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Ongoing High Prevalence of Severe Immune Suppression Among Children in South Africa

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Background: Among children in Southern Africa severe immune suppression (SIS) has declined, but most continue to initiate antiretroviral therapy (ART) with SIS.

Setting: Using data from South Africa, we describe SIS at ART start and on ART between 2007 and 2020, among children <5 years with a CD4%/cell count at ART start and ≥1 subsequent measure.

Methods: Gap in care was defined as >9 months without a recorded visit. We defined SIS according to age and CD4%/cell count. A multistate model was used to estimate transition probabilities between 5 states: SIS on ART; Stable, not SIS; Early Gap, commencing <9 months from ART start; Late Gap, commencing ≥9 months on ART; and Death.

Results: Among 2536 children, 70% had SIS at ART start, and 36% experienced SIS on ART. An increasing proportion were age <1 year at ART initiation (2007–2009: 43% to 2013–2020: 55%). Increasingly, SIS on ART occurred after a gap, in those with SIS on ART for >1 year, and after a period of unknown immune status. Later year of ART initiation was associated with reduced transition from SIS on ART to Stable. Infants and those initiating ART with SIS were more likely to transition from Stable to SIS. Viremia strongly predicted death from both the on ART states.

Conclusions: Increasingly SIS occurred among ART-experienced children. Those starting ART with SIS and during infancy remained especially vulnerable to SIS once on treatment. Managing ART in these children may be more complex and further reducing AIDS-related mortality is likely to remain challenging.

Key Words: severe immune suppression, engagement in care, children living with HIV, antiretroviral therapy, Southern Africa

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INTRODUCTION

The enormous improvements in HIV prevention, early diagnosis, and treatment have led to important reductions in new HIV infections and mortality in children. In Southern Africa, fewer children are becoming infected with HIV, which has resulted in a decline in the number initiating antiretroviral therapy (ART). There has also been a trend among those initiating ART to do so at a younger age and with less advanced disease.[1] Despite these successes, HIV in children continues to be a major public health burden in the region, and although AIDS-related deaths have declined, reductions in annual mortality have slowed.[2]

In Southern Africa, data on the prevalence of severe HIV-related disease in children shows marked declines,[1,3–6] but most continue to initiate ART with severe immune suppression (SIS) or WHO stage III or IV disease, and more recent data are needed. Among adults, advanced HIV disease is increasingly observed in treatment-experienced patients, including those re-engaging in care after treatment interruption.[7] The extent to which this is occurring in children is unknown, and it is possible that SIS is increasing among children on ART because of treatment interruption, poor adherence, or drug resistance.[8]

As the cohort of children initiating ART shifts to younger and healthier children, few studies have described SIS among children at ART start and among those who are ART-experienced. Using a multistate model, we aimed to estimate transition probabilities to and from a severely immune-suppressed state, and to describe associations with transitions.

METHODS

Study Population

We used routinely collected data from Harriet Shezi, Rahima Moosa, and Khayelitsha, 3 South African cohorts participating in the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration. IeDEA is a global research consortium that collects routine

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data from cohorts who submit anonymized data on patients enrolled in HIV care.[9] Ethical approval for this study was obtained from local institutional review boards to contribute anonymized, individual data to IeDEA-SA.

During the study period ART eligibility criteria were revised several times. Initially, South African treatment guidelines recommended ART for children based on clinical or immunologic criteria.[10,11] From 2010, eligibility was expanded to all infants <12 months old, and in 2012 all children with HIV <5 years were eligible.[12,13]

Eligibility Criteria

We included all children aged <5 years initiating ART from 2007 to 2020 with ≥9 months of follow-up between ART start and database closure, which ranged across cohorts from 29 December, 2016, to 4 March, 2021. We excluded those without a CD4%/cell count at ART start and those without ≥1 subsequent CD4 measure.

Measures/States of Care

We defined SIS according to the 2006 WHO guidelines, using age-based thresholds and CD4%, or CD4 cell count where CD4% was not available.[14] CD4%/cell count at ART start was chosen within a window of 6 months prior, to ≤7 days after ART start. We defined a gap in care as having ≥9 months without a recorded visit, ensuring patients were truly out of care and without ART during a gap.

National guidelines for CD4 and VL monitoring on ART changed during the study period. Initially, CD4 and VL monitoring were recommended on a 6 monthly basis. Frequency of monitoring was reduced with the most recent guidelines recommending VL monitoring at month 6, month 12 on ART, and annually thereafter if suppressed, and CD4 monitoring at month 12 and every 6 months thereafter, if indicated through virologic and age-based immunologic criteria.[10,15–19]

For each patient, we assigned periods of follow-up time to one of 5 states of ART care, defined as follows: SIS on ART, most recent CD4 measure within the previous year indicating SIS; Stable on ART, most recent CD4 measure within the previous year indicating no SIS; Early Gap, gap occurring within 9 months of ART start; Late Gap, gap commencing >9 months after ART start; and Death(Fig. 1). We used a censored state for periods with unknown immune status, for time on ART without a recorded CD4 measure in the previous year, and the model assumed periods spent in this censored state were in either of the "on ART" states.

Data on death were obtained from clinic records. Follow-up time was measured until the date of death, transfer, or database closure. Patients were assigned to either of the Gap states if their last registered contact was ≥9 months before database closure. For patients whose last contact was <9 months from database closure, their state at database closure was assigned to one of the following: their current on-ART state, the censored on-ART state if their last CD4 measure was >12 months before database closure. We added 1 day of follow-up for those who had a second CD4 measure on ART but no further contact.

Weight-for-age and height-for-age Z-scores were calculated using WHO Child Growth Reference Standards.[20] For growth measures at ART initiation, a window of 6 months before and ≤15 days after ART start was used. We defined ART regimen categories based on whether regimens included non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs), in combination with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) because these were the main drugs available during the study period.

Statistical Analysis

We described patient characteristics at ART start, trends in the prevalence of SIS at ART start, and the proportion who experienced SIS after starting ART (SIS on ART). Among those who experienced SIS on ART, we described their prior state to SIS and prevalence of viremia. For those with SIS on ART for >1 year, we assigned SIS on ART as prior state. We described the prevalence of viremia (VL > 1000 copies/mL) at the most recent VL within the previous year to SIS on ART, excluding episodes of SIS on ART that occurred immediately after a gap in care.

Model Description

We used a parametric, continuous-time multi-state Markov model to identify factors associated with transitioning between states. For the multistate model, to ensure follow-up time between patients starting ART in different calendar periods was similar, we restricted our analysis to patient data from the first 5 years after ART initiation.

We modelled 12 possible transitions among 5 states, with reverse transitions allowed except to the Early Gap state and from Death (Fig. 1). The probabilities of transition to and from SIS on ART were of primary interest in this study. Early Gap was the initial state for any patient with a gap in care commencing at <9 months on ART, ensuring that transitions to Gap states were independent of time. We included the following fixed covariates to adjust for differences in transition by sex (male or female), year of ART start (2007–2009, 2010–2012, 2013–2021), immune status at ART start (SIS or not SIS), and age at ART start (0–1, 1–2, 2–5 years). We also included the time-updated covariates of ART regimen (PI-based, NNRTI-based) and VL (<1000, ≥1000 copies/mL, missing). We performed stratified analyses to explore differences in transition probabilities by age at ART initiation.

Multistate models assume that transition probabilities between states are independent of previous states. Estimated adjusted hazard ratios are constant over time and multiplicative, similar to adjusted hazard ratios of Cox proportional hazards models. Our model allowed for unobserved transitions between SIS on ART and Stable on ART states, but specified exact transition times to Gap states and to death.

Stata version 15 was used for data management and descriptive statistics, and the msm package in R for the multistate model.[21]

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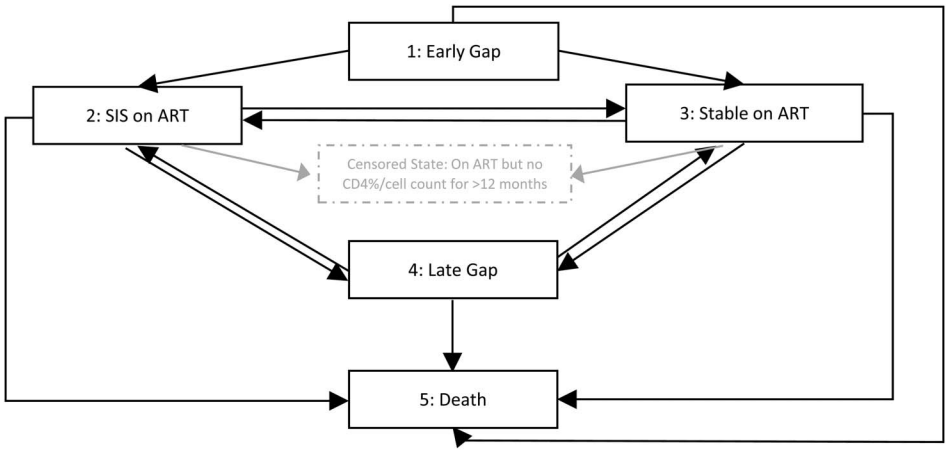


FIGURE 1. Diagram of states and transitions of the multistate model. SIS on ART: SIS after ART start. Stable on ART: Not severely immune suppressed after ART start. Gap in care: no recorded visit for ≥9 months. Early Gap: gap in care commencing ≤9 months from ART start. Late Gap: gap in care commencing >9 months from ART start.

RESULTS

We included 2536 children in the study. Median age at ART initiation was 1.1 years (interquartile range 0.4–2.4), and 49% were girls (Table 1). In more recent years, fewer children initiated ART, and the proportion of children who were aged <1 year at ART initiation increased from 43% in 2007%–2009% to 55% in 2013–2020. At ART initiation, 70% had SIS. Prevalence of SIS at ART start initially declined, plateaued after 2010 and remained extremely high (68%) in the most recent period. The proportion with severe underweight weight-for-age and severely stunted height-for-age z-scores (≤-3) at ART start declined in more recent years, but the proportion with missing z-scores increased. Supplemental Digital Content (see Table S1, http://links.lww.com/QAI/B998) shows characteristics among those included and excluded from the study. Those excluded were younger, had shorter follow-up, and a larger proportion died.

During follow-up, an increasing proportion received PI-based ART (81% in 2007%–2009% to 90% in 2013–2020), and experienced viremia (44% in 2007%–2009% to 57% in 2013–2020). After starting ART, 36% experienced SIS on ART. With later year of ART start, the proportion who experienced SIS on ART initially declined, but increased after 2013. The proportion of children who experienced Early Gap increased, and a decreasing proportion experienced the Stable on ART state.

During the study period, the proportion of person-time in care spent with SIS on ART initially declined, but increased to 13% in 2014(Fig. 2A). Subsequently, time in care with unknown immune status (periods with no recorded CD4 measure in the previous year) increased, whereas time spent in Stable or SIS on ART states declined. Similarly, the proportion of person-time spent with SIS declined with longer duration on ART, from 26% during the first year to 5% during the fifth year, whereas the proportion with unknown immune status increased to 18% during the fifth year (Fig. 2B). Time spent on ART without a recorded VL measure in the previous year accounted for 2.8% of person-time on ART, and did not vary substantially during the study period (2.9% in 2007–2009, 2.2% in 2010–2012, 3.0% from 2013 onward).

Prior State to SIS on ART, and SIS on ART With Viremia

SIS on ART occurred as an initial state, or after a gap in care, a period of being Stable on ART, a period with no recorded CD4 measure, or after a period of prolonged SIS of >1 year. Figure 3 describes prior state to SIS on ART by calendar year. An increasing proportion of SIS on ART occurred when re-engaging in care after a gap, in those with SIS for >1 year, and those with unknown immune status. Of 1378 SIS on ART states that occurred after a period in care, 523 (38%) occurred with viremia. The proportion of SIS on ART states that occurred with viremia increased with calendar year of ART start (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/B998).

Multistate Model

Table 2 summarizes the results from our multistate model. We found later year of ART start was associated with reduced transition from SIS to Stable on ART. Those initiating ART in the most recent period were less likely to transition to SIS from Stable on ART. Those initiating ART with SIS were less likely to experience favorable outcomes, being less likely to transition from Early Gap to Stable, and more likely to transition from Stable to SIS. Compared with infants, those aged 2–5 years were less likely to transition from Stable to SIS, whereas those aged 1–2 years were less likely to transition from SIS to Stable. Viremia was strongly associated with transition from SIS and Stable on ART states to death, and from Stable to SIS.

Age-Stratified Analysis

In our age-stratified analysis, for those aged 1–2 years at ART start, there were too few transitions to model associations from Early Gap to Death, and for those aged 2–5 years from any state to Death. Compared with unstratified analysis, there were some differences by age(see Table S2, Supplemental Digital Content, http://links.lww.com/QAI/B998). Notably, compared with infants initiating ART without SIS, those with SIS at ART start were less likely to transition from SIS to Stable.

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TABLE 1. Characteristics of Children <5 Years Initiating ART Between 2007 and 2020 in South Africa (n = 2536)

Characteristic	2007–2009	2010–2012	2013–2020	Total
Total	1114	762	660	2536
Sex				
Male	567 (50.9%)	381 (50.0%)	348 (52.7%)	1296 (51.1%)
Age at ART start (years)				
Median (IQR)	1.27 (0.5–2.7)	1.10 (0.4–2.6)	0.79 (0.2–1.8)	1.10 (0.4–2.4)
0-1	473 (42.5%)	367 (48.2%)	366 (55.5%)	1206 (47.6%)
1-2	251 (22.5%)	142 (18.6%)	148 (22.4%)	541 (21.3%)
2-5	390 (35.0%)	253 (33.2%)	146 (22.1%)	789 (31.1%)
Immune status at ART start				
Severely immune suppressed	805 (72.3%)	509 (66.8%)	448 (67.9%)	1762 (69.5%)
WHO stage at ART start				
WHO Stage 3 or 4	678 (60.9%)	504 (66.1%)	311 (47.1%)	1493 (58.9%)
missing	329 (29.5%)	78 (10.2%)	114 (17.3%)	521 (20.5%)
Firstline ART regimen				
NNRTI	271 (24.3%)	174 (22.8%)	154 (23.3%)	599 (23.6%)
PI	839 (75.3%)	584 (76.6%)	489 (74.1%)	1912 (75.4%)
NRTI only	3 (0.3%)	1 (0.1%)	8 (1.2%)	12 (0.5%)
other	1 (0.1%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
unknown	0 (0.0%)	2 (0.3%)	9 (1.4%)	11 (0.4%)
PI-Based ART during follow-up	900 (80.8%)	627 (82.3%)	595 (90.2%)	2122 (83.7%)
Viremic during follow-up	565 (50.7%)	419 (55.0%)	378 (57.3%)	1362 (53.7%)
Viremic following viral suppression	378 (33.9%)	220 (28.9%)	166 (25.2%)	764 (30.1%)
Weight-for-age Z-score at ART start				
≤-3	121 (10.9%)	59 (7.7%)	35 (5.3%)	215 (8.5%)
−3 to −2	97 (8.7%)	68 (8.9%)	32 (4.8%)	197 (7.8%)
>-2	278 (25.0%)	189 (24.8%)	153 (23.2%)	620 (24.4%)
Missing	618 (55.5%)	446 (58.5%)	440 (66.7%)	1504 (59.3%)
Height-for-age Z-score at ART start				
≤-3	175 (15.7%)	91 (11.9%)	51 (7.7%)	317 (12.5%)
−3 to −2	137 (12.3%)	74 (9.7%)	41 (6.2%)	252 (9.9%)
>-2	186 (16.7%)	144 (18.9%)	117 (17.7%)	447 (17.6%)
Missing	616 (55.3%)	453 (59.4%)	451 (68.3%)	1520 (59.9%)
Median duration on ART at database closure (IQR)	11.96 (11.1–13.0)	9.66 (8.4–10.3)	4.91 (3.9–6.2)	10.01 (6.8–11.7)
Death	18 (1.6%)	8 (1.0%)	9 (1.4%)	35 (1.4%)
Initial state				
Early gap	109 (9.8%)	100 (13.1%)	109 (16.5%)	318 (12.5%)
SIS on ART	323 (29.0%)	178 (23.4%)	192 (29.1%)	693 (27.3%)
Stable on ART	682 (61.2%)	484 (63.5%)	359 (54.4%)	1525 (60.1%)
SIS during follow-up	436 (39.1%)	250 (32.8%)	241 (36.5%)	927 (36.6%)
Early Gap state during follow-up	109 (9.8%)	100 (13.1%)	109 (16.5%)	318 (12.5%)
Late Gap state during follow-up	789 (70.8%)	541 (71.0%)	372 (56.4%)	1702 (67.1%)
Stable on ART state during follow-up	1030 (92.5%)	681 (89.4%)	546 (82.7%)	2257 (89.0%)

Early Gap, gap in care commencing ≤9 months from ART start; Gap in care: no recorded visit for ≥9 months; IQR, interquartile range; Late Gap: gap in care commencing >9 months from ART start; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; SIS on ART, Severe immune suppression after ART start; Stable on ART, not severely immune suppressed after ART start; Viremic: viral load ≥1000 copies/mL.

Validation

We compared model projections with the observed prevalence of different states and found that the model initially under-predicted SIS and over-predicted the Stable state (see Figure S2, Supplemental Digital Content, http://links.lww.com/QAI/B998). These differences are likely because the observed prevalence assumes patients remain in their previous state if no CD4 measure is recorded, unlike our model, which allows for unobserved transitions between states.

DISCUSSION

In recent years, SIS at ART initiation has declined, but remained extremely high. After ART initiation, over a third of children experienced SIS. With fewer new ART initiations,

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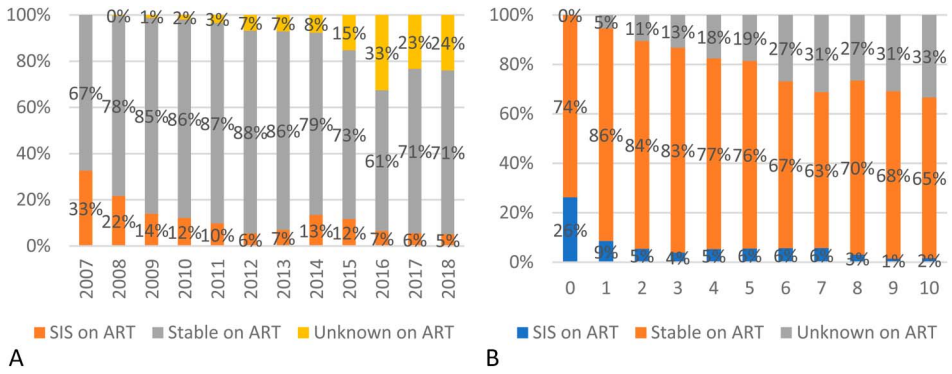


FIGURE 2. Proportion of on-ART person-time spent in each state by (A) calendar year* and (B) year on ART. SIS on ART: SIS after ART start. Stable on ART: Not SIS after ART start. *Data not shown beyond 2018 because not all cohorts reported data for this period. full color online

increasingly, SIS occurred among ART-experienced children. In recent years, just over half of SIS on ART occurred after the initial period of immune recovery, after a gap in care or among those engaged in care. Among children on ART and in care, an increasing proportion had unknown immune status, and some SIS was likely undiagnosed. Close to 40% of children who experienced SIS on ART after a period in care were viremic, and among children initiating ART in more recent years, increasingly more SIS on ART was experienced while viremic.

With later year of ART initiation, those with SIS on ART were increasingly less likely to become stable, but were also less likely to deteriorate to SIS once stable. Treatment is being started at a younger age, increasingly among infants. Compared with older children, infants were more vulnerable to SIS following a period of clinical stability. We also found that infants who were more severely immune-suppressed at ART start were less likely to recover to a stable state after SIS on ART. Children who started ART with SIS were more likely to return to a severely immune-suppressed state once on ART, and less likely to re-engage in care in a stable state after an early gap. Viremia strongly predicted SIS after a stable state, and death from either of the on ART states (SIS or Stable).

Our estimates for SIS at ART start are in line with studies among children of varying ages from Southern Africa,[3–6] including a recent study from sub-Saharan Africa of children aged <5 years, which found that SIS decreased, but remained extremely high, with a prevalence of 55% in 2014–2017.[1] Our results that children with SIS at ART start are more vulnerable to SIS on ART are consistent with evidence that lower baseline immune suppression is associated with less favorable CD4 recovery.[22,23] Infants have also been found to have slower immune recovery,[22] and reported prevalence of SIS at ART initiation among infants has been higher than older children.[24] Few studies have described advanced HIV disease among children after ART initiation.[24,25] A Southern Africa study using data up to 2012 found a higher prevalence than our study, reporting 17% of those who initiated ART during infancy having SIS after 12 months on ART,[24] although our study included older children and more recent data. A multiregional study described clinical disease after ART initiation among those aged <10 years, and found associations with lower CD4 and younger age.[25] Although we found that with later year of ART start, an increasing proportion experienced an early gap, unlike other studies of loss to follow-up,[1,6,26–31] we did not find associations between age, year or immune status at ART start and gaps in care. This may be because we only included patients with ≥1 subsequent CD4 measure after ART initiation and did not examine gaps occurring in the earliest period following ART initiation when program attrition may be highest,[32] or because we did not examine transitions to the Early Gap state.

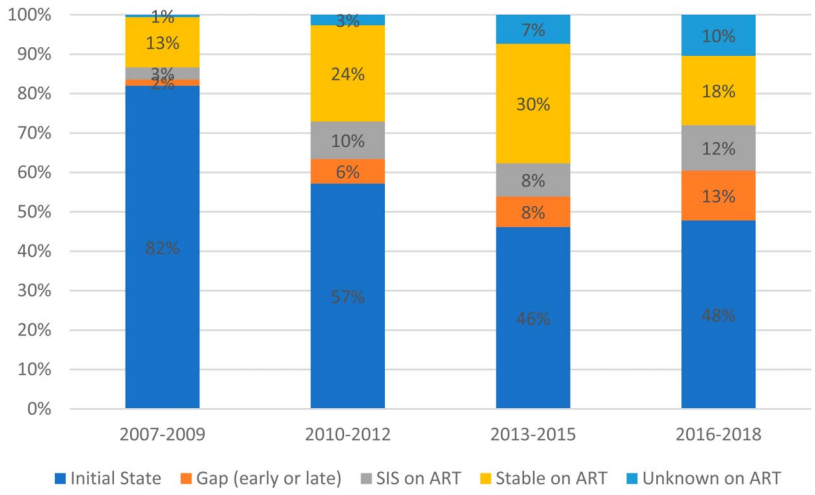


FIGURE 3. Prior state to severe immune suppression (SIS) on ART by calendar year.*Data not shown beyond 2018 since not all cohorts reported data for this period. full color online

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TABLE 2. Estimated Hazard Ratios From a Multivariate Multistate Model, aHR (95% Confidence Interval)

	Sex	Age at ART Initiation (years)		Year of ART Start	
	Girls	1–2	2–5	2010–2012	2013–2020
Reference	**Boys**	**0–1**		**2007–2009**	
Early Gap to					
SIS	1.1 (0.62–1.95)	0.92 (0.44–1.91)	1.15 (0.52–2.55)	1.05 (0.47–2.36)	1.91 (0.92–4)
Stable	0.68 (0.42–1.11)	1.07 (0.58–1.97)	1.31 (0.66–2.61)	0.73 (0.42–1.27)	0.56 (0.31–1.04)
Death	0.04 (0–1821.61)	0.09 (0–662.34)	0.1 (0–18786.88)	0.05 (0–502)	0.05 (0–931.72)
SIS on ART to					
Stable	1.16 (1–1.35)	**0.8 (0.66–0.96)**	0.84 (0.68–1.05)	**0.62 (0.52–0.75)**	**0.75 (0.62–0.9)**
Late Gap	1.25 (0.9–1.73)	1.19 (0.8–1.77)	1.09 (0.67–1.76)	1.18 (0.8–1.73)	1.25 (0.84–1.86)
Death	0.93 (0.34–2.59)	0.76 (0.24–2.39)	0 (0–123636880599010000)	0.48 (0.13–1.8)	0.59 (0.18–1.95)
Stable on ART to					
SIS	0.81 (0.61–1.06)	0.74 (0.52–1.05)	**0.55 (0.36–0.86)**	0.75 (0.54–1.02)	**0.55 (0.38–0.81)**
Late Gap	1.05 (0.95–1.16)	1.02 (0.89–1.16)	1 (0.86–1.16)	**1.24 (1.1–1.39)**	1.03 (0.9–1.18)
Death	0.97 (0.34–2.78)	1.39 (0.46–4.17)	0 (0–266432932453167)	0.97 (0.27–3.49)	1.13 (0.31–4.1)
Late Gap to					
SIS	0.45 (0.19–1.09)	0.73 (0.26–2.01)	0.87 (0.31–2.42)	0.87 (0.37–2.04)	1.18 (0.43–3.26)
Stable	**1.54 (1.08–2.2)**	0.72 (0.47–1.09)	**0.3 (0.15–0.62)**	**0.59 (0.39–0.89)**	0.72 (0.46–1.15)
Death	0.01 (0–42220.15)	2.66 (0.16–45.02)	0.07 (0–19356.71)	24.41 (0–120974.53)	36.97 (0.01–183950.65)

	Immune Status	VL		ART Regimen
	SIS at ART Start	VL≥1000	VL Missing	PI
Reference	**Not SIS at ART Start**	**VL<1000 Copies/ml**		**NNRTI**
Early Gap to				
SIS	2.14 (0.97–4.72)	1 (1–1)	1 (1–1)	2.65 (0.91–7.72)
Stable	**0.42 (0.26–0.67)**	1 (1–1)	1 (1–1)	1.29 (0.62–2.68)
Death	4.97 (0–887192.56)	1 (1–1)	1 (1–1)	4.6 (0–2268559504.22)
SIS on ART to				
Stable	0.89 (0.71–1.12)	0.78 (0.66–0.91)	0.92 (0.67–1.27)	1.08 (0.81–1.44)
Late Gap	0.72 (0.45–1.14)	1.13 (0.81–1.59)	**1.96 (1.04–3.69)**	1.27 (0.67–2.39)
Death	1.23 (0.16–9.29)	**5.88 (1.65–20.97)**	0.15 (0–1370.66)	28.39 (0–51338765061.68)
Stable on ART to				
SIS	**1.71 (1.21–2.41)**	**2.08 (1.53–2.83)**	**3.12 (1.81–5.36)**	1.2 (0.7–2.05)
Late Gap	1.07 (0.96–1.2)	0.96 (0.83–1.1)	**1.69 (1.33–2.15)**	1.18 (0.99–1.4)
Death	0.94 (0.29–3.03)	**5.09 (1.63–15.93)**	**7.33 (1.44–37.16)**	36.76 (0–1941653017356.1)
Late Gap to				
SIS	1.65 (0.58–4.68)	1 (1–1)	1 (1–1)	1.13 (0.32–3.94)
Stable	0.9 (0.62–1.31)	1 (1–1)	1 (1–1)	1.41 (0.55–3.58)
Death	34.34 (0–9858840.11)	1 (1–1)	1 (1–1)	3.99 (0–5523301.08)

Bold indicates the confidence interval does not include the null.

Early Gap, gap in care commencing ≤9 months from ART start; Gap in care, no recorded visit for ≥9 months; Late Gap, gap in care commencing >9 months from ART start; NNRTI, non-nucleoside reverse transcriptase inhibitor; SIS on ART, SIS after ART start; Stable on ART, not SIS after ART start; VL, viral load.

Although several studies have described SIS at ART start among children living with HIV,[1,3–6] and adult studies have described advanced HIV disease among treatment-experienced patients,[7] this is the first study to our knowledge that also describes SIS on ART in this population. Instead of using a linear HIV care cascade approach, our study methods allowed for analysis of repeated periods of immune suppression and stability, and engagement and disengagement from care. Our study provides insights into the outcomes of children who experience SIS on ART and how these have changed with time as HIV programs have evolved and the profile of children initiating ART has changed. Our findings are likely generalizable to other regional cohorts where similar expansion in ART programs has occurred.

Our study has several limitations. The cohorts included in this study may not be representative of children with HIV in the region. In Southern Africa, ART programs differed from South Africa with respect to ART eligibility criteria, regimens and access to CD4 and VL monitoring. It is possible that as HIV services have decentralized, the cohorts in our study increasingly represent a sicker profile of patients. Our estimates from the most recent period were higher than others

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from the region, and this may be reflective of this bias. Although we restricted the data used in the multistate model to the first 5 years on ART, our results regarding trends over time are subject to some bias because those starting ART more recently have shorter follow-up. Multistate models assume transition probabilities are independent of time, but adherence to ART and retention in care may in fact vary with duration on ART. We removed some potential bias by modelling an early and a late gap in care state. Our use of 2 Gap states is supported by evidence that early gaps in care, unlike later gaps occurring at longer duration on ART, are associated with increased mortality among children.[33] However, we could not completely remove the potential bias that those starting ART more recently experienced transitions at an earlier duration on ART. It is possible that patients received care at another health facility when our data indicated gaps in care. We were limited by lack of clinical information, which would have allowed us to more accurately describe severe HIV-related disease. During the study period eligibility for ART initiation included immunologic and clinical criteria for some children. Older children initiating ART in the earlier periods without immune suppression were likely to have clinical illness and have worse prognosis than those initiating ART without immune suppression in more recent years. With limited CD4 measures in later years, we did not model CD4%/cell count trajectory, which may have more accurately predicted transitions between Stable and SIS on ART states. We excluded those without a CD4 measure at ART start and at least one subsequent measure. Many of the sickest children starting ART may die during this period, as was evident among those excluded from our study, and our description of SIS at ART start and subsequently may therefore underestimate the true burden of SIS.

We found that those starting ART with SIS or during infancy remained especially vulnerable to SIS once on treatment, and recovery to a stable state was more challenging. This supports evidence suggesting that young children born to mothers who failed to access HIV treatment in the era of widespread ART coverage, are an emerging vulnerable population,[1] and may experience extra challenges in accessing and adhering to treatment. In adults, an increasing proportion of advanced HIV disease is among those re-engaging in care after treatment interruptions.[7] Although we found that an increasing proportion of SIS on ART in children was among those re-engaging in care after a gap, our study found a greater proportion of SIS on ART was among children engaged in care who were experiencing long periods of SIS or immune decline despite being engaged in care and receiving treatment. Children initiating ART more recently who experienced SIS on ART were increasingly viremic, and we found that viremia strongly predicted death from either of the on-ART states. These findings demonstrate the ongoing difficulties in managing effective treatment for children. Children on ART with SIS and viremia are unlikely to experience immune recovery without further intervention, and likely require more intensive follow-up, closer clinical management, adherence support, and potentially new ART regimens. Better tolerated ART, such as dolutegravir, has the potential to improve outcomes and reduce SIS on ART. Further research on SIS on ART is needed as these regimens become available in the region. Although VL monitoring has become the preferred tool for children stable on ART, it may not be enough to ensure children remain stable. CD4 monitoring among ART-experienced children at high risk of immune deterioration, especially those with viremia, remains critical. With such a high proportion of children continuing to initiate ART with SIS, our findings support WHO guidelines that consider all children age <5 years as having advanced HIV disease,[34] and demonstrate that ART alone is not enough to reduce ongoing HIV-related morbidity and mortality. Our findings support prioritizing the implementation of the advanced HIV disease package of care for children,[35] and emphasize the importance of understanding and addressing the needs of children with SIS or viremia.

In conclusion, although children are starting ART younger, most continued to initiate ART with SIS. Over a third experienced SIS once established on treatment, and SIS increasingly occurred among ART-experienced children, and among those who were viremic. Those starting ART with SIS and during infancy remained especially vulnerable to SIS once on treatment, and recovery to a stable state for these children was more challenging. Although there are fewer HIV-infections among children because of effective PMTCT programs, those starting ART in the current era of HIV programs are potentially more vulnerable children. Managing ART in these children may be more complex and achieving further reductions to AIDS-related mortality is likely to remain challenging.

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