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Age-specific mortality rate ratios in adolescents and youth aged 10–24 years living with perinatally versus nonperinatally acquired HIV

Sophie Desmonde[a], Andrea L. Ciaranello[b], Karen Malateste[c,d], Beverly Musick[e], Gabriela Patten[f], An Thien Vu[g], Andrew Edmonds[h], Anne M. Neilan[i], Stephany N. Duda[j], Kara Wools-Kaloustian[e], Mary-Ann Davies[f], Valériane Leroy[a], on behalf of the IeDEA Consortium

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Objective: To measure mortality incidence rates and incidence rate ratios (IRR) in adolescents and youth living with perinatally acquired HIV (YPHIV) compared with those living with nonperinatally acquired HIV (YNPHIV), by region, by sex, and during the ages of 10–14, 15–19, and 20–24 years in IeDEA.

Design and methods: All those with a confirmed HIV diagnosis, antiretroviral therapy (ART)-naive at enrollment, and who have post-ART follow-up while aged 10–24 years between 2004 and 2016 were included. We estimated post-ART mortality incidence rates and 95% confidence intervals (95% CI) per 100 person-years for YPHIV (enrolled into care <10 years of age) and YNPHIV (enrolled ≥10 years and <25 years). We estimate mortality IRRs in a negative binomial regression model, adjusted for sex, region time-varying age, $CD4^+$ cell count at ART initiation (<350 cells/μl, ≥350 cells/μl, unknown), and time on ART (<12 and ≥12 months).

Results: Overall, 104 846 adolescents and youth were included: 21 340 (20%) YPHIV (50% women) and 83 506 YNPHIV (80% women). Overall mortality incidence ratios were higher among YNPHIV (incidence ratio: 2.3/100 person-years; 95% CI: 2.2–2.4) compared with YPHIV (incidence ratio: 0.7/100 person-years; 95% CI: 0.7–0.8). Among adolescents aged 10–19 years, mortality was lower among YPHIV compared with YNPHIV (all IRRs <1, ranging from 0.26, 95% CI: 0.13–0.49 in 10–14-year-old boys in the Asia-Pacific to 0.51, 95% CI: 0.30–0.87 in 15–19-year-old boys in West Africa).

Conclusion: We report substantial amount of deaths occurring during adolescence. Mortality was significantly higher among YNPHIV compared to YPHIV. Specific interventions including HIV testing and early engagement in care are urgently needed to improve survival among YNPHIV.

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[a]Inserm U1027, Université Paul Sabatier Toulouse 3, Toulouse, France, [b]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA, [c]Inserm U1219, [d]Bordeaux Population Health Center, Université de Bordeaux, Bordeaux, France, [e]School of Medicine, Indiana University, Indianapolis, Indiana, USA, [f]School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa, [g]Children's Hospital 2, Ho Chi Minh City, Vietnam, [h]Department of Epidemiology, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, [i]Division of General Academic Pediatrics, Department of Pediatrics, Massachusetts General Hospital for Children, Boston, Massachusetts, and [j]Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, Tennessee, USA.

Correspondence to Sophie Desmonde, Inserm U1027, CERPOP, 37 Allées Jules Guesde, 31073 Toulouse Cedex 7, France.

E-mail: desmonde.s@chu-toulouse.fr

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Background

Adolescents (10–19 years) and youth (15–24 years) living with perinatally acquired HIV (YPHIV) or nonperinatally acquired HIV (YNPHIV) represent increasing proportions of people living with HIV. In 2016, an estimated 2.1 million adolescents were living with HIV worldwide, a 30% increase since 2005 [1]. Additionally, there were 3.9 million youth living with HIV worldwide in 2017 [2]. In particular, young women aged 15–24 years make up 58% of new infections globally and 67% of new infections in sub-Saharan Africa [2].

As the introduction of antiretroviral therapy (ART), mortality has declined in people living with HIV, except in adolescents [3–7]. However, mortality among adolescents living with HIV/AIDS remains high [8,9]. Adolescent-focused interventions are essential to improve health outcomes in this population and reduce mortality. In a context of limited funding to conduct population-based surveys, policy decision-makers often rely on simulation models to estimate the magnitudes of the adolescent and youth HIV epidemics globally, and in turn, these models require high-quality data to inform them [8,10]. The Spectrum software is the most widely used source of global estimates for the numbers of people living with HIV, new HIV infections, and AIDS-related deaths each year. These estimates are used by countries to inform policies, set national targets, and evaluate programmatic gaps [10–12]. The Spectrum model provides pediatric estimates up to the age of 15 years. However, as adolescents and youth with perinatally acquired HIV age into adulthood, the overall population of youth living with HIV is made up of both YPHIV and YNPHIV. Therefore, estimates of mortality in this specific population are necessary to correctly estimate HIV indicators in youth aged 15–24 years.

The objective of this study was to first provide incidence rates for mortality and second, incidence rate ratios for mortality in YPHIV compared with YNPHIV, by region and by sex during the periods of 10–14, 15–19, and 20–24 years of age, using programmatic data from the multiregional pediatric International epidemiology Databases to Evaluate AIDS (IeDEA) collaboration.

Methods

Study population, participants, and data collection

We pooled individual patient data from the six pediatric cohorts within IeDEA: Asia-Pacific; West Africa; East Africa; Central Africa; Southern Africa; and the Caribbean, Central, and South America Network (CCASAnet) [13]. Study inclusion criteria was: confirmed HIV diagnosis; ART initiation at any age in the IeDEA cohort; post-ART follow-up between the ages of 10 and 24 years between 2004 and 2016 in any participating IeDEA site. Although individual clinics within IeDEA have distinct protocols for routine follow-up, participants with HIV who have initiated ART are generally seen quarterly or biannually. Data abstracted for this analysis were generated during these routine care encounters and included region, country, site, demographics [sex, date of birth, HIV diagnosis date (whenever available), and date of enrollment in care], $CD4^+$ cell count/percentage at ART initiation, date of last clinical contact, and, if applicable, dates of death, and transfer out.

All participating IeDEA regions obtained local institutional review board approvals. Anonymized data collected during routine clinical care were used for this analysis.

Outcomes and key definitions

We compared incidence rates of mortality in two distinct populations: YPHIV, defined as having enrolled in care before the age of 10 years, and YPNHIV, defined as having enrolled in care at at least 10 years of age. In the absence of data on mode of HIV transmission in most of databases, we selected care entry before age 10 years as a conservative proxy on identifying those infected through mother-to-child transmission. Given that some YPHIV may enter care after age 10, we thus conducted a sensitivity analysis using age less than 15 years at enrolment as a proxy age for identifying perinatal infection. Loss to follow-up (LTFU) was defined as having no clinical contact for at least 365 days; in the case of LTFU, follow-up was censored at the date of last clinical contact. Those still in care at database closure were also censored at the date of their last visit. Baseline was defined as age 10 years or date of ART initiation, whichever occurred latest.

Statistical analyses

First, we estimated crude incidence rates of mortality per 100 person-years of follow-up, stratified by combinations of time-varying age (10–14, 15–19, and 20–24 years), region, and sex. These age bands allow us to distinguish early adolescence (10–14 years) from the later periods (15–19 and 20–24 years) where risk behaviors and sex inequities may differ [14]. We calculated incidence rates as the number of events divided by the total number of person-years of follow-up for each age and year stratum, and computed confidence intervals (CIs) using the semi-exact method. Second, we used a negative binomial regression analysis, accounting for over-dispersion of the data, to derive incidence rate ratios (IRR) and their 95% CIs for YPHIV compared with YNPHIV. All IRRs were adjusted for time-varying age (10–14, 15–19, and 20–24 years), and for region, sex, time on ART ($<$ or $\geq$12 months) and $CD4^+$ cell count at ART initiation ($<$350, $\geq$350 cells/μl, or unknown). IRRs were adjusted for time-varying age (10–14, 15–19, and 20–24 years), and for region and sex.

Analyses were conducted in SAS (version 9.4; SAS Institute Inc., Cary, North Carolina, USA), increasing the number of iterations when needed to ensure convergence.

Results

Overall, 104 846 adolescents and youth had post-ART follow-up between the ages of 10 and 24 years, yielding 224 393 person-years of follow-up between 2004 and 2016. Of the total, 21 340 (20%) were YPHIV and contributed 67 737 person-years (30%); median age at ART initiation was 8 years. The remaining 83 506 YNPHIV contributed 156 656 PY and median age at ART initiation was 22 years. Characteristics at ART initiation and mortality/LTFU outcomes of both YPHIV and YNPHIV are shown in Table 1. The majority of participants were from Southern Africa (54% of YPHIV and 70% of YNPHIV); 50% were women among YPHIV whereas 80% were women in the YNPHIV group. Among YPHIV, 2% died and 15% were LTFU. Of YNPHIV, 4% died and 35% were LTFU; these rates were two-fold higher than seen in YPHIV. Furthermore, LTFU was higher among women (21%) compared with men (16%).

Among YPHIV, ages 10–24 years, the overall mortality incidence rate was 0.7/100 person-years (95% CI: 1.3–1.6) and was similar across regions, except West Africa, where it was significantly higher (1.8/100 person-years, 95% CI: 1.5–2.20) (Table 2, Fig. 1 and Supplemental Content, Table A, http://links.lww.com/QAD/B925). Mortality increased as age increased, and was three-fold higher in 20–24 years (2.4/100 person-years; 95% CI: 2.2–5.1) compared with those aged 10–14 years (0.7/100 person-years; 95% CI: 0.6–0.8) and 15–19 years (0.8/100 person-years; 95% CI: 0.7–1.0). Additionally, among YPHIV aged 20–24 years, mortality was higher among females reaching 3.9/100 person-years (95% CI: 1.8–8.7) compared with males (0.7/100 person-years, 95% CI: 0.1–5.3) (Fig. 1, Supplemental Digital Content, Tables A–C, http://links.lww.com/QAD/B925).

Among YNPHIV, the overall mortality incidence rate was 2.3/100 person-years (95% CI: 2.3–2.4), which was a three-fold higher than the mortality incidence rate estimated among YPHIV (0.7/100 person-years, 95% CI: 1.3–1.6) (Table 2 and Fig. 1). Overall, mortality incidence rate was higher among men (2.7/100 person-years, 95% CI: 2.5–2.8) compared with females (2.0/100 person-years, 95% CI: 1.9–2.1). Across regions, there was no significant differences across age groups, except in Southern African, where mortality increased as age increased (Supplemental Digital Content, Table D–F, http://links.lww.com/QAD/B925).

Table 1. Baseline characteristics and antiretroviral therapy outcomes among adolescents and youth aged 10–24 years in the International epidemiologic Databases to Evaluate AIDS global consortium, by mode of HIV infection.

	Adolescents and youth living with perinatally acquired HIV		Adolescents and youth living with nonperinatally acquired HIV	
Baseline characteristics				
	Patients (*n*)	Person-years (%)	Patients (*n*)	Person-years (%)
Overall	21 340	67 737	83 506	156 656
Region	*n* (%)		*n* (%)	
Asia-Pacific	2114 (13%)		485 (2%)	
CCASAnet	784 (5%)		1276 (2%)	
Central Africa	963 (5%)		2617 (4%)	
East Africa	3494 (14%)		16 359 (18%)	
Southern Africa	12 107 (54%)		59 588 (70%)	
West Africa	1878 (9%)		3181 (4%)	
Female (%)	50%		80%	
Age at ART initiation (years) median (IQR[a])	8 (5–9)		22 (18–23)	
$CD4^+$ cell count (cells/μl) median (IQR[a])	392 (188–684)		237 (122–368)	
Antiretroviral therapy outcomes				
	Reported deaths *n* (%)	Lost to follow-up[b] *n* (%)	Reported deaths *n* (%)	Lost to follow-up[b] *n* (%)
Overall	480 (2%)	3149 (15%)	3603 (4%)	29 542 (35%)
Region				
Asia-Pacific	49 (2%)	53 (3%)	43 (9%)	21 (4%)
CCASAnet	38 (5%)	98 (13%)	82 (6%)	433 (34%)
Central Africa	11 (1%)	83 (7%)	97 (4%)	552 (21%)
East Africa	87 (2%)	409 (12%)	709 (4%)	5708 (35%)
Southern Africa	186 (2%)	2319 (19%)	2404 (4%)	21 994 (37%)
West Africa	109 (6%)	187 (10%)	268 (8%)	834 (26%)
Sex				
Male	231 (2%)	1591 (10%)	1092 (3%)	5526 (16%)
Female	249 (2%)	1558 (10%)	2511 (2%)	24 016 (21%)

[a]Interquartile range.
[b]Lost to follow-up is defined as more than 365 days since last clinical contact.

Table 2. Mortality incidence rates (per 100 person-years) and 95% confidence interval among adolescents and youth aged 10–24 years living HIV and on antiretroviral therapy during follow-up, by region and time-updated age, in the International epidemiologic Databases to Evaluate AIDS global consortium.

	Adolescents and youth living with perinatally acquired HIV				Adolescents and youth living with nonperinatally acquired HIV			
Time-varying age	10–14 years	15–19 years	20–24 years	Overall	10–14 years	15–19 years	20–24 years	Overall
Overall	**0.7 [0.6–0.8]**	**0.8 [0.7–1.0]**	**2.4 [1.2–5.1]**	**0.7 [0.6–0.8]**	**2.3 [2.1–2.5]**	**2.2 [2.0–2.3]**	**2.4 [2.3–2.5]**	**2.3 [2.2–2.4]**
Asia-Pacific	0.5 [0.3–0.7]	0.8 [0.5–1.3]	1.4 [0.2–9.7]	0.6 [0.4–0.7]	2.2 [1.5–3.4]	1.5 [0.9–2.4]	1.6 [0.5–4.8]	1.8 [1.4–2.5]
CCASAnet	0.9 [0.6–1.4]	1.0 [0.6–2.0]	3.0 [1.1–8.0]	1.0 [0.8–1.4]	6.2 [4.1–9.5]	3.6 [2.5–5.2]	1.7 [1.2–2.5]	2.8 [2.2–3.4]
Central Africa	0.3 [0.1–0.6]	0.5 [0.2–1.6]	-	0.3 [0.2–0.6]	3.1 [2.2–4.4]	1.3 [0.9–1.8]	0.9 [0.7–1.3]	1.4 [1.2–1.7]
East Africa	1.0 [0.8–1.2]	0.6 [0.2–1.3]	0.0 -	1.0 [0.8–1.2]	2.3 [1.8–2.8]	2.3 [1.9–2.7]	2.8 [2.5–3]	2.6 [2.4–2.8]
Southern Africa	0.5 [0.4–0.6]	0.6 [0.4–0.9]	1.8 [0.3–12.7]	0.5 [0.4–0.6]	1.8 [1.6–2.0]	2.0 [1.9–2.2]	2.3 [2.2–2.4]	2.2 [2.1–2.3]
West Africa	1.7 [1.4–2.1]	2.6 [1.7–4.0]	5.1 [0.7–36.4]	1.8 [1.5–2.2]	6.7 [5.4–8.3]	5.0 [4.0–6.3]	3.0 [2.4–3.6]	4.2 [3.7–4.8]

Incidence rate ratios (IRR) for YPHIV compared with YNPHIV, stratified by region, sex and time-varying age, and adjusted for time on ART and $CD4^+$ cell count at ART initiation are presented in Table 3. In participants aged 10–14 years, we found lower risks of mortality for YPHIV compared with YNPHIV in all regions except CCASAnet. Among men, the IRR varied from 0.3 (95% CI: 0.1–0.5) in Asia-Pacific to 0.5 (95% CI: 0.3–0.8) in West Africa. Among women, the difference in IRR between groups was less significant with mortality incidence rate among female YPHIV aged 10–14 years significantly lower compared their YNPHIV counterparts in only two regions, Asia-Pacific (IRR = 0.5, 95% CI: 0.2–0.9) and Southern Africa (IRR = 0.5, 95% CI: 0.4–0.6). We report similar results among 15–19-year-olds. However, in older youth, ages 20–24 years, we found no significant difference in mortality incidence rates between YPHIV and YNPHIV, in neither men nor women (Fig. 2).

In sensitivity analyses, using age less than 15 years for perinatal infection, overall mortality incidence rate was 1.4/100 person-years (95% CI: 1.3–1.6) in YPHIV and 2.5/100 person-years (95% CI: 2.4–2.6) in YNPHIV; incidence rates were comparable between 15–19 years and 20–24 years within each group (Supplemental Digital Content, Table G, http://links.lww.com/QAD/B925). Among YPHIV, mortality remained similar across sex and age (Supplemental Digital Content, Table H, http://links.lww.com/QAD/B925). However, among YNPHIV, we found significantly higher mortality rates

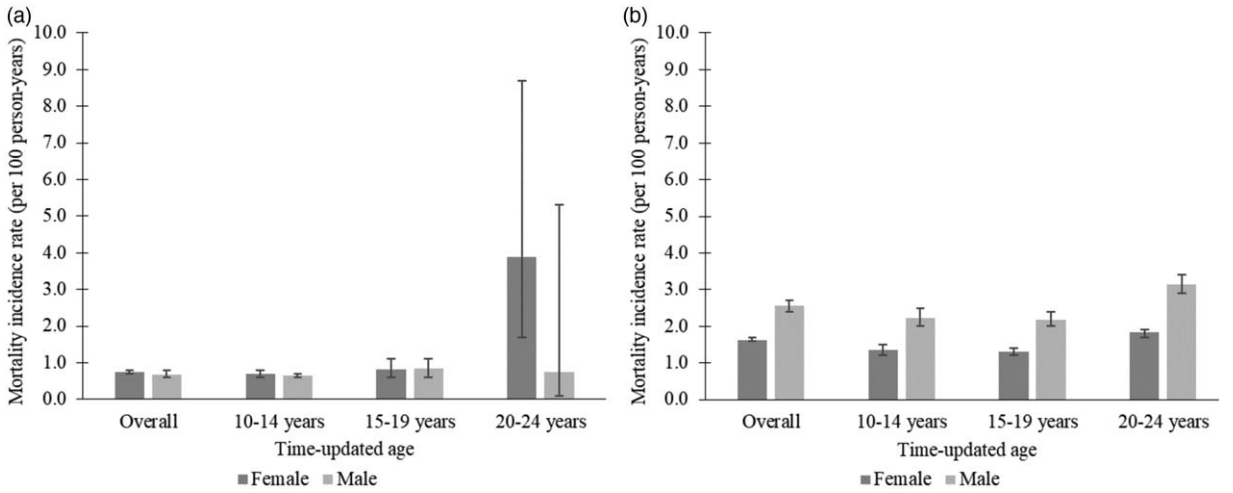

Fig. 1. Mortality incidence rates per 100 person-years and 95% confidence intervals, by time-updated age and sex among (a) adolescents and youth living with perinatally-acquired HIV and (b) adolescents and youth living with nonperinatally acquired HIV, receiving antiretroviral therapy in the International epidemiologic Databases to Evaluate AIDS global consortium.

Table 3. Mortality incidence rate ratios among antiretroviral-treated adolescents and youth aged 10–24 years living with perinatally acquired HIV compared with those living with nonperinatally acquired HIV, stratified by sex, region, and time-updated age in the International epidemiologic Databases to Evaluate AIDS global consortium.

	Perinatal infection defined as enrolment in care <10 years				Perinatal infection defined as enrolment in care <15 years			
	Male IRR[a]	95% CI[b]	Female IRR[a]	95% CI[b]	Male IRR[a]	95%CI[b]	Female IRR[a]	95%CI[b]
Asia-Pacific								
10–14 years	0.26	[0.13–0.49]	0.46	[0.24–0.87]				
15–19 years	0.26	[0.13–0.52]	0.46	[0.23–0.92]	0.61	[0.08–4.45]	0.96	[0.13–7.02]
20–24 years	0.51	[0.13–2.01]	0.92	[0.24–3.54]	0.79	[0.11–5.84]	1.24	[0.18–5.84]
CCASAnet								
10–14 years	0.66	[0.34–1.28]	1.18	[0.62–2.27]				
15–19 years	0.67	[0.34–1.34]	1.20	[0.61–2.38]	0.79	[0.49–1.27]	1.25	[0.77–2.01]
20–24 years	1.33	[0.36–4.93]	2.38	[0.65–8.71]	1.02	[0.61–1.71]	1.61	[0.96–2.70]
Central Africa								
10–14 years	0.25	[0.12–0.56]	0.46	[0.21–1.00]				
15–19 years	0.26	[0.11–0.59]	0.46	[0.20–1.06]	0.62	[0.37–1.03]	0.97	[0.58–1.62]
20–24 years	0.51	[0.12–2.19]	0.92	[0.22–3.88]	0.79	[0.45–1.39]	1.25	[0.72–2.19]
East Africa								
10–14 years	0.41	[0.28–0.60]	0.74	[0.51–1.08]				
15–19 years	0.42	[0.26–0.68]	0.75	[0.46–1.21]	0.27	[0.20–0.37]	0.43	[0.32–0.58]
20–24 years	0.83	[0.23–2.98]	1.48	[0.42–5.28]	0.35	[0.24–0.52]	0.55	[0.38–0.81]
Southern Africa								
10–14 years	0.27	[0.20–0.35]	0.48	[0.36–0.63]				
15–19 years	0.27	[0.18–0.40]	0.48	[0.33–0.71]	0.35	[0.29–0.41]	0.54	[0.45–0.64]
20–24 years	0.54	[0.15–1.87]	0.96	[0.28–3.30]	0.44	[0.33–0.60]	0.70	[0.52–0.93]
West Africa								
10–14 years	0.50	[0.32–0.79]	0.90	[0.58–1.40]				
15–19 years	0.51	[0.30–0.87]	0.91	[0.55–1.53]	0.60	[0.43–0.82]	0.94	[0.69–1.30]
20–24 years	1.01	[0.28–3.70]	1.81	[0.50–6.51]	0.77	[0.51–1.15]	1.22	[0.81–1.81]

[a]Incidence rate ratio.
[b]95% confidence interval.

among men (3.6/100 person-years, 95% CI: 3.3–3.9) compared with women (2.2/100 person-years, 95% CI: 2.1.–2.3). This was mainly driven by Central, East, and Southern Africa. In both the CCASAnet region and West Africa, we found comparable rates between men and women. Comparisons were limited in the Asia-Pacific region, where only one death was recorded among YNPHIV and overall person-time was less than 100 person-years (Supplemental Digital Content, Table I, http://links.lww.com/QAD/B925). In multivariate analyses, adjusted for sex, region and time-varying age, mortality incidence rates were significantly lower in 15–19-year-old YPHIV compared with YNPHIV of the same age in East Africa (IRR = 0.3, 95% CI: 0.2–0.4 in men and IRR = 0.4, 95% CI: 0.3–0.6 in women) and Southern Africa (IRR = 0.3, 95% CI: 0.3–0.4 in men and IRR = 0.5, 95% CI: 0.4–0.6 in women). This was also true in older youth, aged 20–24 years (IRR = 0.4, 95% CI: 0.3–0.5 in men and IRR = 0.6, 95% CI: 0.4–0.8 in women, in East Africa and IRR = 0.4, 95% CI:

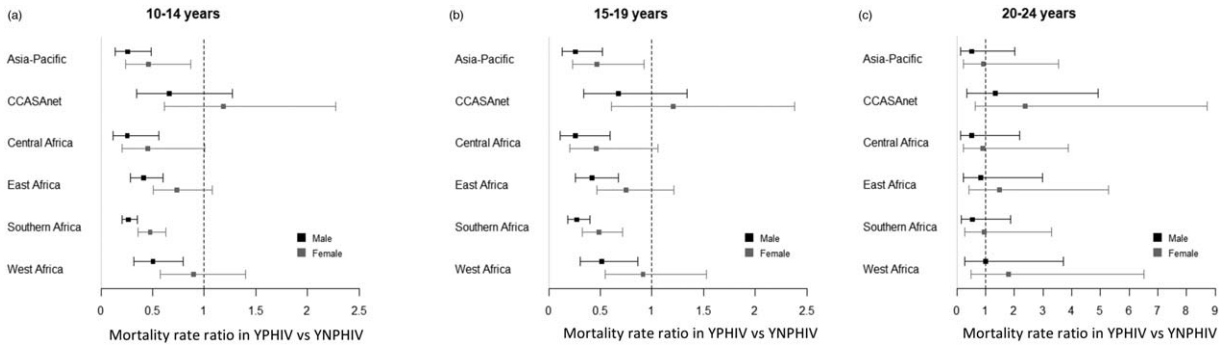

Fig. 2. Incidence mortality rate ratios in adolescents and youth receiving antiretroviral therapy, comparing those living with perinatally acquired HIV (YPHIV) to those living with nonperinatally acquired HIV (YNPHIV), by sex and region in (a) 10–14-year-olds, (b) 15–19-year-olds, and (c) 20–24-year-olds, in the International epidemiologic Databases to Evaluate AIDS global consortium.

0.3–0.6 in men and IRR = 0.7, 95% CI: 0.5–0.9 in women in Southern Africa). We also found lower mortality incident rate in West African male YPHIV aged 15–19 years compared with their YNPHIV counterparts (IRR = 0.6, 95% CI: 0.4–0.8). In all other regions, age and sex combinations, we did not observe any significant difference in mortality between YPHIV and YNPHIV in this analysis. We do note, however, in some regions a nonsignificant trend towards higher mortality among female YPHIV aged 20 to 24 years compared with YNPHIV of the same age and sex (Table 3).

Discussion

This study directly compares mortality rates in adolescents and youth living with perinatally acquired HIV to those living with nonperinatally acquired HIV, according to age, sex, and region in a large multiregional cohort collaboration in low-income and middle-income countries. In this study, we make several observations. First, we observed higher overall mortality rates in YPHIV aged 20–24 years compared with those aged 10–14 years and 15–19 years. Second, among YNPHIV, mortality rates were also higher among 20–24 years compared with 10–14 years and 15–19 years, and was in general higher in men compared with women in sub-Saharan Africa regions. Third, among adolescents aged 10–19 years, mortality rates were lower in YPHIV compared with YNPHIV.

Among YPHIV, 3% died and the overall estimated mortality rate was 0.7/100 person-years, which was comparable in men and women. Similar rates have been reported in other cohorts of adolescents living with HIV across sub-Saharan Africa as well as in high-income countries [15–18]. However, in high-income countries, youth were in general older than our cohort, where the 10–19 years strata primarily drive the results and little person time was spent in the age 20–24 stratum. Compared with younger age groups, we observed significantly higher overall mortality rates among YPHIV aged 20–24 years. This observation highlights an issue that is specific to the YPHIV population, exposed to a history of suboptimal therapy regimens as childhood in a context of limited pediatric formulations, leading to poor virologic response [19]. In addition, as YPHIV grow into adolescence and adulthood, they transition from complete dependence on adult caregivers to becoming their own caregivers, which may result in poor adherence and virologic control [20]. Furthermore, the observed mortality increases among YPHIV as they grow older, and appears to have been driven by female deaths, given that six of every seven reported deaths occurred in young women. Although we lack statistical power to compare mortality rates by sex in this age group, our results are in line with previous studies reporting higher burden of mortality among young women compared with their male counterparts [21]. As YPHIV continue to age into adulthood, more data will become available in older youth at least 20 years and future analyses will allow more accurate comparisons.

Among YNPHIV, we also found that overall mortality rates in each sex stratum increased as age increased. This is in line with previous work describing increasing absolute numbers of deaths among older youth living with HIV [21,22]. In East and Central Africa, mortality incidence reports among YNPHIV were higher among men than women. We explain this in part by the increased access to HIV testing and subsequent care among women through Prevention of Mother-to-Child-Transmission (PMTCT) services (80% of YNPHIV were women). As such, young women likely initiated ART at earlier stages of the disease than their male counterparts who may be more likely to access HIV testing and care following a symptomatic clinical event. Successful identification of young women through PMTCT services highlights the need for innovative strategies to test young men who are less likely to access routine health services and test for HIV [16,23–25]. However, we observed higher rates of LTFU among women than men, underscoring the need to retain young women in care, including those enrolled through PMTCT services. On the other hand, in West Africa, we observed higher mortality incidence rates in women compared with men, particularly among 15–24-year-olds. This could be related to the cultural and legal specificities of the region, where early marriage is permissible and adolescent girls and young women have limited access to HIV testing and care [26]. In 2014, UNAIDS reported on a study among married adolescent girls age 15–19 years in six West African countries: only 16–26% stated that they had a final say in their own healthcare [26,27]. Furthermore age-of-consent laws can be a barrier to adolescents accessing relevant HIV/AIDS services, resulting in late presentation to care and early mortality [25].

We observed lower mortality incidence rates among YPHIV 19 years of age or less compared with YNPHIV of the same age, among both men and women, in all regions. However, this observation is contrary to the general assumption that deaths in older adolescents are predominantly among YPHIV as YNPHIV are mostly newly infected [22]. Worsened mortality among those entering care older than 15 years has been reported elsewhere [9]. In our analysis, we used a 10-year age at enrollment cutoff as a proxy for perinatal infection. Consequently, YPHIV who accessed care at a later age (between 10 and 15 years) may be misclassified as YNPHIV and we advise caution in the interpretation of these results. Indeed, we found higher incidence rates among male YNPHIV aged 10–14 years compared with older YNPHIV, in line with a higher burden of mortality among YPHIV who do not enter care until 10–14 years of age, which has been reported elsewhere [9]. Nevertheless, in sensitivity analyses using age at

enrolment less than 15 years as a proxy for perinatal infection, we still found overall higher incident rates among YNPHIV compared with YPHIV. In multivariate analyses IRRs indicating lower mortality rates in YPHIV compared YNPHIV remained significant in East and Southern Africa, the two largest regions of our database. However, in other regions, differences in mortality rates between YPHIV and YNPHIV were no longer significant, if not contrary to those observed in the primary analyses in 20–24-year-old women, with higher mortality rates in YPHIV compared with YNPHIV.

In addition to the above risk of misclassification bias, this study presents other limitations. First, there may be a selection bias in the YNPHIV group. Indeed, a considerable number of adolescents and youth living with nonperinatally acquired HIV are unaware of their status and remain undiagnosed; those who enroll in care are mostly either pregnant adolescent female individuals, potentially healthier, or symptomatic men, and therefore possibly sicker than the overall population of YNPHIV. Second and conversely, the YPHIV included in our study are a selected population of children who survived early childhood and did not initiate ART until a median age of 8 years. We attempted to address this by adjusting our analyses for $CD4^+$ cell count at ART initiation as well as ART duration. We acknowledge that as more young children are reached with early diagnosis and ART, YPHIV aged 10–24 years may no longer be a specific population who survived early childhood and this analysis will require updating. Third, we observed high proportions of LTFU among both YPHIV and YNPHIV (15 and 35%). In this context, mortality may be underestimated as we did not adjust for unascertained deaths among those LTFU [28]. However, in our study, we found that LTFU was three-fold higher in YNPHIV than YPHIV, suggesting that there may be more unascertained mortality among YNPHIV than YPHIV. If mortality among those LTFU were the same in both groups, our findings of higher mortality rates in YNPHIV compared with YPHIV would hold. Finally, we were unable to describe causes of death, because of limitations in routine data collection as well as limited diagnostic testing in our settings. Further studies investigating cause of deaths among adolescents would be of value in this population.

This study provides disaggregated data on mortality by age, sex, and region comparing YPHIV and YNPHIV. The high mortality rates reported among YNPHIV underline the urgency to advocate for and strengthen HIV testing uptake among the adolescent and youth population. These data are useful to provide mortality rate trends to inform UNAIDS estimates for these regions [21]. However, we advise caution in interpretation and note that these analyses should be updated in the future, as the dynamics of the adolescent population living with HIV evolves over time.

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Conflicts of interest

There are no conflicts of interest.

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