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ORIGINAL ARTICLE

Trends of severe HIV disease and mortality among children in rural Tanzania

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Abstract

Objective: To assess trends of severe HIV disease (SHD) and mortality/loss to follow-up (LTFU) among children living with HIV in rural Tanzania.

Methods: Among children aged 0–14 years living with HIV enrolled in the prospective Kilombero & Ulanga Antiretroviral Cohort in January 2005–December 2023, we determined WHO-defined SHD prevalences at enrolment, mortality/LTFU incidence during follow-up using Kaplan–Meier methods, and associated factors using regression models.

Results: At enrolment, among 1089 children [567 (52%) males, 587 (54%) aged <5 years and 530 (49%) with a HIV WHO stage III/IV], 112/332 (34%) had CD4 cell count <200 cells/μL among those aged 5–14 years. In children aged 5–14 years, SHD was diagnosed in 265/502 (53%) with a prevalence of 35–94% declining after 2013. Among children aged <5 years, 374/587 (64%) had SHD with no change over time. Male gender [adjusted odds ratio = 1.45; 95% confidence interval: 1.10–1.90], age <5 years versus older (1.64; 1.13–2.37), hospitalization versus outpatients (6.72; 3.35–13.5), antiretroviral treatment (ART) start within 30 days versus later (2.18; 1.52–3.13), and enrolment during 2013–2016 versus before (2.29; 1.54–3.41) were associated with SHD. After a median follow-up of 3.3 years [interquartile ratio: 0.8–7.8], 130 (12%) children died and 359 (35%) were LTFU. Predictors of mortality/LTFU were SHD [adjusted hazard ratio (aHR) = 1.54; 95% CI: 1.26–1.89], age <5 years versus older (1.28; 1.01–1.66), hospitalization versus outpatients (1.93; 1.42–2.63), living ≥50 km versus ≤1 km away (1.72; 1.37–2.16) and delayed ART initiation versus within 30 days (3.40; 2.70–4,27), while enrolment 2017–2023 versus before (0.51; 0.37–0.70) was protective.

Conclusions: The persisting high prevalence of paediatric SHD and high mortality/LTFU underscores the need for early diagnosis and care.

L.S. Moshi and J. Okuma contributed equally to this work.

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KEYWORDS
advanced HIV diseases, mortality, paediatric HIV, prospective study, severe HIV disease

INTRODUCTION

In sub-Saharan Africa (SSA), the extensive rollout of strategies to prevent HIV vertical transmission [1, 2] has led to a 53% reduction in newborn HIV infection rates between 2010 and 2020 [3]. In parallel, children are diagnosed with HIV at a younger age, translating to an earlier start of antiretroviral treatment (ART) and a decline in the number of children with advanced HIV disease (AHD) – defined as WHO stage III/IV and/or a CD4 cell count < 200 cells/μL in children aged 5–14 years [4]. Notably, the WHO classifies all children under the age of 5 years as having AHD, irrespective of their CD4 count or WHO stage [4]. A large-scale retrospective study, including 32 221 children with HIV aged 1–4 years from 16 SSA countries from 2006 to 2017, reported a decrease in the average age of ART initiation from 20.4 to 19.2 months and an increase in the proportion of children starting ART before the age of 2 years from 5.1% to 10% [5].

In children aged <5 years of age, severity of diseases is further classified into non-severe and severe immunosuppression, the latter being defined as WHO stage III/IV and/or CD4% <25% (age 0–11 months), <20% (age 12–35 months), or <15% (age 36–59 months). In a large cohort study including children from 16 countries in SSA, the proportion of children with severe HIV dropped from 74.7% to 55.2%, leading to a decrease in 2-year mortality from 6.5% to 2.9% [5].

Despite these successes, rates of AHD, severe HIV and HIV-associated mortality in children across African countries remain high [6–8]. The highest mortality is reported from West Africa [10.6%; 95% confidence interval (CI): 9.3–12.0], with Central Africa (2.9%; 95% CI: 1.8–4.4) recording the lowest [5]. A study performed in East Africa (Kenya, Rwanda, Tanzania and Mozambique) from 2005 to 2015 reported 48% of newly HIV-diagnosed children presenting with WHO stage III/IV – 32% had severe immunodeficiency and 7% had died by 24 months [7]. In Tanzania, a national survey conducted in 2011–2014, reporting on 29 531 children from 740 HIV care and treatment clinics, found a similarly high proportion of children with WHO stage III/IV (46%), with 39% of these children either becoming lost to follow-up (LTFU) or dying [9].

While early start of ART is key, in newly HIV-diagnosed hospitalized children aged 0–12 in Kenya the PUSH trial failed to show a mortality reduction in those starting immediately (23%) versus those starting late (20%) [10]. The 2013 WHO guidelines aimed to address such delays by recommending universal ART for all children, regardless of CD4 count or clinical stage, simplifying treatment initiation and expanding access [11]. However, despite these changes, around 66% of children in low- and middle-income countries still began ART with severe immunodeficiency [8]. Updated data on severe HIV disease at ART initiation and impact on outcomes in those with severe HIV illness during the 'test and treat' strategy [8, 12] are needed to develop targeted interventions aiming at reducing the number of children presenting with AHD, severe immunosuppression and HIV-associated mortality in countries with a high burden of paediatric HIV [6, 12, 13].

In this study, we determined trends in prevalence of AHD and severe HIV disease (SHD) at enrolment, and incidence of mortality/LTFU among children <15 years enrolled over a 15-year period. We also evaluated risk factors associated with SHD and mortality/LTFU.

MATERIALS AND METHODS

Study design, setting and participants

This is a nested study of the prospective Kilombero and Ulanga Antiretroviral Cohort (KIULARCO). KIULARCO prospectively enrols consenting people living with HIV seen at the Chronic Diseases Clinic of Ifakara, St Francis Referral Hospital, in rural Southern Tanzania [14, 15]. Since its start in January 2005 to December 2023, KIULARCO has enrolled 12 985 participants, of which 1118 were children aged 0–14 years. Since 2013, prevention of mother-to-child transmission and paediatric HIV services have been delivered through a family-centred clinic integrated within the reproductive and child health clinic (One Stop Clinic of Ifakara) [16] according to the National AIDS Control Programme guidelines [17]. Within KIULARCO, predefined demographic, clinical and laboratory parameters are prospectively assessed at each visit and captured in an electronic medical record system (OpenMRS; https://openmrs.org/). Detailed procedures of KIULARCO have been described elsewhere [14, 15].

For this study, we included all children aged 0–14 years enrolled into KIULARCO from January 2005 to December 2023 with at least one clinical assessment and a CD4 or HIV WHO stage measurement within 1 month from enrolment.

Ethical considerations and informed consent

KIULARCO is approved by the Ifakara Health Institute institutional review board (IHI/IRB/No16-2006) and the National Institute of Medical Research (NIMR/HQ/R.8a/Vol.IX/620) with yearly renewals. Consent of children and adolescents was provided by parents/caretakers at enrolment into KIULARCO.

Definitions and covariates

Baseline was defined as time of enrolment into KIULARCO. As per WHO, we defined AHD in children aged 5–14 years as HIV clinical stage III/IV and/or CD4 count <200 cells/μL [4]. Children below 5 years (0–59 months according to the WHO definition) are considered to have AHD [4, 17]. SHD is defined as WHO stage III/IV in all children and/or CD4 cell counts <100 cells/μL for those aged 5–14 years, <25% for those aged 0–11 months, <20% for those aged 12–35 months and <15% for those aged 36–59 months (Table S1) [18, 19]. The nearest recorded measurement of HIV WHO stage and CD4 measurement up to 6 months before and 1 month after baseline was used. LTFU was defined as >60 days passed since a participant's next planned visit. We used the 'last' status of the participant at database closure on 31 December 2023 [20].

Covariates included were sex, age, presumed mode of infection, point of care entry point, distance of residence from the clinic (estimated based on centre of residence ward), wasting, stunting, ART status at enrolment and calendar year. The calendar years of enrolment into KIULARCO (2005–2012, 8 years; 2013–2016, 4 years; 2017–2023, 7 years) were categorized according to important policy changes in the Tanzania national guidelines on ART use in children. Due to the phased transition approach employed by the National AIDS Control Programme to optimize regimen implementation and minimize wastage, some calendar years do not align exactly with the timing of specific policy or guideline changes and are explained in Table S2. Wasting was defined as weight-for-age (WAZ) Z-scores < -2 standard deviations (SD), and severe wasting as < -3 SD, and stunting was defined as height-for-age (HAZ) Z-scores < -2 SD, and severe stunting as < -3 SD. Z-scores were calculated using WHO 2006 child growth standards [21].

Statistical analysis

Participants' baseline characteristics were summarized using median and interquartile range (IQR) for continuous data, and frequencies and percentages for categorical data, presented overall and by SHD at enrolment. To define SHD at enrolment among those with a missing CD4 or WHO measurement, the available measurements were used, i.e. SHD was defined using available WHO measurements only for those missing CD4 measurement and vice versa. The prevalence of SHD at enrolment by CD4/WHO classification criteria and age group was presented by calendar year. We assessed baseline characteristics associated with SHD at enrolment using logistic regression models, reporting odds ratios (ORs) and 95% CIs. We fitted univariable models and a full multivariable model on complete data of the covariates noted earlier, but excluding covariates with large amounts of missing data. As a sensitivity analysis, we also fitted a multivariable model, using missing indicators for covariates with missing values in order to include all participants in the models (i.e. participants with missing data for a given variable were classified in a separate 'missing' category).

We combined the outcomes of LTFU and mortality in our analysis based on findings in our cohort, which revealed significant underreporting of deaths among individuals categorized as LTFU [22]. We evaluated the incidence of and factors associated with mortality and/or LTFU as a combined outcome and also as mortality only, with LTFU censored at the last event using Kaplan–Meier methods and Cox regression models. Participants did not contribute time at risk during intermittent periods of LTFU, with those LTFU being censored at their last LTFU event. Participants who transferred were censored at the time of transfer and re-entered in case of transfer back into care. Participants who turned 15 years old were censored on the day of their 15th birthday, and participants who were in active follow-up at the time of database censoring were censored as of that date. We fitted univariable and multivariable models in a similar way as for the logistic regression models. Analyses were performed using Stata version 16 (StataCorp LP, College Station, TX, USA).

RESULTS

Study population and baseline characteristics

Out of 1118 children, we excluded 29 children who had both CD4 counts and HIV WHO stage measurements missing (Figure 1). Of 1089 children included in the study, 567 (52%) were male and 587 (54%) were children below 5 years of age (Table 1). In 442/533 (83%) children, the presumed mode of HIV infection was perinatal transmission. Distance from residency to the clinic was ≥50 km in

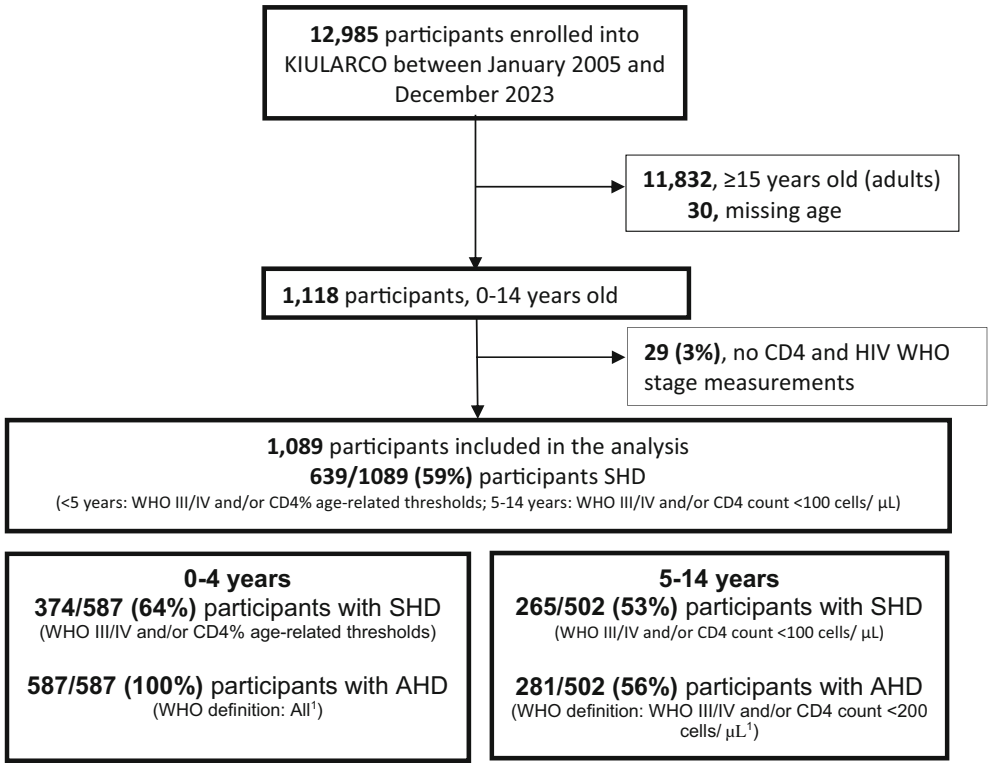

FIGURE 1 Flow chart of children in KIULARCO. KIULARCO, Kilombero and Ulanga Antiretroviral Cohort. AHD, advanced HIV disease; SHD, severe HIV disease. [1]Children aged 0–4 years per WHO definition are considered to have AHD [8, 23].

364/1019 (36%) children; 271/841 (32%) children were severely wasted and 198/666 (30%) were severely stunted. HIV WHO stage III/IV was diagnosed in 530/1071 (49%) children. Among children aged below 5 years, CD4 cells were < 25% for 75/171 (44%) children aged 0–11 months, <20% for 105/277 (38%) of those aged 12–35 months and < 15% for 34/139 (25%) of those aged 36–59 months. Among those aged 5–14 years, 112/332 (34%) had CD4 counts of <200 cells/µL. The majority of children (725/1089, 67%) were newly initiated on ART within 30 days of enrolment and about half (560/1089, 51%) were enrolled in the earlier time period (2005–2012).

Prevalence of AHD and SHD

At enrolment, overall 639 out of 1089 children (59%) had SHD, 374/587 (64%) among those aged below 5 years and 265/502 (53%) among those aged 5–14 years. AHD was present in 281/502 (56%) among those aged 5–14 years (Figure 1).

In 18 (2%) children, classification was based on CD4 count or % alone due to WHO stage being missing. Conversely, there were 333 (31%) children who were classified based on WHO stage alone due to CD4 count or % being missing. Of these, 190 (17% of the total 1089) children had HIV WHO stage I/II and were classified as no SHD but may have been classified as SHD if the CD4 count or % had been measured. This may have resulted in an underestimation of SHD prevalence, illustrated by the slightly higher estimates of SHD prevalence among participants with complete data (Figure S1). Assuming data were missing completely at random and based on the observed SHD prevalence on the complete data, we anticipate that approximately 29 (3%) children may have been misclassified.

Characteristics among the 639 (59%) participants with SHD at enrolment were broadly similar to the 450 (41%) without SHD, except that those with SHD were more likely to be aged below 5 years [374 (59%) vs. 213 (47%) in those without SHD], in-patients [108, (17%) vs, 11 (2%)], started ART within 30 days of enrolment [460 (72%) vs. 265 (59%)], severely wasted [211 (42%) vs. 60 (18%)] or severely stunted [149 (36%) vs. 49 (19%)] and less likely to be enrolled in 2005–2012 [282 (44%) vs. 278 (62%)] (Table 1).

Trends in prevalence of SHD

From 2007 to 2023, the prevalence of SHD exhibited distinct trends between the two age groups. In children aged

TABLE 1 Baseline characteristics among children aged 0–14 years living with HIV enrolled in KIULARCO between January 2005 and December 2023.

Characteristics	Severe HIV disease	No severe HIV disease	ALL
Number (row %)	639 (59%)	450 (41%)	1089 (100%)
Sex [*n* (%)]			
Male	349 (54%)	218 (48%)	567 (52%)
Female	290 (46%)	232 (52%)	522 (48%)
Age (years) [*n* (%)]			
0 to <5	374 (59%)	213 (47%)	587 (54%)
5 to <10	162 (25%)	154 (34%)	316 (29%)
10–14	103 (16%)	83 (18%)	186 (17%)
Presumed mode of infection [*n* (%)]			
Perinatal	296 (84%)	146 (82%)	442 (83%)
Heterosexual	24 (7%)	9 (5%)	33 (6%)
Unknown/other	34 (10%)	23 (13%)	58 (11%)
Missing	285 (45%)	271 (60%)	556 (51%)
Point of care entry point [*n* (%)]			
Voluntary testing and counselling	282 (44%)	264 (59%)	546 (50%)
Hospitalization	108 (17%)	11 (2%)	119 (11%)
Outpatient department	59 (9%)	36 (8%)	95 (9%)
Others	190 (30%)	139 (31%)	329 (30%)
Distance of residence from clinic [*n* (%)]			
≤1 km	183 (31%)	162 (38%)	345 (34%)
2 to <50 km	188 (32%)	122 (29%)	310 (30%)
≥50 km	222 (37%)	142 (33%)	364 (36%)
Missing	46 (7%)	24 (5%)	70 (6%)
WAZ (weight-for-age) [*n* (%)]			
≥−2 (normal)	181 (65%)	181 (36%)	399 (47%)
<−2 SD to ≥-3SD (wasted)	111 (22%)	60 (18%)	171 (20%)
<−3SD (severely wasted)	211 (42%)	60 (18%)	271 (32%)
Missing	136 (21%)	112 (25%)	248 (23%)
HAZ (height-for-age) [*n* (%)]			
≥−2 (normal)	147 (36%)	145 (56%)	292 (44%)
<−2 SD to ≥-3SD (stunted)	113 (28%)	63 (25%)	176 (26%)
<−3SD (severely stunted)	149 (36%)	49 (19%)	198 (29%)
Missing	230 (36%)	193 (42%)	423 (39%)
HIV WHO stage[a] [*n* (%)]			
I/II	100 (16%)	441 (100%)	541 (51%)
III/IV	530 (84%)	0 (0%)	530 (49%)
Missing	9 (1%)	9 (2%)	18 (2%)
CD4 count (cells/μL)[ab] [*n* (%)]			
<200	96 (53%)	16 (11%)	112 (34%)
200–499	47 (26%)	49 (33%)	96 (29%)
≥500	40 (22%)	84 (56%)	124 (37%)
Missing	82 (31%)	88 (37%)	170 (34%)

TABLE 1 (Continued)

Characteristics	Severe HIV disease	No severe HIV disease	ALL
CD4% [*n* (%)][ac]			
<20%	202 (62%)	0 (0%)	209 (50%)
≥20%	128 (38%)	79 (100%)	207 (50%)
Missing	68 (17%)	103 (57%)	171 (29%)
On ART at enrolment [*n* (%)]			
No	103 (16%)	125 (28%)	228 (21%)
Yes	76 (12%)	60 (13%)	136 (13%)
Initiated within 30 days	460 (72%)	265 (59%)	725 (67%)
Calendar year [*n* (%)]			
2005–2012	282 (44%)	278 (62%)	560 (51%)
2013–2016	182 (29%)	53 (12%)	235 (22%)
2017–2023	175 (27%)	119 (26%)	294 (27%)

Note: Results are number and column percent of those with non-missing data except where otherwise indicated; missing data rows are number and column %.
Abbreviation: ART, antiretroviral therapy.
[a]HIV WHO stage and CD4 measurement closest to baseline within 6 months before and 1 months after.
[b]Among children aged 5–14 years.
[c]Among children aged 0–4 years.

below 5 years, SHD prevalence remained consistently high, ranging from 29% to 91%, with no significant decline observed over time (Figure 2). Conversely, in children aged 5–14 years, a significant decline in SHD prevalence was observed after 2013 (Figure 2b). As shown in Table 2, the adjusted odds of presenting with SHD were significantly higher during 2013–2016 than during the reference period of 2005–2012 [adjusted odds ratio (aOR) = 2.39, 95% CI: 1.54–3.51], but declined to aOR = 0.74 (95% CI: 0.48–1.14) during 2017–2023. This trend is further supported by quadratic regression analysis, which identified a turning point around 2013, after which SHD prevalence significantly decreased in the age group 5–14 years ($p = 0.03$).

Factors associated with SHD at enrolment

In the modelling, presumed mode of transmission (51% missing), weight-for-age (23% missing) and height-for-age (39% missing) were excluded because of large amounts of missing data. Factors associated with SHD at enrolment were male gender (aOR = 1.45, 95% CI: 1.10–1.90), younger age (1.64, 1.13–2.37 for < 5 years vs. 10–14 years), being hospitalized (6.72, 3.35–13.5 for in-patients vs. outpatients), start of ART within 30 days of enrolment (2.18, 1.52–3.13 vs. later), and later enrolment (2.29, 95% CI 1.54–3.41 for 2013–2016 vs. 2005–2012, with no evidence of a difference between the years 2017–2023 and 2005–2012) (Table 2). There was no evidence of a difference in SHD prevalence by distance of residence from clinic. The results were similar to those of sensitivity analyses including all children using a missing indicator for the 70 children with missing distance of residence.

Mortality and lost to follow-up

After a median follow-up of 3.3 years (IQR: 0.8–7.8), there were 130 (12%) deaths, 359 (35%) LTFU and 281 (26%) children transferred to other clinics. One-year and 5-year incidence of mortality/LTFU were 26% (95% CI: 23–29) and 46% (95% CI: 43–50), respectively, and 8% (95% CI: 6–10) and 14% (95% CI: 12–17), respectively, for mortality only. One-year incidence of mortality/LTFU was higher in younger children [33% (95% CI: 29–37) for those aged < 5 years vs. 19% (95% CI: 14–27) for those aged 10–14 years], those with SHD [31% (95% CI: 27–35) vs. those without 18% (95% CI: 14–22)] and those enrolled in early years [30% (95% CI: 26–35) for 2005–2012 vs. 22% (95% CI: 17–27) for 2017–2023] (Figure 3a–c).

Also for modelling factors associated with mortality/LTFU, we excluded presumed mode of transmission, weight-for-age and height-for-age from the models because of large amounts of missing data. Predictors of mortality/LTFU were SHD at enrolment (aHR = 1.54, 95% CI: 1.26–1.89), younger age (1.28, 1.01–1.66 for those aged <5 years vs. those aged 10–14 years), hospitalization (1.93, 1.42–2.63 for hospitalization vs. others), living far from the clinic (1.72,

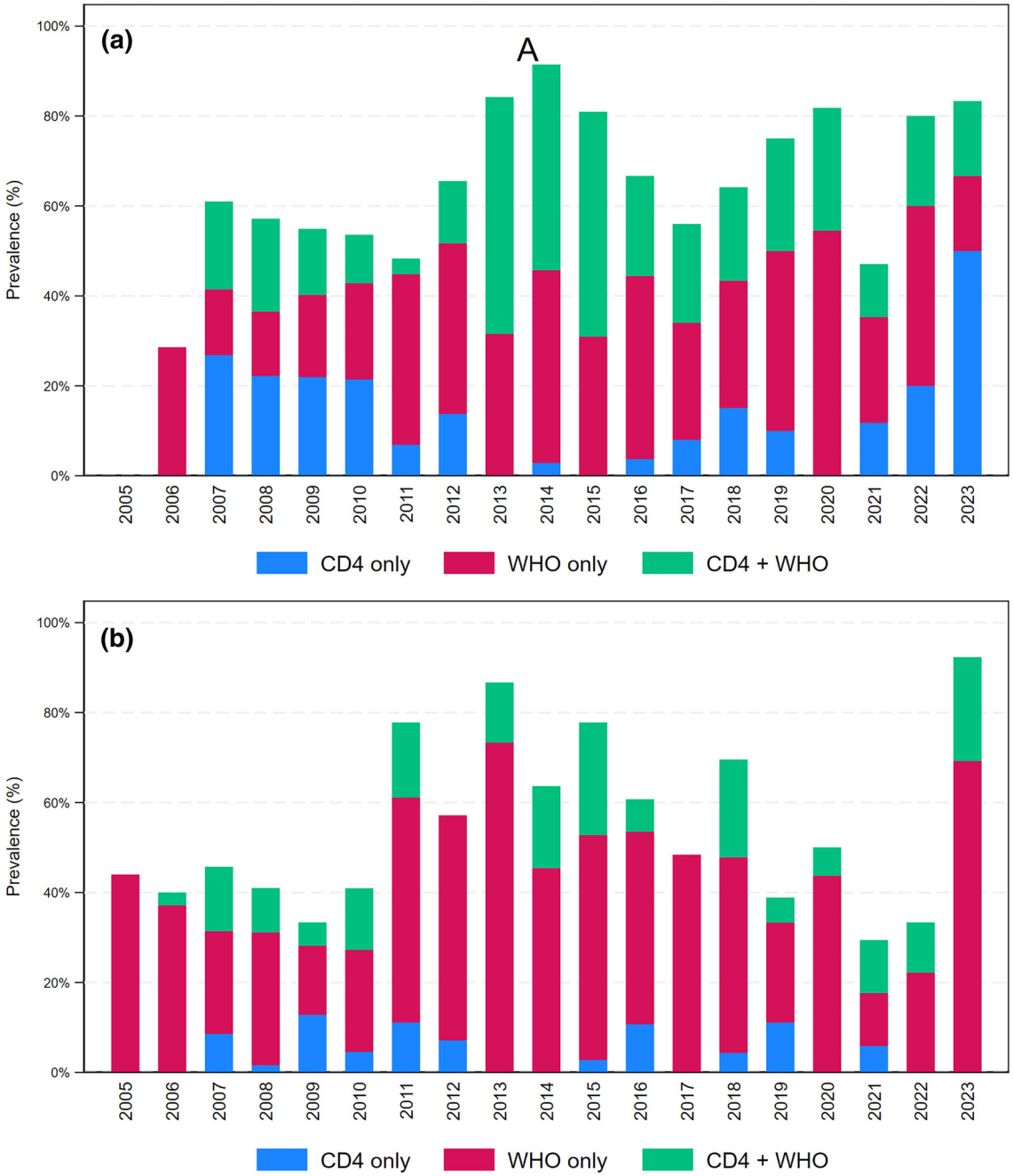

FIGURE 2 Prevalence of severe HIV disease at enrolment by CD4 cell count and WHO stage according calendar year for age groups 0 to <5 years (a) and 5–14 years (b).

1.37–2.16 for ≥50 km vs. ≤1 km), and delayed ART initiation (3.40, 2.70–4.27 for later vs. within 30 days of enrolment), while later enrolment years were associated with lower risk of mortality/LTFU (0.51, 0.37–0.70 for 2017–2023 vs. 2005–2012) (Table 3). The results were similar to those of sensitivity analyses including all children, using a missing indicator for the 70 children with missing distance of residence. Predictors of mortality (LTFU censored) were broadly similar to those of the combined outcome of mortality/LTFU except for age and distance of residence to the clinic, for which there was no evidence of an association (Table S3).

DISCUSSION

In this study in rural Tanzania over a 15-year period, SHD at enrolment was common in children living with HIV, especially in those aged below 5 years (64%) without a clear trend over time. In those aged 5–14 years,

TABLE 2 Factors associated with severe HIV disease at enrolment among children aged 0–14 years living with HIV.

Characteristics	Univariable (complete case)		Multivariable, $N = 1019$ (complete case)		Multivariable, $N = 1089$ (missing indicator used for missing covariate values)	
	OR (95% CI)[a]	*p*-value[a]	OR (95% CI)[ab]	*p*-value[ab]	OR (95% CI)[ab]	*p*-value[ab]
Sex						
Female	Reference		Reference		Reference	
Male	1.28 (1.01–1.63)	0.05	1.45 (1.10–1.90)	0.007	1.41 (1.09–1.84)	0.01
Age (years)		<0.001		<0.001		<0.001
0 to <5	1.41 (1.01–1.98)		1.64 (1.13–2.37)		1.50 (1.05–2.15)	
5 to <10	0.85 (0.59–1.22)		0.84 (0.56–1.25)		0.87 (0.59–1.28)	
10–14	Reference		Reference		Reference	
Point of care entry point		<0.001		<0.001		<0.001
VCT	0.78 (0.59–1.03)		0.73 (0.49–1.08)		0.73 (0.50–1.06)	
Hospitalization	7.18 (3.72–13.9)		6.72 (3.35–13.5)		7.04 (3.54–14.0)	
Outpatient department	1.20 (0.75–1.92)		1.43 (0.85–2.42)		1.36 (0.82–2.27)	
Others	Reference		Reference		Reference	
Distance of residence from clinic		0.06		0.61		0.28
≤1 km	Reference		Reference		Reference	
2–49 km	1.36 (1.00–1.86)		1.18 (0.85–2.42)		1.29 (0.86–1.67)	
≥50 km	1.38 (1.03–1.87)		1.12 (0.81–1.55)		1.36 (0.82–2.27)	
Missing	-		-		1.73 (0.97–3.05)	
On ART at enrolment		<0.001		<0.001		<0.001
No	Reference		Reference		Reference	
Yes	1.54 (1.00–2.36)		1.57 (0.91–2.69)		1.49 (0.89–2.50)	
Initiated within 30 days	2.11 (1.56–2.85)		2.18 (1.52–3.13)		2.17 (1.54–3.07)	
Calendar year		<0.001		<0.001		<0.001
2005–2012	Reference		Reference		Reference	
2013–2016	3.39 (2.39–4.79)		2.29 (1.54–3.41)		2.38 (1.61–3.51)	
2017–2023	1.45 (1.09–1.93)		0.74 (0.48–1.14)		0.76 (0.51–1.19)	

Note: The following variables were excluded from the modelling due to a high number of missing values: presumed mode of transmission (missing, 51%), weight-for-age (missing, 23%) and height-for-age (missing, 39%) excluded from the modelling because of the large amount of missing data.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; VCT, voluntary counselling and testing.
[a]Odds ratios, 95% confidence intervals and *p*-values obtained from logistic regression models.
[b]Adjusted for all other baseline covariates shown.

SHD prevalences peaked in 2013–15 followed by a decrease. During follow up, 1-year incidence of mortality was high at 8% and the combination of mortality/LTFU was even higher, at 26%. Factors associated with SHD were male gender, younger age, hospitalization, early ART and enrolment in early calendar years. Predictors for mortality/LTFU were SHD, younger age, hospitalization, living far from the clinic and delayed ART initiation.

The prevalence of SHD at enrolment in children aged 0–14 years in our cohort, at 59%, was nearly double the reported 34.5% in a large East African cohort study including children aged < 15 years at 192 HIV care facilities in Kenya, Mozambique, Rwanda and Tanzania from January 2005 to June 2011 [7]. A study conducted from 2006 to 2017 across 16 sub-Saharan African countries showed that 79.6% of children < 5 years old had a CD4 percentage below 25%, while 38.1% of children > 5 years had CD4 counts < 200 cells/μL at ART initiation [6]. In the IeDEA cohort in South Africa including 30 000 ART-naïve children at 12 sites in four countries (Zambia, Zimbabwe, South Africa and Malawi), 70% of children started ART with severe immunosuppression defined as SHD in our study [23].

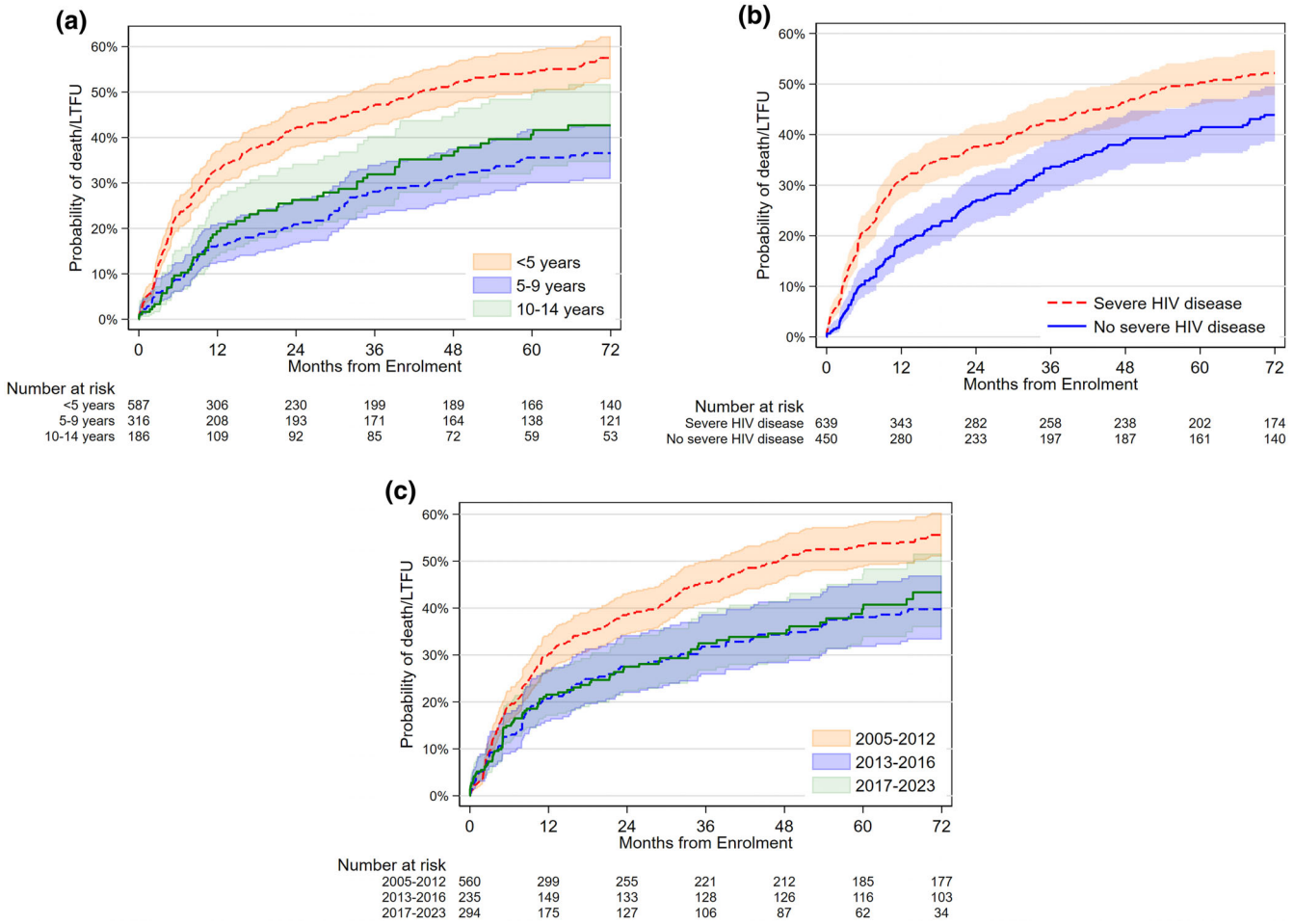

FIGURE 3 Combined rates of mortality/lost to follow-up (LTFU) by age group (a), severity of HIV disease (b), and calendar year (c).

The peak in prevalence of SHD in our cohort during the years 2013–2014 is probably due to implementation of a bundle of newly introduced measures directed at enhancing paediatric HIV diagnosis. This led to an increased paediatric HIV case identification and linkage into care [16]. The drop of SHD in children aged 5–14 years from 2016 onwards might be due intensified community testing but also updated WHO and national treatment guidelines allowing for same-day ART start [24] in line with the 'test and treat strategy' [17, 24, 25]. In the IeDEA cohort in four countries (Zambia, Zimbabwe, South Africa and Malawi), the proportion of children starting ART with severe immunosuppression decreased from 81% in 2005 to 63% in 2010 [23]. SHD in our cohort was more prevalent among children aged <5 years and did not decrease over time in this age group. This might be due to the referral status of the hospital, those being hospitalized having SHD in a higher proportion [16]. Male gender was a risk factor for SHD in our study, and has been shown to be associated with AHD in adult populations [26] and children with an increased mortality rate [6, 26, 27]. Also young age was associated with SHD, which has also been shown in children aged <5 years in a study from India, conducted in the years 2006 and 2016 [27]. One study from South Africa from 2003 to 2008 found a hazard ratio of 2.42 (95% CI: 1.37–4.30) for the association of age <3 years and mortality at presentation [28]. These numbers speak for gaps in the programmes to reduce the mother-to-child transmission of HIV with missed prevention during pregnancy and the breastfeeding period, but also missed early diagnosis of those vertically infected at young age [29]. This was also shown in a study conducted between 2014 and 2015 in a tertiary hospital in northern Tanzania, in which HIV testing of all hospitalized children identified a significant number of previously unknown HIV infections, with 84% of those children presenting with SHD [25].

Severe HIV disease, hospitalization, younger age, delayed start of ART, living far from the clinic and hospitalization at presentation were associated with mortality/

TABLE 3 Risk factors associated with mortality and loss to follow-up among children aged 0–14 years living with HIV.

	Univariable (complete case)		Multivariable, $N = 1019$ (complete case)		Multivariable, $N = 1089$ (missing indicator used for missing covariate values)	
Characteristics	**HR (95% CI)[a]**	***p*-value[a]**	**HR (95% CI)[ab]**	***p*-value[ab]**	**HR (95% CI)[ab]**	***p*-value[ab]**
Severe HIV disease						
No	Reference		Reference		Reference	
Yes	1.39 (1.16–1.66)	<0.001	1.54 (1.26–1.89)	<0.001	1.58 (1.30–1.93)	<0.001
Sex						
Male	Reference		Reference		Reference	
Female	1.09 (0.92–1.30)	0.32	1.03 (0.86–1.24)	0.74	1.03 (0.86–1.23)	0.34
Age (years)		<0.001		<0.001		<0.001
0 to <5	1.45 (1.13–1.85)		1.28 (1.01–1.66)		1.26 (0.99–1.62)	
5 to <10	0.85 (0.64–1.13)		0.76 (0.57–1.02)		0.77 (0.58–1.02)	
10–14	Reference		Reference		Reference	
Point of care entry point		<0.001		<0.001		<0.001
VCT	0.68 (0.55–0.85)		0.41 (0.31–0.54)		0.40 (0.31–0.51)	
Hospitalization	2.10 (1.58–2.78)		1.93 (1.42–2.63)		1.77 (1.31–2.38)	
Outpatient department	0.91 (0.64–1.30)		0.79 (0.54–1.16)		0.81 (0.56–1.17)	
Others	Reference		Reference		Reference	
Distance of residence from clinic		<0.001		<0.001		<0.001
≤1 km	Reference		Reference		Reference	
2–49 km	1.46 (1.16–1.85)		1.32 (1.04–1.68)		1.33 (1.05–1.69)	
≥50 km	1.97 (1.57–2.47)		1.72 (1.37–2.16)		1.74 (1.38–2.19)	
Missing	-		-		2.21 (1.50–3.26)	
On ART at enrolment		<0.001		<0.001		<0.001
No	3.40 (2.79–4.11)		3.40 (2.70–4.27)		3.53 (2.83–4.40)	
Yes	1.06 (0.79–1.44)		0.92 (0.66–1.29)		0.94 (0.68–1.30)	
Initiated within 30 days	Reference		Reference		Reference	
Calendar year		0.001		<0.001		<0.001
2005–2012	Reference		Reference		Reference	
2013–2016	0.68 (0.54–0.87)		0.47 (0.36–0.63)		0.47 (0.36–0.62)	
2017–2023	0.73 (0.58–0.93)		0.51 (0.37–0.70)		0.46 (0.34, 0.63)	

Note: The following variables were excluded from the modelling due to a high number of missing values: presumed mode of transmission (missing, 51%), weight-for-age (missing, 23%) and height-for-age (missing, 39%).

Abbreviations: ART, antiretroviral therapy; VCT, voluntary counselling and testing.

[a]Hazard ratios (HRs) and 95% confidence intervals (CIs) obtained from Cox models.

[b]Adjusted for all other baseline covariates shown.

LTFU. These findings partially align with other studies, e.g., a retrospective cohort study of children aged 0–15 years in Vietnam between 2006 and 2019, which found severe HIV disease as a risk factor for mortality. However, unlike our findings, the Vietnam study did not observe an association between age and mortality rates among children on ART [30]. In line with this, a large multisite study conducted in Africa, Asia-Pacific, Central and South America between 2001 and 2017 found younger age and male sex to be associated with higher mortality [6]. A retrospective cohort analysis from a similar setting included children with HIV from 192 facilities in Kenya, Rwanda, Tanzania and Mozambique and found lower mortality rates at 12 and 24 months of 5% and 7%, respectively, and LTFU rates of 16% and 22%, respectively. Also in this study, mortality was associated with younger age and SHD, with no evidence of differences in LTFU or death based on the point of entry [7].

Interestingly, enrolment in later years (2017–2023) was associated with a lower risk of death/LTFU, possibly due to better clinical management and/or earlier presentation due to test-and-treat programmes.

The strength of this study is the prospective consistent assessment of SHD in a long-term cohort study design, which allows monitoring of trends. We believe that our cohort is representative of rural areas in sub-Saharan Africa. Limitations are the high proportion of missing CD4 counts at enrolment due to frequent stock-out of reagents, which might have led to underestimation of true prevalence of SHD, although we estimated that only around 3% of children may have been misclassified as no SHD. This is particularly relevant in the context before implementation of the 'test and treat' strategy, in which treatment start was CD4 count- and WHO stage-dependent. However, also in recent years, the shift to viral load testing for routine patient monitoring has led to reduced availability of CD4 testing reagents. Further, LTFU rates in our cohort are high and mortality rates are likely to be higher among those LTFU [22].

To conclude, in this rural SSA setting, unacceptably high prevalence rates of AHD, SHD and higher incidence of mortality/LTFU persist, especially in children aged <5 years. The findings re-emphasize the need for early infant diagnosis, close monitoring and early treatment to reduce mortality and LTFU of children living with HIV.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors report that there are no competing interests.

DATA AVAILABILITY STATEMENT

Data will be made available upon request.

PATIENT CONSENT AND APPROVAL STATEMENT

This study is nested within the ongoing KIULARCO cohort, which has been approved by the Ifakara Health Institute Institutional Review Board (IHI/IRB/No. 16-2006) and the National Institute of Medical Research (NIMR/HQ/R.8a/Vol. IX/620), with yearly extensions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A: THE KILOMBERO AND ULANGA ANTIRETROVIRAL COHORT STUDY GROUP (KIULARCO)

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