policy periods. Wilcoxon signed-rank test was used to compare CD4 counts between enrollment and ART initiation within each policy period, and the chi-squared test for trend was used to assess the proportion of children with severe immunodeficiency over time.

Univariate logistic regression models for each variable were built to assess associations with severe immunodeficiency. Cases with missing data were omitted during the univariate analysis. The likelihood ratio test was used to assess the statistical significance of each association, while the difference between a level and the reference level within a variable was assessed by Wald test.

A multivariable logistic regression model was used to identify associations with severe immunodeficiency. Variables in the model were selected based on *a priori* hypotheses and included: policy period, district, health facility type (district referral center vs. peripheral health facility), sex, child's age, and parents' vital status. Inclusion of additional variables (e.g., parents' age) were considered but were excluded from the model due to excessive missingness and lack of statistical significance in univariate analyses ($p>0.05$). An interaction between policy period and age was also considered and included in the model. Calendar year was not included in the model due to a high correlation with policy period (Cramer's V = 0.774 and 0.755, at enrollment and ART initiation, respectively). Missing data for parents' vital status were imputed by iterative chained equations using the mice R package,[27] with a total of 50 imputations, while accounting for all variables included in the multivariable regression model. The significance of each term in the model was assessed by using the univariate Wald test based on the pooled regression coefficient and standard error from 50 imputed datasets.

All statistical analyses were conducted using R statistical software.[28]

## RESULTS

Among ART-naïve children ≥5 to <15 years of age receiving HIV care and treatment from VUMC/FGH-supported health facilities in Zambézia, 1,815/2,537 (72%) had valid absolute CD4 count data available at enrollment into HIV care, and 1,922/2,569 (75%) had CD4 count data available at ART initiation. There was significant variability in missingness of CD4 data between districts and health facilities, but there was no trend in missingness of CD4 data over time or across policy periods (data not shown).

At enrollment into HIV care, the median age was 8.5 years (interquartile range [IQR]: 6.5–10.8). There was no significant trend in median age at enrollment or at ART initiation across calendar years (p=0.14 at enrollment; p=0.30 at ART initiation) or policy periods (p=0.75 at enrollment; p=0.45 at ART initiation). Fifty-eight percent were girls but there were no significant differences between boys and girls in terms of missingness of CD4 data. Among the 980 (54%) for whom parents' vital status was known, both parents were alive for 56% of the children, only the mother was alive for 18%, only the father was alive for 15%, and 11% were orphans/both parents were deceased. One-third of the cohort was from Quelimane district, the urban capital of Zambézia Province, while the remaining children were from the eight other rural districts from which we collected pediatric CD4 data. Approximately one-quarter of children were enrolled in care at a district capital health facility (i.e., district referral centers), while 73% were enrolled at peripheral health facilities within the respective districts. Fifty-four percent of children were enrolled in HIV care during Period 1, 14% during Period 2, and 32% in Period 3 (Table 2).

Median CD4 count at enrollment into HIV care and at ART initiation were similar at 504 cells/mm$^3$ (IQR: 277–798) and 501 cells/mm$^3$ (IQR: 275–809), respectively (Table 2). Median CD4 counts at enrollment and at ART initiation were also similar across policy periods (495 vs. 477 cells/mm$^3$ in Period 1 (p=0.418), 568 vs. 555 cells/mm$^3$ in Period 2 (p=0.925), and 504 vs. 529 cells/mm$^3$ in Period 3 (p=0.421)). However, the proportion of children with severe immunodeficiency (i.e., CD4 count <200 cells/mm$^3$) decreased over time (by calendar year and across policy periods). Severe immunodeficiency at enrollment decreased from 28% in 2013 to 15% in 2018 (p<0.001 for trend) and at ART initiation decreased from 33% in 2013 to 15% in 2018 (p<0.001 for trend). As shown in Figure 1A and Table 3, the there was a non-significant trend in the proportion of children with severe immunodeficiency at enrollment across policy periods (20% in Period 1, 19% in Period 2, and 16% in Period 3; p=0.120 for trend), and a significant decrease in the proportion of children with severe immunodeficiency at ART initiation across policy periods (21% in Period 1, 17% in Period 2, and 15% in Period 3; p=0.003 for trend). The proportion of children with severe immunodeficiency did not significantly differ between districts (p=0.13 at enrollment, and p=0.09 at ART initiation) or health facilities (p=0.16 at enrollment, and p=0.14 at ART initiation).

In univariate analyses (Table 3), older age (p<0.001 at enrollment and at ART initiation) and receiving care at a peripheral health facility (p=0.041 at enrollment; p=0.037 at ART initiation) were associated with severe immunodeficiency. Having a living mother was protective against severe immunodeficiency at enrollment in HIV care (p=0.003) and at ART initiation (p=0.005). When considering parents' vital status simultaneously (Figure 1B), compared to orphans (i.e., both mother and father were deceased), children for whom both parents were alive were significantly less likely to have severe immunodeficiency at the time of enrollment into HIV care (OR=0.56; 95% CI: 0.35–0.93) and trended toward lower odds of having severe immunodeficiency at ART initiation (OR=0.62; 95% CI: 0.39–1.03). Parents' age was not associated with severe immunodeficiency at enrollment (mother's age, p=0.196; father's age, p=0.900) or at ART initiation (mother's age, p=0.113; father's age, p=0.790).

In multivariable analyses (Table 4), children who enrolled in HIV care during Period 3 trended toward lower odds of severe immunodeficiency at enrollment (aOR=0.80; 95% CI: 0.61–1.06), and were significantly less likely to have severe immunodeficiency at ART initiation (aOR=0.67; 95% CI: 0.51–0.88) compared to Period 1. With each year increase in age there was 13% increased odds of enrollment into HIV care with severe immunodeficiency (aOR=1.13; 95% CI: 1.06–1.20) and 14% increased odds of ART initiation with severe immunodeficiency (aOR=1.14; 95% CI: 1.08–1.21). Those enrolled in care at a district referral center were less likely to have severe immunodeficiency than those enrolled at peripheral health facilities, both at enrollment (aOR=0.72; 95% CI: 0.52–0.99) and at ART initiation (aOR=0.71; 95% CI: 0.51–0.97). Receiving care in the district of Gilé was also associated with lower odds of enrollment in HIV care (aOR=0.21; 95% CI: 0.06–0.77) and initiating ART (aOR=0.18; 95% CI: 0.05–0.66) with severe immunodeficiency; however, children in Gilé only accounted for 3% of the cohort and <1% of cases of severe immunodeficiency, so the explanation for this finding is uncertain and we cannot exclude the possibility that this was due to the small sample size in this district. While not statistically significant, there was a trend toward boys being more likely to enroll in HIV care (aOR=1.26; 95% CI: 0.99–1.61) and initiate ART (aOR=1.26; 95% CI: 0.99–1.60) with severe immunodeficiency compared to girls. Compared to orphans, there was a non-statistically significant trend toward children with a living mother and father being less likely to enroll in care (aOR=0.67; 95% CI: 0.43–1.04) and initiate ART (aOR=0.72; 95% CI: 0.45–1.15) with severe immunodeficiency.

## DISCUSSION

In this evaluation we described the degree of immunodeficiency and identified risk factors for enrolling in HIV care and starting ART with severe immunodeficiency among children during a period of evolving ART initiation policies in Zambézia Province, Mozambique. Our main findings were that in the setting of progressively more inclusive WHO pediatric ART initiation guidelines being implemented in Mozambique, there were decreasing proportions of children with severe immunodeficiency at ART initiation, and that older children and those enrolled at peripheral health facilities were more likely to be severely immunodeficient.

It was anticipated that the prevalence of severe immunodeficiency would decrease over time and across policy periods, continuing the trend previously reported from low- and middle-income countries (LMIC) prior to 2013,[21,22] but it is difficult to know whether this improvement was attributable to specific ART initiation policy changes. However, the fact that we found a non-significant trend in severe immunodeficiency at enrollment in HIV care across policy periods and a significant difference in severe immunodeficiency at ART initiation across policy periods suggests that policy changes may have played a causal role in the observed improvements. Regardless, it is notable that we observed a decrease in severe immunodeficiency at ART initiation from 33% in 2013 to 15% in 2018. Similar LMIC cohorts reported 58–66% of children starting ART with severe immunodeficiency in 2010,[22] and 42–64% in 2013;[21] however, inclusion of children younger than 5 years of age in these cohorts limits comparability.

Median CD4 counts and the proportion of children with severe immunodeficiency, overall, were similar at enrollment and at ART initiation, which suggests that delays in ART initiation were not the sole cause for starting ART with severe immunodeficiency. It seems that many children who start ART with severe immunodeficiency do so after entering care already severely immunodeficient. This is consistent with our finding that older children, most of whom were probably perinatally infected and had been living with untreated HIV for years,[29] were more likely to have severe immunodeficiency both at enrollment and at ART initiation. The association between older age and starting ART at a late stage of disease has also been reported in other studies,[22,30] indicating that barriers to early diagnosis and treatment of CLHIV persist. Unfortunately, we did not capture high quality data from children younger than 5 years of age to better understand this relationship, but it stands to reason that earlier diagnosis of HIV and improved linkage to HIV care and treatment would further decrease the proportion of children entering into care and starting ART with severe immunodeficiency.

We also found that children enrolled at district capital health facilities were less likely to have severe immunodeficiency at enrollment and at ART initiation compared to children enrolled at peripheral health facilities. Other studies have also found that pediatric HIV service delivery and outcomes are worse in more remote clinical settings.[31–34] Nevertheless, great progress has been made in recent years to bolster and decentralize both community- and facility-based services provided to HIV-affected populations.[30,35–43] These findings support the importance of these investments and suggest that even more should be done to support pediatric HIV service delivery at peripheral sites.

There was no statistically significant relationship between sex and severe immunodeficiency in our multivariable model; however, there was a non-significant trend toward boys being more likely to have severe immunodeficiency than girls. Other studies have also noted sex-based differences in HIV outcomes: barriers to engagement of adult men in HIV services in LMIC have been reported;[44–46] men in Zambézia were more likely to initiate ART with severe immunodeficiency in a recent study;[23] and, adolescent boys in Zambézia enroll in care with more advanced HIV disease, take longer to initiate ART, and are more likely to experience pre-ART loss to follow-up than adolescent girls.[47] Taken together with the fact that only 42% of children in this cohort were boys, there are possibly sex-based disparities that need to be addressed to ensure timely access to pediatric HIV care and treatment for both boys and girls.

While not consistently meeting thresholds for statistical significance, our findings do seem to point toward orphans having worse baseline immunologic status than children with living parents. Other studies have also linked maternal health and mortality to pediatric outcomes in the context of HIV exposure and infection,[48–50] and others have emphasized the vulnerability of HIV-affected orphans,[51–53] but less is known about the causal pathway between parents' vital status and children's risk for HIV-associated immunodeficiency. Nonetheless, it appears that providing optimal care for CLHIV should also include efforts to ensure optimal health for and engagement of caregivers, including biological parents. Furthermore, when children are orphaned, additional resources and caregiver support may be necessary to ensure timely diagnosis and treatment of these children living with HIV.

We acknowledge several limitations for this analysis and evaluation. Firstly, we excluded children younger than 5 years of age (n=5,697; 69% of those 0 to <15 years of age) due to a paucity of CD4 percentage data. We attempted to circumvent this issue by calculating CD4 percentage when both absolute CD4 and lymphocyte counts were obtained on the same day, but even after systematically performing this exercise, there was still 71% missingness of CD4 percentage data. Therefore, it was determined that the sample of children less than 5 years of age would lack the external validity needed to extrapolate findings to the general population. This led to a smaller sample size for our analyses, but there were still nearly 2,000 children older than 5 years of age and with valid CD4 data from which we were able to generate generalizable results. Moreover, another recently published study including CLHIV from multiple sites in sub-Saharan Africa helps to fill in some of the gaps in our data, and demonstrated similar temporal improvements in baseline degree of immunodeficiency in those younger than 5 years of age at the time of ART initiation.[54] Regardless, this limitation highlights an important monitoring and evaluation and service delivery issue; health facilities providing pediatric HIV care and treatment should be able to routinely obtain and document CD4 percentage results. Some might argue that in the era of Test and Start, CD4 monitoring is less important than it was in the past when immunologic criteria were used to determine ART eligibility; however, CD4 data are still very relevant for determining immune competence, risk for opportunistic infections, and prognosis.[24]

Another limitation is that there were some factors (e.g., WHO clinical stage, HIV viral load, and important co-infections such as tuberculosis and malaria) we were unable to account for in multivariable analysis because the data were either unavailable, had a high degree of missingness, or were non-informative. It would have also been useful to know more about the mothers' and children's peripartum engagement in PMTCT services. Sustained engagement in PMTCT services not only helps to promote maternal viral suppression thereby mitigating risk for vertical transmission, but PMTCT care is also centrally important to ensuring timely diagnosis and linkage to ART for the subset of infants who become HIV-positive. One would expect that mothers who were aware of their HIV status and on ART throughout pregnancy and the period of breastfeeding, would be more likely to have children with early and sustained engagement in HIV care. Similarly, one would expect that HIV-exposed infants who received post-partum antiretroviral prophylaxis would be more likely to have early engagement and sustained retention in HIV care. However, data quality was insufficient to assess these hypotheses. Regardless, these factors are probably more important for younger children, while in this study we were only able to assess children 5 years of age and older, the vast majority of whom were presumably perinatally infected but missed earlier opportunities for HIV diagnosis and treatment. Altogether, this emphasizes the need for more thorough data collection for and assessment of HIV-exposed infants.

In conclusion, implementation of progressively more inclusive pediatric ART initiation guidelines was associated with decreasing proportions of children with severe immunodeficiency at ART initiation. However, considering that in 2018, 15% of this Mozambican cohort of CLHIV commenced ART with severe immunodeficiency, there is still much work to be done. In particular, it seems that additional efforts and resources are needed to promote pediatric case finding to ensure early diagnosis and treatment of CLHIV, especially at lower-resourced peripheral clinics and among orphans and other vulnerable children. Additionally, more research is needed to understand and improve care initiation and treatment outcomes for vulnerable subgroups of children, namely orphans, boys, and those receiving longitudinal care at peripheral health facilities.

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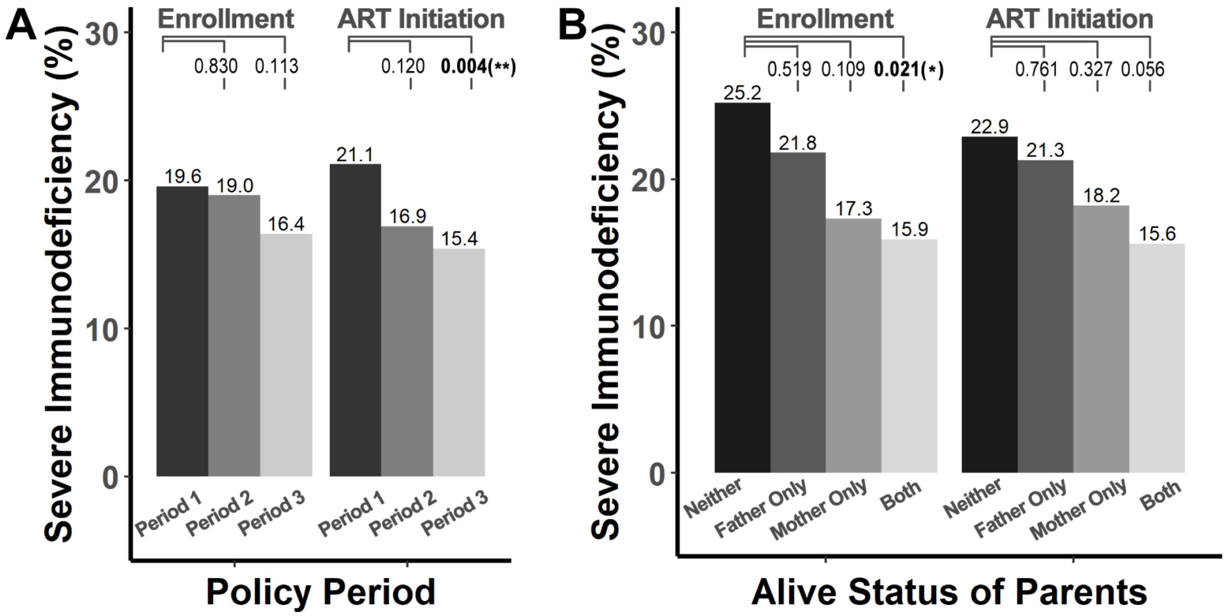


**Figure 1.**

Prevalence of severe immunodeficiency at enrollment or ART initiation stratified by (**A**) policy periods, or (**B**) parents' vital status. P values of Wald test in the univariate logistic model are shown above the bars. The statistical significance is highlighted by *(p<0.05) and **(p<0.01).

**Table 1:**
**Pediatric antiretroviral therapy (ART) initiation policy periods.**

There was phased implementation of ART initiation guidelines across districts over time, with evolution from immune-based criteria (CD4 count) to Test and Start.

| District | Period 1<br>ART for ≥5 years of age with CD4 count <350 cells/mm$^3$ or WHO clinical stage 3 or 4<br>Sept 30, 2012 –<br>July 31, 2016 | Period 2<br>ART for ≥5 years of age with CD4 count <500 cells/mm$^3$ or WHO clinical stage 3 or 4<br>Roll-out of Test & Start<br>Aug 1, 2016 –<br>Oct 31, 2017 | Period 3<br>Test & Start<br>(all districts)<br>Nov 1, 2017 –<br>Sept 30, 2018 |
|---|---|---|---|
| Alto Molòcué | | | Test & Start |
| Gilé | | | Test & Start |
| Ile * | | | Test & Start |
| Inhassunge | | | Test & Start |
| Maganja da Costa | | | Test & Start |
| Mocubela | | | Test & Start |
| Namacurra ** | | Test & Start | Test & Start |
| Pebane | | | Test & Start |
| Quelimane | | Test & Start | Test & Start |

Note: Periods in which immune-based criteria (CD4 count) were used to determine eligibility for ART initiation are indicated in grey.

* For Ile, Test and Start was implemented February 1, 2018.

** For Namacurra, Test and Start was implemented April 11, 2017.

**Table 2:**

Child, caregiver, and program characteristics at enrollment in HIV care and at the time of antiretroviral therapy (ART) initiation.

| | Enrollment (N=1815) | ART Initiation (N=1922) |
|---|---|---|
| CD4 count (cells/mm$^3$) [a] | 504 [277–798] | 501 [275–809] |
| <200 (severe immunodeficiency) [b] | 335 (18%) | 357 (19%) |
| ≥200 (not severe) | 1480 (82%) | 1565 (81%) |
| Age (years) | 8.5 [6.5–10.8] | 8.4 [6.5–10.7] |
| 5–9 | 1203 (66%) | 1266 (66%) |
| 10–14 | 612 (34%) | 656 (34%) |
| Sex | | |
| Female | 1061 (58%) | 1115 (58%) |
| Male | 754 (42%) | 807 (42%) |
| Mother's age (years) | 30 [25–35] | 30 [25–35] |
| Missing [c] | 697 (38%) | 733 (38%) |
| Father's age (years) | 36 [30–42] | 36 [30–42] |
| Missing | 948 (52%) | 1001 (52%) |
| Parents' vital status | | |
| Both mother and father alive | 547 (56%) | 589 (57%) |
| Only mother alive | 179 (18%) | 181 (17%) |
| Only father alive | 147 (15%) | 150 (14%) |
| Both mother and father deceased | 107 (11%) | 118 (11%) |
| Missing | 835 (46%) | 884 (46%) |
| District | | |
| Alto Molòcué (rural) | 88 (5%) | 93 (5%) |
| Gilé (rural) | 58 (3%) | 60 (3%) |
| Ile (rural) | 88 (5%) | 88 (5%) |
| Inhassunge (rural) | 164 (9%) | 176 (9%) |
| Maganja da Costa (rural) | 185 (10%) | 190 (10%) |
| Mocubela (rural) | 170 (9%) | 173 (9%) |
| Namacurra (rural) | 314 (17%) | 339 (18%) |
| Pebane (rural) | 162 (9%) | 176 (9%) |
| Quelimane (urban) | 586 (32%) | 627 (33%) |
| Policy period | | |
| Period 1 | 981 (54%) | 1004 (52%) |
| Period 2 | 253 (14%) | 273 (14%) |
| Period 3 | 581 (32%) | 645 (34%) |

| | Enrollment (N=1815) | ART Initiation (N=1922) |
|---|---|---|
| Year | | |
| 2013 | 201 (11%) | 160 (8%) |
| 2014 | 248 (14%) | 257 (13%) |
| 2015 | 262 (14%) | 283 (15%) |
| 2016 | 323 (18%) | 371 (19%) |
| 2017 | 333 (18%) | 364 (19%) |
| 2018 | 448 (25%) | 487 (25%) |
| Health facility type | | |
| District referral center | 492 (27%) | 514 (27%) |
| Peripheral facility | 1323 (73%) | 1408 (73%) |

[a:] For continuous variables, median [interquartile range] are shown.

[b:] For categorical variables, frequency (percentage) are shown.

[c:] “Missing” category appears only when there are missing values for a variable.

### Table 3:

Univariate analysis of associations with severe immunodeficiency at enrollment in HIV care and at the time of antiretroviral therapy (ART) initiation.

| | Enrollment | | ART initiation | |
|---|---|---|---|---|
| | **Severe immunodeficiency n/N (%)** | **p-value*** | **Severe immunodeficiency n/N (%)** | **p-value*** |
| Age (years) | | **<0.001** | | **<0.001** |
| 5–9 | 190/1203 (16%) | | 206/1266 (16%) | |
| 10–14 | 145/612 (24%) | | 151/656 (23%) | |
| Sex | | 0.090 | | 0.120 |
| Female | 182/1061 (17%) | | 194/1115 (17%) | |
| Male | 153/754 (20%) | | 163/807 (20%) | |
| District | | 0.097 | | 0.066 |
| Alto Molòcué | 17/88 (19%) | | 19/93 (20%) | |
| Gilé | 3/58 (5%) | | 3/60 (5%) | |
| Ile | 18/88 (21%) | | 18/88 (21%) | |
| Inhassunge | 35/164 (21%) | | 37/176 (21%) | |
| Maganja da Costa | 36/185 (20%) | | 38/190 (20%) | |
| Mocubela | 32/170 (19%) | | 34/173 (20%) | |
| Namacurra | 49/314 (16%) | | 55/339 (16%) | |
| Pebane | 27/162 (17%) | | 27/176 (15%) | |
| Quelimane | 118/586 (20%) | | 126/627 (20%) | |
| Setting | | 0.206 | | 0.235 |
| Urban | 118/586 (20%) | | 126/627 (20%) | |
| Rural | 217/1229 (18%) | | 231/1295 (18%) | |
| Policy period | | 0.271 (0.120 for trend) | | **0.009** (**0.003** for trend) |
| Period 1 | 192/981 (20%) | | 212/1004 (21%) | |
| Period 2 | 48/253 (19%) | | 46/273 (17%) | |
| Period 3 | 95/581 (16%) | | 99/645 (15%) | |
| Year | | **0.001** (**<0.001** for trend) | | **<0.001** (**<0.001** for trend) |
| 2013 | 56/201 (28%) | | 52/160 (33%) | |
| 2014 | 55/248 (22%) | | 58/257 (23%) | |
| 2015 | 42/262 (16%) | | 56/283 (20%) | |
| 2016 | 48/323 (15%) | | 54/371 (15%) | |
| 2017 | 66/333 (20%) | | 66/364 (18%) | |
| 2018 | 68/448 (15%) | | 71/487 (15%) | |
| Health facility type | | **0.041** | | **0.037** |
| District referral center | 76/492 (15%) | | 80/514 (16%) | |
| Peripheral facility | 259/1323 (20%) | | 277/1408 (20%) | |

*P-values from likelihood ratio tests are reported, except where p-values from chi-squared tests for trend in proportions are noted in parentheses.

**Table 4:**

Multivariable analysis of associations with severe immunodeficiency at enrollment in HIV care and at the time of antiretroviral therapy (ART) initiation.

| | Enrollment aOR (95% CI) | ART Initiation aOR (95% CI) |
|---|---|---|
| Policy period | | |
| Period 1 | reference | reference |
| Period 2 | 1.02 (0.70–1.51) | 0.80 (0.55–1.17) |
| Period 3 | 0.80 (0.61–1.06) | **0.67 (0.51–0.88)** |
| Age (per 1-year increase) | **1.13 (1.06–1.20)** | **1.14 (1.08–1.21)** |
| Sex | | |
| Female | reference | reference |
| Male | 1.26 (0.99–1.61) | 1.26 (0.99–1.60) |
| Health facility type | | |
| Peripheral facility | reference | **0.72 (0.52–0.99)** |
| District referral center | reference | **0.71 (0.51–0.97)** |
| Parents' vital status | | |
| Both mother and father dead | reference | reference |
| Only mother alive | 0.69 (0.40–1.19) | 0.87 (0.52–1.44) |
| Only father alive | 0.91 (0.55–1.51) | 0.97 (0.57–1.66) |
| Both mother and father alive | 0.67 (0.43–1.04) | 0.72 (0.45–1.15) |
| District | | |
| Alto Molòcué | reference | reference |
| Gilé | **0.21 (0.06–0.77)** | **0.18 (0.05–0.66)** |
| Ile | 1.06 (0.50–2.27) | 0.95 (0.45–1.99) |
| Inhassunge | 1.00 (0.52–1.95) | 0.84 (0.44–1.59) |
| Maganja da Costa | 0.93 (0.48–1.80) | 0.83 (0.44–1.57) |
| Mocubela | 0.79 (0.39–1.57) | 0.69 (0.35–1.35) |
| Namacurra | 0.69 (0.37–1.30) | 0.61 (0.33–1.12) |
| Pebane | 0.75 (0.38–1.50) | 0.60 (0.31–1.17) |
| Quelimane | 0.81 (0.43–1.52) | 0.71 (0.39–1.29) |

NOTE: An interaction between age and policy period was accounted for in the model