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RESEARCH ARTICLE

Time-varying age- and CD4-stratified rates of mortality and WHO stage 3 and stage 4 events in children, adolescents and youth 0 to 24 years living with perinatally acquired HIV, before and after antiretroviral therapy initiation in the paediatric IeDEA Global Cohort Consortium

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Abstract

Introduction: Evaluating outcomes of paediatric patients with HIV provides crucial data for clinicians and policymakers. We analysed mortality and clinical events rates among children, adolescents, and youth with perinatally acquired HIV (PHIV) aged 0 to 24 years stratified by time-varying age and CD4, before and after antiretroviral therapy (ART), in the paediatric IeDEA multiregional collaboration (East, West, Central and Southern Africa, Asia-Pacific, and Central/South America and the Caribbean).

Methods: ART-naïve children with HIV enrolled before age 10 (proxy for perinatal infection) at IeDEA sites between 2004 and 2016, with ≥1 CD4 measurement during follow-up were included. We estimated incidence rates (IR) and 95% confidence intervals (95% CI) of mortality and first occurrence of WHO-4 and WHO-3 events, excluding tuberculosis, during person-years (PY) spent within different age (<2, 2 to 4, 5 to 9, 10 to 14, 15 to 19, 20 to 24) and CD4 (percent when <5 years [<15%, 15% to 24%, ≥25%]; count when ≥5 years [<200, 200 to 499, ≥500 cells/μL]) strata. We used linear mixed models to predict CD4 evolution, with trends modelled by region.

Results: In the pre-ART period, 49 137 participants contributed 51 966 PY of follow-up (median enrolment age: 3.9 years). The overall pre-ART IRs were 2.8/100 PY (95% CI: 2.7 to 2.9) for mortality, 3.3/100 PY (95% CI: 3.0 to 3.5) for first occurrence of a WHO-4 event, and 7.0/100 PY (95% CI: 6.7 to 7.4) for first occurrence of a WHO-3 event. Lower CD4 and younger age strata were associated with increased rates of both mortality and first occurrence of a clinical event. In the post-ART period, 52 147 PHIVY contributed 207 945 PY (ART initiation median age: 4.5 years). Overall mortality IR was 1.4/100 PY (95% CI: 1.4 to 1.5) and higher in low CD4 strata; patients at each end of the age spectrum (<2 and >19) had increased mortality post-ART. IRs for first occurrence of WHO-4 and WHO-3 events were 1.3/100 PY (95% CI: 1.2 to 1.4) and 2.1/100 PY (95% CI: 2.0 to 2.2) respectively. These were also associated with lower CD4 and younger age strata.

Conclusions: Mortality and incidence of clinical events were highest in both younger (<2 years) and older (>19 years) youth with PHIV. Scaling-up services for <2 years (early access to HIV diagnosis and care) and >19 years (adolescent- and youth-focused health services) is critical to improve outcomes among PHIVY.

Keywords: HIV; paediatrics; adolescents; mortality; severe morbidity

Additional information may be found under the Supporting Information tab for this article.

1 | INTRODUCTION

With the rollout of antiretroviral therapy (ART), children living with perinatally acquired HIV (PHIV) are now surviving into adolescence and young adulthood [1-3]. In 2016, of the 1.3 million adolescents ages 15 to 19 living with HIV, over a third acquired HIV perinatally. Globally, adolescents experience poorer health outcomes compared to adults with HIV [4-7]. Updated data detailing rates of mortality and clinical events among people with PHIV are essential to both clinicians and policymakers [5,7,8]. Understanding current rates of important clinical events, including mortality, for children, adolescents and youth living with PHIV in low-income settings as they age is critical, and this understanding should inform interventions designed for this vulnerable population.

The International epidemiology Databases to Evaluate AIDS (IeDEA) research consortium (https://www.iedea.org/) harmonizes globally diverse HIV/AIDS data from routine clinical care. The objective of this study was to describe the incidence of mortality and first occurrence of WHO-4 and WHO-3 events stratified by time-updated age and CD4 before and after ART initiation among a large, multiregional IeDEA cohort of children, adolescents and youth living with (PHIVY).

2 | METHODS

2.1 | Study population, participants and data collection

Individual patient data from the six paediatric cohorts within IeDEA were pooled: Asia-Pacific; West Africa; East Africa; Central Africa; Southern Africa; and the Caribbean, Central and South America Network (CCASAnet) [9]. Study inclusion criteria included enrolment in care before 10 years of age (as a proxy for perinatal infection) at any participating IeDEA site between 2004 and 2016; confirmed HIV diagnosis; being ART-naïve at enrolment; and, having at least one CD4 measurement (count or percent) during follow-up.

Data abstracted for this analysis were generated during routine care encounters and included region, country, site, demographics (sex, date of birth, HIV diagnosis date [when available], and date of enrolment in care), laboratory values (CD4 count/percent), ART regimens, and, if applicable, date of last clinical contact, transfer out or death.

All sites contributed to the mortality analyses, and a subset of sites contributed to the clinical events analyses. For the clinical events analyses, regional data managers assessed the reliability and completeness of data using a 6-item survey, which gathered data on the frequency and details of event data collected at each site. Sites were selected based on reporting in both the pre- and post-ART periods. Overall, 27/61 IeDEA sites that care for children were included in the clinical events analyses; all regions contributed at least one site, except West Africa, where sites do not record clinical diagnoses.

Diagnoses recorded in regional databases were derived by the clinician treating the patient utilizing clinical assessments and locally available diagnostic testing, including clinical, radiographic, laboratory and pathological evaluations. Clinical events were categorized by 2007 WHO staging criteria as Stage 4 (WHO-4) or Stage 3 (WHO-3)+++, excluding tuberculosis (TB) [10]. While technologies such as Xpert MTB/RIF are being implemented in some IeDEA sites, most sites rely on presumptive clinical diagnoses for TB [11]. Given widespread variations in these diagnosis and documentation practices [12], we excluded TB from the primary analyses to avoid biased estimates. We conducted a separate analysis evaluating the incidence of TB events; importantly, reported diagnoses were not supported by any additional data.

The data presented here are based on retrospective de-identified information collected on a routine basis in sites participating in the IeDEA consortium. These data were approved for use by the local institutional review boards in each of the IeDEA countries included in the analysis and consent requirements were deferred to the local institutional review boards. Furthermore, the research did not include any planned intervention by the researcher or direct interaction with individuals or groups and no results can identify specific individuals.

2.2 | Outcomes and key definitions

Outcomes included mortality, first occurrence of WHO-4 event, and first occurrence of WHO-3 event, excluding TB, during follow-up (Appendix, Data S1). We defined two distinct follow-up periods: (i) the pre-ART period, from enrolment until 30 days after ART initiation (or loss to follow-up [LTFU], transfer or death, whichever came first) and (ii) the post-ART period, from the 31st day on ART until database closure date (or LTFU, transfer, or death, whichever came first). Events occurring in the first 30 days after ART initiation were included in the pre-ART period, to account for the likelihood that such events likely represented unmasking of a previously existing condition. We limited this period to 30 days to avoid diluting high rates of mortality and infectious morbidity previously reported in the pre-universal ART era [2,13]. LTFU was defined as having no clinical contact for ≥6 months since the last visit recorded in the database in the pre-ART period and for ≥3 months in the post-ART period; in case of LTFU, follow-up was censored at date of last clinical contact. Those still in care at database closure were also censored at date of last visit.

Baseline was defined as date of enrolment in the pre-ART period and date of ART initiation in the post-ART period.

2.3 | Statistical analyses

Time varying age was divided in six stratums (<2, 2 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 to 24 years) and CD4 levels were divided into three stratums: we used exclusively CD4 percentage in children aged <5 years (<15%, 15% to 24%, ≥25%) and absolute CD4 cell count for older children aged ≥5 years (<200, 200 to 499, ≥500 cells/µL). First, we estimated the incidence rates (IRs), events per 100 person-years (PY) of follow-up, of mortality stratified by the combination of time-varying age and CD4 level, and conducted a sensitivity analysis where all LTFU was considered as underreported mortality. Second, we estimated IR/100 PYs for the first occurrence of WHO-4 and WHO-3 events, also stratified by time-varying age and CD4 in a subset of sites. We report IRs separately in the pre-ART and post-ART periods, given that some sites only provided care in the post-ART periods.

To calculate the total person-time contributed by participants in each age/CD4 stratum, we used random effect models and used estimated dates when strata thresholds were crossed. If only one CD4 value was available and the follow-up duration was <6 months, we carried this CD4 value through an individual's entire follow-up time. If a participant had >1 CD4 value or follow-up duration ≥6 months, we estimated the date when strata thresholds were crossed based on the overall CD4 pattern observed among the participants in their region. Pre-ART, we estimated the CD4 decline since birth (the estimated time of infection) using linear mixed models. Post-ART, we estimated the CD4 increase since ART initiation using linear mixed models. We modelled an increased slope for the first six months post-ART initiation, reflecting the expected initial robust immune response pattern post-ART [14,15]. If a patient only had one CD4 measurement available, dates at which CD4 thresholds were crossed were based on the average slope of CD4 decline (pre ART) or increase (post ART) for the cohort. Separate models were built for each IeDEA region.

We calculated IRs as the number of events divided by the total number of PY of follow-up for each age and year stratum, and computed confidence intervals (CIs) for Poisson means using normal approximation, based on the logarithmic transformation of the rates. We assessed IR trends across all strata using Poisson models for trend.

3 | RESULTS

Overall, 65 903 children, adolescents, and youth were included, contributing a total of 259 912 person-years of follow-up; 49 137 participants contributed to the pre-ART period and 52 147 to the post-ART period (Table 1).

During the pre-ART period, 49 137 participants contributed 51 967 PY (87% from sub-Saharan Africa, 10% from the Asia-Pacific, and 3% from CCASAnet). Median age at enrolment was 3.9 years (interquartile range [IQR]: 1.5 to 6.7); 51% were female and >80% enrolled between 2004 and 2012. Overall median follow-up was 4.0 months [IQR: 1.8 to 13.0] and 77% initiated ART. More person-time was spent in the 5 to 9 years age stratum (48%) than any other age stratum, and 52% of person-time was spent in the highest CD4 stratum (Table 2).

During the post-ART period, 52 147 participants contributed 207 945 PY. Of note, 68% of these participants also contributed pre-ART person-time. Of the entire cohort, 32% were enrolled in care on the day of ART initiation. More than half (59%) were from Southern Africa, 50% were female, and the median age at ART initiation was 4.5 years (IQR: 1.9 to 7.4) (Table 1). Similar to the pre-ART period, most person-time was spent between the ages of 5 and 9 years (44%), and 77% was spent in the highest CD4 stratum (Table 2). Median follow-up time was 42 months (IQR: 17 to 74).

3.1 | Mortality incidence in the pre-ART period

Overall, 1449 deaths were recorded pre-ART; the overall mortality rate was 2.8/100 PY (95% CI: 2.7 to 2.9). Incidence of mortality was highest in children <2 years (9.8/100 PY, 95% CI: 9.1 to 10.6, Figure 1a) and decreased as age

Table 1. Characteristics of IeDEA participants at baseline and during follow-up

Characteristic	Pre-ART participants	Post-ART participants
Region, n (%)		
Asia-Pacific	3450 (7)	3755 (7)
CCASAnet	979 (2)	1252 (2)
Central Africa	1538 (3)	1564 (3)
East Africa	9742 (20)	8344 (16)
Southern Africa	29 649 (60)	33 321 (64)
West Africa	3779 (8)	3911 (8)
Overall	49 137 (100)	52 147 (100)
Person-time, years (%)		
Asia-Pacific	5372 (10)	21 833 (11)
CCASAnet	1460 (3)	8716 (4)
Central Africa	2901 (6)	7449 (4)
East Africa	13 754 (27)	30 279 (15)
Southern Africa	24 454 (47)	121 596 (59)
West Africa	4024 (8)	18 073 (9)
Overall	51 967 (100)	207 945 (100)

Baseline	At enrolment	At ART initiation
Year, n (%)		
<2004	2065 (4)	2686 (5)
2004 to 2007	18 781 (38)	18 921 (36)
2008 to 2012	20 858 (43)	22 086 (42)
2013 to 2014	5153 (11)	5993 (11)
2015 to 2016	2280 (5)	2461 (5)
Female, n (%)	24 897 (51)	25 871 (50)
Pre-ART follow-up, n (%)		35 381 (68)
Age, median (IQR), years	3.9 (1.5 to 6.7)	4.5 (1.9 to 7.4)
Outcomes		
Initiated ART, n (%)	37 591 (77)	
Deceased, n (%)	1449 (3)	2932 (6)
Lost to follow-up,[a] n (%)	8063 (16)	20 600 (40)

ART, antiretroviral therapy; CCASAnet, the Caribbean, Central and South American Network; IQR, interquartile range.
[a]Lost to follow-up in the pre-ART period was defined as 6 months since last clinical contact and in the post-ART period as 3 months since last clinical contact.
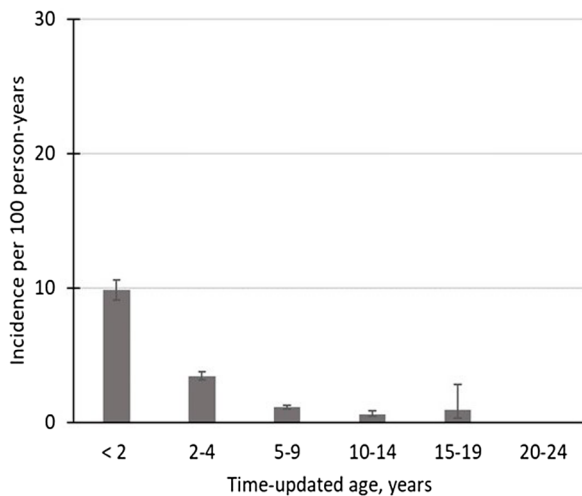
increased, reaching 0.6/100 PY (95% CI: 0.5 to 0.8) in adolescents aged 10 to 14 years (*p*-value for trend, based on Poisson model: *p* < 0.001). We then observed a slight uptick in mortality within the 15 to 19 stratum (Figure A, Tables A and C, Data S1). When stratified by CD4 and age, mortality was highest in the lowest CD4 stratum and the youngest age stratum, 14.0/100 PY (95% CI: 12.7 to 15.4) in children <5 years with CD4 < 15% (Figure 1b, Tables B and C, Data S1). In sensitivity analyses, including LTFU as mortality, the overall mortality rate reached 19.0/100 PY (95% CI: 18.6 to 19.3) with similar trends including the marked increase in IR among those aged 15 to 19 years (Tables A and D, Data S1).

Table 2. Distribution of person-time by time-updated age and CD4 count (or CD4% if <5 years) in both the pre-ART and the post-ART periods

Person-time, years (%), by time-updated age and CD4 strata

	Pre-ART participants				Post-ART participants			
	CD4 cell %/count				CD4 cell %/count			
	<15%	15% to 24% 200 to 499	≥25%		<15% <200	15% to 24% 200 to	≥25%	
Age	<200 cells/µL	cells/µL	≥500 cells/µL	Overall	cells/µL	499 cells/µL	≥500 cells/µL	Overall
<2 years	1171 (2)	3210 (6)	2487 (5)	6868 (13)	727 (0)	3391 (2)	5970 (3)	10 087 (5)
2 to 4 years	1842 (4)	6443 (12)	4915 (9)	13 200 (25)	1703 (1)	8335 (4)	28 066 (13)	38 103 (18)
5 to 9 years	1629 (3)	7318 (14)	16 134 (31)	25 081 (48)	2902 (1)	12 041 (6)	75 815 (36)	90 758 (44)
10 to 14 years	368 (1)	2727 (5)	3391 (7)	6485 (12)	2027 (1)	12 030 (6)	44 240 (21)	58 297 (28)
15 to 19 years	39 (0)	159 (0)	133 (0)	330 (1)	749 (0)	3047 (1)	6604 (3)	10 400 (5)
20 to 24 years	0 (0)	1 (0)	2 (0)	2 (0)	53 (0)	76 (0)	171 (0)	300 (0)
Overall	5049 (10)	19 857 (38)	27 060 (52)	51 967 (100)	8160 (4)	38 920 (19)	160 866 (77)	207 946 (100)

Overall column and line totals may not sum to overall total due to rounding of person-time years. ART, antiretroviral therapy.
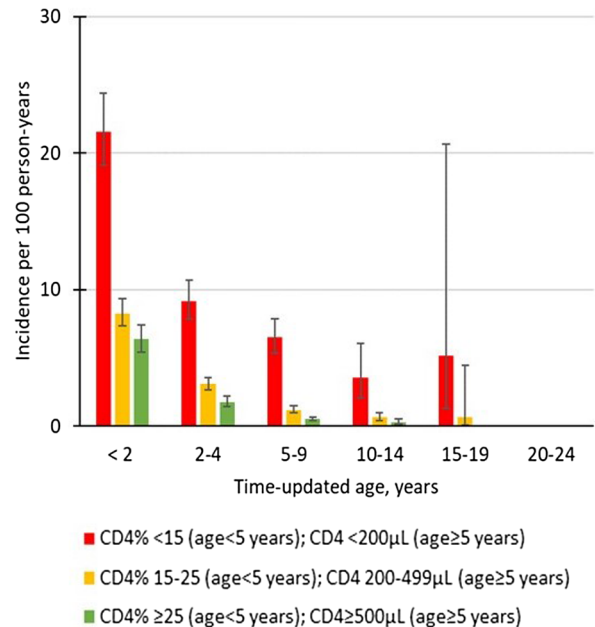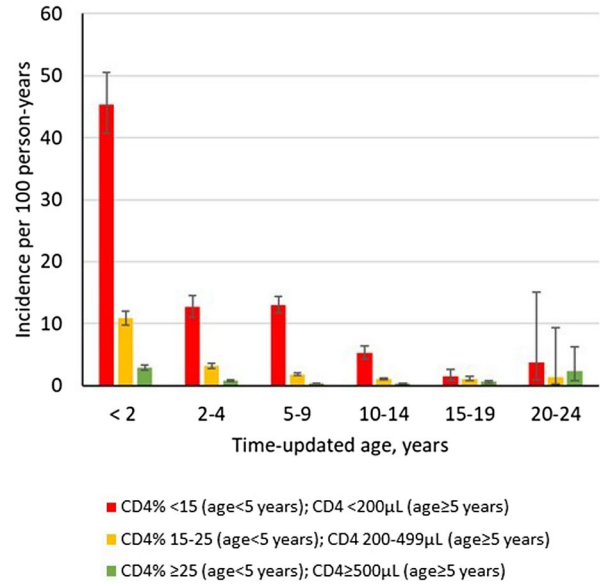

Figure 1. Incidence rates of pre-ART mortality by (a) time updated age, and (**b**) CD4 and time updated age, IeDEA multiregional cohort, 2004 to 2016 . Error bars indicate 95% confidence intervals.

3.2 │ Incidence of first occurrence of WHO-4 and WHO-3 events in the pre-ART period

Of the 49 137 participants with pre-ART follow-up, a subset of 16 596 (33%) children contributed to the analyses of incidence of WHO-4 and WHO-3 events.

Of the 16 596 participants included in the clinical event analysis, 424 (3%) presented with a WHO-4 event at enrolment and were excluded from the analyses of incident first WHO-4 events. The 16 172 remaining children contributed

23 883 PY and 723 (4%) had at least one WHO-4 event during pre-ART follow-up. Pneumocystis pneumonia (21%) constituted the most frequent diagnosis (Table E, Figure B, Data S1). The overall IR for first occurrence of WHO-4 event was 3.3/100 PY (95% CI: 3.0 to 3.5). The highest IR was observed in the stratum of lowest CD4 levels and youngest ages (<2 years with CD4 < 15%: 16.4/100 PY; 95% CI: 13.0 to 20.7); the lowest IR was observed among those 10 to 14 years with CD4 ≥ 500 (0.5/100 PY; 95% CI: 0.3 to 1.0; $p < 0.001$) (Figure 2a and b, Table F, Data S1).

(a)WHO-4 event, time-updated age
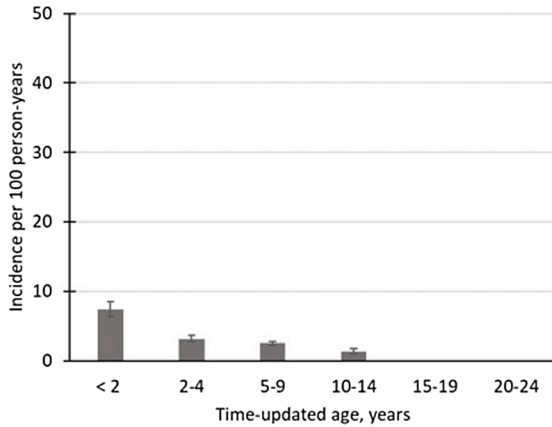
(b)WHO-4 event, CD4 and time-updated age
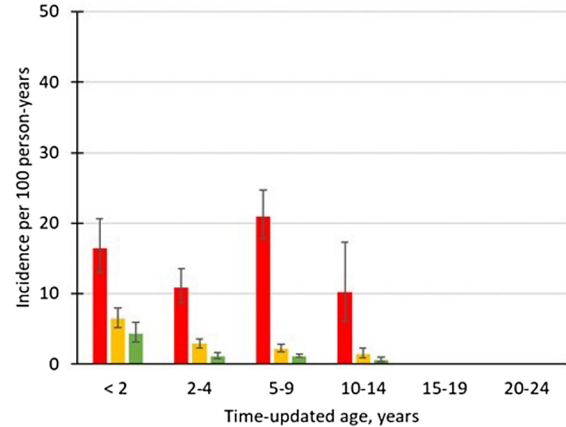
(c)WHO-3 event, time-updated age
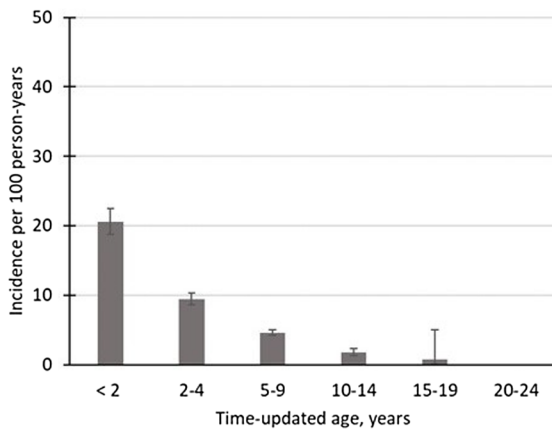
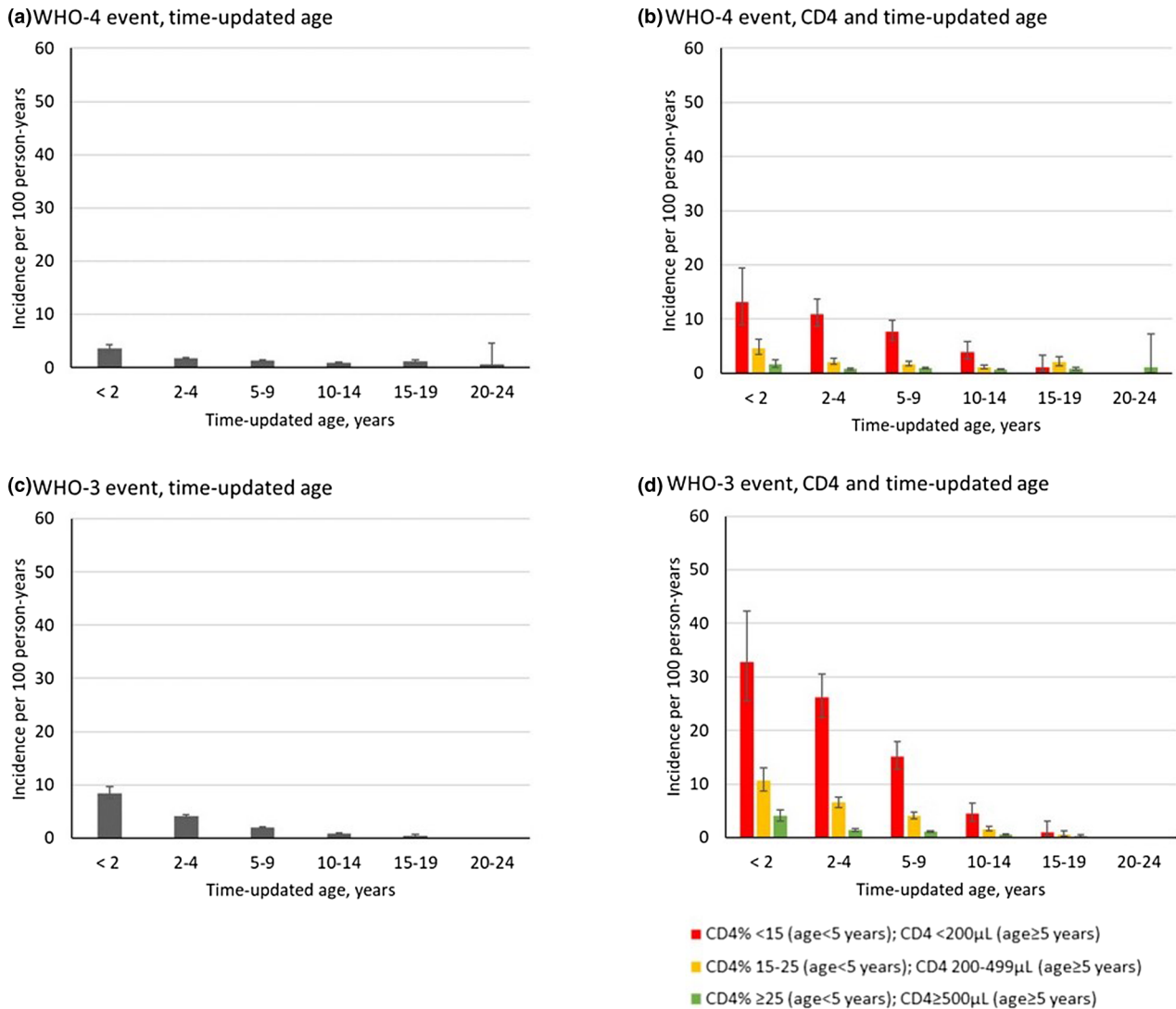### (d) WHO-3 event, CD4 and time-updated age
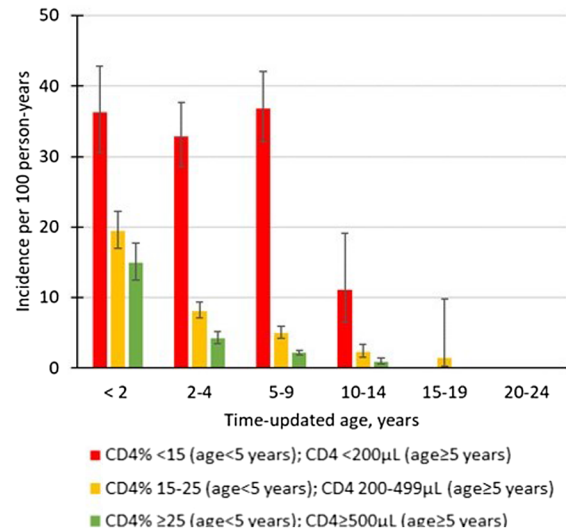
Figure 2. Incidence rates of pre-ART WHO-4 event by (a) time-updated age, and (**b**) CD4 and time-updated age, and WHO-3 event by (**c**) time-updated age, and (**d**) CD4 and time-updated age IeDEA multiregional cohort, 2004 to 2016. Error bars indicate 95% confidence intervals.

Of the 16 596 participants, 1430 (9%) had a prevalent WHO-3 clinical event at enrolment and were excluded from the analyses of incident WHO-3 events. Among the remaining 15 166 children, 1528 WHO-3 events occurred during 21 731 PY of follow-up (7.0/100 PY, 95% CI: 6.7 to 7.4). Oral candidiasis constituted 46% of the diagnoses (Figure B, Data S1). We observed the highest IR in the stratum of lowest CD4 levels and youngest ages (<2 years with CD4 < 15%: 36.2/100 PY; 95% CI: 30.6 to 42.9), and the lowest IR among those 10 to 14 years with CD4 ≥ 500: 0.9/100 PY; 95% CI: 0.5 to 1.4; *p* < 0.001) (Figures 2c and d, Table G, Data S1).

Overall, we observed higher IRs for both WHO-4 and WHO-3 clinical events in the Asia-Pacific and CCASAnet regions compared to sub-Saharan Africa, (Figures C and D, Tables E and G, Data S1).

Additionally, we reported 1414 TB events occurring among 15 881 children at risk (IR 6.2/100 PY, 95% CI: 6.0 to 6.6). Rates were significantly higher in younger children in and among those with low CD4 counts (Table H of Data S1).

3.3 | Mortality incidence in the post-ART period

Overall, 2932 deaths (6%) were recorded post-ART; the overall post-ART mortality IR was 1.4/100 PY (95% CI: 1.4 to 1.5). Similar to the pre-ART period, mortality was highest within the < 2 years stratum (<2 years: 8.6/100 PY; 95% CI: 8.1 to 9.2). Mortality then followed a decreasing trend within the middle age strata and then increased within the older ages (Figure 3a, Table A, Data S1). In all age groups, mortality was highest in the lowest CD4 stratum (Figure 3b). Furthermore, in this stratum, in children <2 years, post-ART mortality was more than 2-fold higher than pre-ART mortality IR (45.4/ 100 PY; 95% CI: 40.8 to 50.6, compared to 21.6/100 PY; 95% CI: 19.1 to 24.4). Higher post-ART mortality in the lowest CD4 stratum was observed in all age groups. Overall, mortality IRs did not differ by region; detailed results are available in Figure E and Table I, Data S1. In sensitivity analysis the overall mortality rate reached 12.0/100 PY (95% CI: 11.9 to 12.2); we observed the same trends as in the primary analysis (Table A, Table J, Data S1).
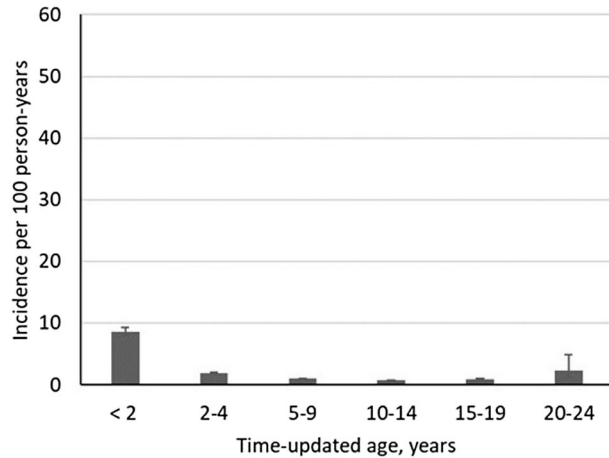
Figure 3. Incidence rates of post ART mortality by (a) time updated age, and (**b**) CD4 and time updated age, IeDEA multiregional cohort, 2004 to 2016. Error bars indicate 95% confidence intervals.

3.4 | Incidence of first occurrence of WHO-4 and WHO-3 events in the post-ART period

In the post-ART period, a subset of 16 079 participants contributed to the WHO-4 and WHO-3 events analyses.

At the start of the post-ART period, 18 children (<1%) had a prevalent WHO-4 condition and were excluded from the analyses of incident post-ART WHO-4 events. Overall, 899 WHO-4 events occurred among 16 061 children, during 72 412 PY of follow-up. Recurrent severe bacterial infection and PCP represented >40% of these events (Table K, Figure B, Data S1). Post-ART, the overall IR of first occurrence of a WHO-4 event was 1.3/100 PY (95% CI: 1.2 to 1.4, Figure 4). Incidence was highest among <2-year-olds (3.5/100 PY, 95% CI: 2.9 to 4.4). IRs decreased in the older groups, remaining comparable between the older strata (Figure 4a, Tables A and G, Data S1). We also observed higher IRs in the lower CD4 strata (Figure 4b, Table B, Data S1). Regional data are available in Figure F and Table L, Data S1.

Twenty-five children (<1%) had a prevalent WHO-3 condition at the start of the post-ART period and were excluded from the analyses of incident post-ART WHO-3 conditions. Among the remaining 16 054 children, 1410 (9%) experienced a first WHO-3 event during 21 732 person-years of follow-up, yielding an overall IR of 2.1/100 PY (95% CI: 2.0 to 2.2). Oral candidiasis (31%) was the most frequently observed event (Figure B, Data S1). The IR of a first WHO-3 event decreased as age increased, ranging from 8.4 (95% CI: 7.4 to 9.7) in <2-year-olds to 0.5/100 PY (95% CI: 0.3 to 0.7) in 15 to 19-year-olds, with no events recorded in 20 to 24-year-olds (Figure 4 and Table A, Data S1). We also found a significant difference between the IRs of first WHO-3 events pre- and post-ART in older youth >15 years by CD4 count strata: the highest IRs were observed in the lowest CD4 stratum

(Figure 4 and Table B, Data S1). Regional data are available in Figure G and Table M of Data S1.

Additionally, 1125 TB events occurred in the post-ART period; the estimated IR was 1.6/100 PY (95% CI: 1.5 to 1.7) (Table N of Data S1).

4 | DISCUSSION

This large multiregional cohort study analyzed time-updated age- and CD4-adjusted incidence rates of mortality and first occurrence of WHO-4 and WHO-3 events (excluding TB) before and after ART initiation among 65 903 children, adolescents and youth living with PHIV over 259 912 PY of follow-up. We make several key findings. First, post-ART mortality rates were the highest at each end of the age spectrum relative to ages in the middle of the spectrum. Second, as age increased, participants in the lowest CD4 stratum had the highest mortality rates in the post-ART period. Third, pre-ART, IRs of both mortality and first occurrence of WHO-4 and WHO-3 events decreased as age and CD4 levels increased. Fourth, despite low incidence rates of clinical events, there remains a substantial burden of poor HIV-related immune status and WHO-4 and WHO-3 events, both pre- and post-ART.

We report an overall post-ART mortality rate (1.4/100 PY) that is similar to those reported in other studies [16-22]. Younger children (<2 years) and those with low CD4 levels experienced higher rates of mortality, consistent with previous findings [16-20,22-24]. We also found that mortality rates increased as participants reached ages 15 to 24. Indeed, these older children may have already experienced a fair amount of morbidity and resistance during their childhood, before entering HIV care, making them more vulnerable. In addition, this

Figure 4. Incidence rate of post-ART WHO-4 events by (a) time-updated age, and (**b**) CD4 and time-updated age and WHO-3 events by (**c**) time-updated age, and (**d**) CD4 and time-updated age, IeDEA multiregional cohort, 2004 to 2016. Error bars indicate 95% confidence intervals.

current generation of adolescents and youth who survived childhood with HIV, are challenged by a wide range of adolescent-specific barriers to care, retention, and medication adherence exposing them to additional infectious morbidity and STIs [5,25,26]. This result underlines the need to identify and implement youth-targeted interventions to ensure adolescents and youth living with PHIV are on effective regimens and engaged in care, and thus improve survival outcomes [25].

Notably, mortality incidence was higher at the lowest CD4 stratum during the post-ART period compared to the pre-ART period, for the same age strata. In this study were unable to link morbidity to mortality, however, given that the median age at ART initiation was 4.5 years, this likely reflects the late stage at which children, adolescents, and youth were accessing ART: children are initiating ART at very low CD4 counts, and mortality is occurring before immune reconstitution is possible [27-29]. At database closure, 4% of children in care had still not initiated ART in 2016. As universal ART is scaling-up in accordance with 2017 WHO guidelines, there is an urgency

to identify these children and initiate them on treatment as soon as possible [30].

Pre-ART, the overall mortality rate was 2.8/100 PY. The <2-year-old mortality was close to 4-fold higher (9.8/100 PY). However, these pre-ART rates are lower than those observed in earlier studies [24,31]. In our study, we report comparable rates only among those in the lowest CD4 stratum, ranging from 13 to 26/100 PY in sub-Saharan African regions. Two key factors may have led us to underestimate mortality: first, median age at enrolment was 3.9 years. More than 50% of children born with HIV die by age 2 without ART, and thus many children may have died before accessing diagnosis and care, particularly in the earlier years [32]. Second, 16% of youth were classified as LTFU and were censored at the date of their last clinic visit while waiting to initiate ART, and some of those classified as LTFU may have actually died [33]. Indeed, in sensitivity analyses, we report high pre ART mortality among infants, reaching 36.1/100 PY (95% CI: 34.7 to 37.6) among those <2 years.

Few studies document the incidence of WHO-4 and WHO-3 events in children prior to initiating ART, and those that do were conducted in the pre-ART era in high-income countries. Overall, the pre-ART IRs observed in our study are lower than those reported elsewhere [34]. Post-ART, we make the same observation [23,35]. We also noted marked differences between regions, where morbidity IRs were lower in sub-Saharan Africa. This is most likely due to regional differences in the healthcare infrastructure and capacity to diagnose WHO-4 and WHO-3 events. In addition to having excluded TB events, the low pre-ART opportunistic infection rates may be due to several factors, including the lower diagnostic capacity for opportunistic infections in resource-limited settings and survivor bias (the sickest children either initiated ART or died before an event was recorded). Furthermore, we found that younger children were more at risk of disease progression and mortality. Those who survived to reach the older age groups in the pre-ART period were likely children whose disease progression was slower. Of note, 13% of the 10 to 24-year-old age group had not yet initiated ART. Our results suggest that even in the setting of treat-all policies, there remains a substantial burden of WHO-4 and WHO-3 events associated with poor HIV-related immune status, in particular among younger children, and highlights the need to implement or re-inforce strategies to reduce preventable infectious diseases in this population [36,37].

Our study is affected by several limitations. First, survivor bias, as described above, likely led to an underestimation of mortality and clinical events IRs. Second, inclusion criteria included at least one CD4 measurement during both pre and post ART follow-up, likely excluding those who died before access to CD4 was possible. Third, LTFU was high, particularly in the post-ART period; this also may have led to unascertained morbidity and mortality: to account for this, and provide an interval in which true mortality IRs lie, we conducted a sensitivity analysis, under a maximum bias assumption where all LTFU was mortality. Fourth, excluding TB from the clinical events analysis underestimates WHO-4 and WHO-3 clinical events IRs. Indeed, in secondary analysis, we found high TB IRs. Although these findings are in line with previous studies, in the absence of reliably consistent application of TB case definitions, we feel our estimates are more robust as presented with this caveat [38,39]. In addition, it is assumed that data on WHO-4 and WHO-3 events were incomplete and we were unable to link these events to mortality, both due to operational challenges in routine data collection as well as diagnostic limitations in our settings. We tried to address incompleteness by narrowing the study sample to a subset of our cohort in the clinical events analysis. Fifth, few data and follow-up time are available in the 20 to 24 years age stratum, in particular in the pre-ART period, making comparisons less meaningful. Despite this, as universal ART is scaled up, we feel this dataset provides a unique opportunity to describe this population of untreated 20 to 24-year-olds living with PHIV. Finally, we were unable to stratify results by sex, due to multiple stratifications leading to little person-time per stratum.

Nonetheless, this study provides the largest report of both pre- and post-ART, time-updated age- and CD4-stratified data on paediatric and adolescent mortality and WHO-4 and WHO-3 IRs (excluding TB) in the post-ART era. The data presented are likely the most recent available describing children and adolescents living with HIV who are have not yet initiated ART and remain crucial to document the natural history of HIV progression. Furthermore, our results are strengthened by the study's global scope and duration of follow-up, providing estimates from infancy through age 24. While we likely underestimate IRs, but as CD4 testing becomes less available as countries shift to viral load monitoring, our data provide a valuable perspective on regional and global trends of IRs of morbidity and mortality by time-updated age and CD4 level that will help to gauge current access to and quality of care. CD4 monitoring continues to play an important role in the clinical management of HIV, particularly for patients presenting late to care, and for treatment monitoring where viral load monitoring is restricted [40]. As Treat-All implementation is scaling up in these regions, children living with PHIV will access ART at an earlier stage of their disease, likely impacting the morbidity and mortality IRs of the future generation of adolescents and youth living with PHIV.

5 | CONCLUSIONS

Mortality and clinical event IRs were lower in our global cohort after ART initiation compared to before, except in younger children at low CD4 levels. Our data reflect the advanced stage of disease at which these children initiated ART across our cohorts and highlight the urgency in treating children at the earliest age possible. The high post-ART mortality rates observed among children <2 years of age underscore the importance of prioritizing access to early HIV diagnosis and care in infants. Furthermore, while IRs decreased as age increased, this was no longer true in adolescents and young adults aged 15 to 24 years. Strengthening adolescent-focused HIV services remains critical to improve long-term outcomes among youth living with PHIV.

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COMPETING INTERESTS

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AUTHORS' CONTRIBUTIONS

SDe, AMN, ALC, KWK, MAD and VL designed the study. KC, AE, KWK, SDu, MAD and VL provided data. KM, BM and GP extracted the data. SDe analysed the data. SDe and AMN drafted the manuscript. All authors have read, revised and approved the final version.

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CENTRAL AFRICA

EAST AFRICA IEDEA

IEDEA SOUTHERN AFRICA

WEST AFRICA

SITE INVESTIGATORS AND COHORTS

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article.

Data S1. Supplemental digital content 1.

Data S2. This file provides the complete IeDEA global funding acknowledgments for each region.