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Determining standardized causes of death of infants, children, and adolescents living with HIV in Asia

Annette H. Sohn[a], **Pagakrong Lumbiganon**[b], **Nia Kurniati**[c], **Keswadee Lapphra**[d], **Matthew Law**[e], **Viet C. Do**[f], **Lam Van Nguyen**[g], **Khanh H. Truong**[h], **Dewi K. Wati**[i], **Pradthana Ounchanum**[j], **Thanyawee Puthanakit**[k], **Tavitiya Sudjaritruk**[l], **Penh S. Ly**[m], **Nik K.N. Yusoff**[n], **Sieu M. Fong**[o], **Thahira J. Mohamed**[p], **Revathy Nallusamy**[q], **Nagalingaswaran Kumarasamy**[r], **Azar Kariminia**[s], **IeDEA Asia-Pacific**

[a]TREAT Asia, amfAR – The Foundation for AIDS Research, Bangkok [b]Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand [c]Cipto Mangunkusumo – Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia [d]Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand [e]The Kirby Institute, UNSW Sydney, Sydney, New South Wales, Australia [f]Children's Hospital 2, Ho Chi Minh City [g]National Hospital of Pediatrics, Hanoi [h]Children's Hospital 1, Ho Chi Minh City, Vietnam [i]Sanglah Hospital, Udayana University, Bali, Indonesia [j]Chiangrai Prachanukroh Hospital, Chiang Rai [k]Department of Pediatrics, Faculty of Medicine and Research Unit in Pediatric and Infectious Diseases, Chulalongkorn University, Bangkok [l]Department of Pediatrics, Faculty of Medicine, Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand [m]National Centre for HIV/AIDS, Dermatology and STDs, Phnom Penh, Cambodia [n]Hospital Raja Perempuan Zainab II, Kota Bharu [o]Hospital Likas, Kota Kinabalu [p]Pediatric Institute, Hospital Kuala Lumpur, Kuala Lumpur [q]Penang Hospital, Penang, Malaysia [r]VHS-Infectious Diseases Medical Centre, Chennai, India, [s]The Kirby Institute, UNSW Sydney, Sydney, New South Wales, Australia

Abstract

Objective—To implement a standardized cause of death reporting and review process to systematically disaggregate causes of HIV-related deaths in a cohort of Asian children and adolescents.

Design—Death-related data were retrospectively and prospectively assessed in a longitudinal regional cohort study.

Methods—Children under routine HIV care at sites in Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam between 2008 and 2017 were followed. Causes of death were reported and

Correspondence to Annette H. Sohn, MD, TREAT Asia/amfAR – The Foundation for AIDS Research, Exchange Tower, 388 Sukhuvmit Road, Suite 2104, Klongtoey, Bangkok 10110, Thailand, Tel: +66 2 663 7561; annette.sohn@treatasia.org.

Author contributions: A.H.S. and A.K. developed the concept for the study, and drafted and finalized the article. P.L., N.K., K.L., V.C.D., L.V.N., K.H.T., D.K.W., P.O., T.P., T.S., P.S.L., N.K.N.Y., S.M.F., T.J.M., R.N., and N.K. collected and managed patient-level data and completed death reporting forms. A.Z. and M.L. conducted the analysis. All co-authors participated in the cause of death review process at the site and/or central levels, and reviewed and approved the article.

Conflicts of interest

There are no conflicts of interest.

then independently and centrally reviewed. Predictors were compared using competing risks survival regression analyses.

Results—Among 5918 children, 5523 (93%; 52% male) had ever been on combination antiretroviral therapy. Of 371 (6.3%) deaths, 312 (84%) occurred in those with a history of combination antiretroviral therapy (crude all-cause mortality 9.6 per 1000 person-years; total follow-up time 32 361 person-years). In this group, median age at death was 7.0 (2.9–13) years; median $CD4^+$ cell count was 73 (16–325) cells/μl. The most common underlying causes of death were pneumonia due to unspecified pathogens (17%), tuberculosis (16%), sepsis (8.0%), and AIDS (6.7%); 12% of causes were unknown. These clinical diagnoses were further grouped into AIDS-related infections (22%) and noninfections (5.8%), and non-AIDS-related infections (47%) and noninfections (11%); with 12% unknown, 2.2% not reviewed. Higher $CD4^þ$ cell count and better weight-for-age *z*-score were protective against death.

Conclusion—Our standardized cause of death assessment provides robust data to inform regional resource allocation for pediatric diagnostic evaluations and prioritization of clinical interventions, and highlight the continued importance of opportunistic and nonopportunistic infections as causes of death in our cohort.

Keywords

Asia; cause of death; HIV; mortality; pediatric

Introduction

Infants and children with perinatally acquired HIV are extremely vulnerable to opportunistic infection. Delaying combination antiretroviral therapy (cART) for even a few months after birth has been associated with a 76% increased risk of death [1]. It is challenging to tease out causes of pediatric HIV-associated mortality because of the limited range of and access to diagnostic testing for this population in low-income and middle-income countries (LMICs). It has been simpler to consider all early deaths among infants and children with HIV due to AIDS [2]. In addition, although pediatric deaths may be more thoroughly ascertained than those of adults [3], available approaches to death reporting are not specific to children with HIV. This limits the ability of providers and implementers to use cause of death data to guide selection of diagnostic evaluations, or prioritize clinical resources to address preventable causes of death.

When the TREAT Asia Pediatric HIV Observational Database (TApHOD) study was established in 2008, a systematic approach to describing and determining causes of death was instituted to address this evidence gap[4]. The Coding Causes of Death (CoDe) model, originally developed for the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study in adults with HIV, was already in use in parallel adult cohort studies in the Asia-Pacific and Australia [5,6]. Informed by prior experience with the ‘adult CoDe’ process, we used a ‘pediatric CoDe’ process to allow for the addition of key data variables without changing the structure of the original method. We conducted an analysis of the pediatric CoDe results to characterize the process and describe the deaths reported over the first 10 years of our regional cohort study.

Methods

Study population

The study was conducted within TApHOD, a member cohort of IeDEA Asia-Pacific [4]. The database was established in 2006 and includes routinely collected, patient-level data from more than 6500 infants, children, and adolescents with HIV who have ever been followed at 16 network sites in Cambodia (n=1), India (n=1), Indonesia (n=2), Malaysia (n=4), Thailand (n=5), and Vietnam (n=3). Network sites are pediatric referral clinics within larger healthcare facilities (n=12) or freestanding pediatric hospitals (n=4); all but one (a research clinic) are public HIV treatment centers. National HIV treatment guidelines were based on WHO global guidelines and updated over time based on $CD4^{b}$specific and age-specific criteria [7–9]. Individuals of any age taking or naïve to cART with a pediatric HIV clinic visit on or after January 2008 were eligible for study inclusion. The analysis database included data up to September 2017.

All network sites, the coordinating center (TREAT Asia/ amfAR, Thailand), and the data management and biostatistics center (Kirby Institute, UNSW Australia) have local institutional review board (IRB) approval to participate in the cohort study. Consent by parents or legal guardians and assent of the children and adolescents under care are not routinely obtained unless required by an IRB (i.e. in some sites in India, Malaysia, and Thailand).

Clinical and laboratory data

Baseline values for laboratory (e.g. $CD4^{+}$) and clinical measurements (e.g. weight) were based on a single measure in the 6 months prior and closest to the baseline date. At cART initiation, we used a window of 6 months before and 1 week after start. For the last available clinic visit, we used the closest value that fell within 12 months prior. To calculate height-for-age z-score, we used the WHO 2006/2007 child growth standards [3,10,11]. For weight-for-age z-score, we used the WHO 1977 standards because the 2006/2007 standards are limited to children of 10 years or less [12,13]. Second-line ART was defined as the second triple-drug regimen with an antiretroviral class switch [e.g. nonnucleoside reverse transcriptase inhibitor (NNRTI) to protease inhibitor], excluding those exposed to mono/dual nucleoside reverse transcriptase inhibitor therapy and known to have been switched without failure of first-line therapy.

Cause of death ascertainment

Causes of death were reported by local providers using standardized CoDe forms originally developed for the D:A:D study [5,6,14]. The CoDe process captures patient data leading up to and around the time of death, and site provider comments and determinations about the specific immediate (one diagnosis), contributing (up to four diagnoses), and underlying (one diagnosis) causes of death. Immediate causes are diseases or injuries directly leading to death (e.g. cardiorespiratory failure), contributing causes are those that contributed to death but are not considered the main reasons for death, and underlying causes are those that initiated the train of events leading directly or indirectly to death. The forms were revised for use in our pediatric population with the modification of some variables (e.g. full date of birth

rather than year) and the addition of others (e.g. birth weight). Additional details and the data collection tool are provided as an Appendix. The primary objective of the process is to use all available data (including immediate and contributing causes) to inform the identification of a single underlying cause of death.

Sites were asked to provide additional information (e.g. birth weight) for infants and young children in their narrative comments. Forms were completed in English by local site staff and reviewed by the site's study Principal Investigator, if they were not written by them. Deaths were assessed retrospectively for those that occurred prior to the site data being added to the database, and prospectively thereafter.

The CoDe forms were independently reviewed by two regional pediatric HIV experts and site investigators from within the network to concur with or present differing conclusions regarding reported causes of death; reviewers were blinded to each other's assessments. Provider and reviewer forms were then centrally reviewed. In the standard adult CoDe process, deaths in which the reviewers do not concur undergo secondary review by a central committee. In the pediatric CoDe process, all deaths underwent secondary review by an unblinded adjudication committee of three network investigators, one of whom (A.H.S.) chaired all review meetings, to arrive at consensus over the final immediate, contributing, and underlying causes of death. The committee further determined whether deaths were AIDS-related on the basis of the contributing and underlying causes [by US Centers for Disease Control and Prevention (CDC) clinical staging criteria [15]]. Deaths with insufficient clinical information were classified as due to unknown causes. All provider, reviewer, and committee forms were then submitted to the data management and biostatistics center for analysis.

Statistical analysis

The beginning of study follow-up (baseline) was 1 January 2008, the first reported clinic visit, or the date of cART initiation, whichever occurred later. Data were censored at loss to follow-up (LTFU), transfer out of the clinic, death, the 24th birthday, or database closure, whichever occurred first. LTFU was defined as having no clinic contact (visit, lab test) in the 12 months prior to the site-specific database closure date, with the date of LTFU defined as 12 months following the last clinic contact. Treatment failure was defined as having at least one HIV viral load test over 1000 copies/ml before regimen change or a 50% or more decline in $CD4^+$ cell count from its peak value, or a fall in $CD4^+$ before the baseline (precART) value.

The underlying cause assigned to each death was considered the primary outcome for the analysis. These were grouped into: AIDS, infection; AIDS, noninfection; non-AIDS, infection; and non-AIDS, noninfection. These categorizations were made on the basis of the individual clinical diagnosis and their inclusion in US CDC AIDS staging criteria byage [16,17]. Consequently, some pathogens could appear in both AIDS and non-AIDS categories depending on the age at diagnosis, severity (e.g. local vs. disseminated disease), or chronicity (e.g. one-time or recurrent condition).

The percentages and rates (per 1000 person-years) of death attributed to each group and to each specific underlying cause of death were calculated overall and by sex. Age at death was evaluated for trend over calendar time. We used a cumulative incidence function to estimate the probabilities of different categories of death during follow-up. We assessed independent predictors of AIDS vs. non-AIDS mortality, and infection-related vs. noninfection-related mortality using four separate competing risks survival regression analyses based on Fine and Gray's proportional sub-hazards model [18]. In this analysis, we used an alternate classification in which contributing causes of death were taken into account to distinguish AIDS and non-AIDS deaths on the basis of whether those contributing causes met CDC Stage C criteria. For example, a child whose underlying cause of death was pneumonia of unknown cause (CDC Stage B) and who had severe malnutrition and wasting (CDC Stage C) as contributing causes of death would have been categorized in the 'AIDS, infection' group.

Sex, calendar year at first cART, and facility level were considered in the analyses. Age, history of AIDS diagnosis, $CD4^+$ cell count, weight-for-age *z*-score, and receiving second-line ART were included as time-updated variables. $CD4^+$ cell count and weight-for-age *z*-score were lagged by 6 months so that the most recent value was less likely to be the consequence of a clinical event leading to death. For these two variables, missing data were imputed by carrying forward values from the nearest previous visit for up to 6 months if no subsequent measurement was recorded. We created a category for missing observations and considered them as a separate group in the analyses. Potential predictors with *P* less than 0.20 in univariable analyses were included in multivariable analyses. The final model included variables with *P* less than 0.05. The adjusted subdistribution hazard ratios (asHR) were reported with their 95% confidence intervals (95% CI).

Data management and analyses were performed at the Kirby Institute, UNSW Australia, using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and Stata (StataCorp, STATA 14.0 for Windows, College Station, Texas, USA).

Results

There were 6567 children and adolescents enrolled in the cohortat database closure (upto September2017), of whom 5918 had a clinic visit during or after January 2008 and 91% acquired HIV perinatally. Over the follow-up period, 5523 (93%; 52% male) had ever been on cART, with 394 (6.7%) never starting antiretrovirals; one received only mono/dual therapy and was excluded from further analysis. Overall, there were 371 (6.3%) deaths; 312 in those who had ever been on cART, 58 among those who had not started any antiretrovirals, and one who had been on mono/dual therapy. CoDe forms were available for 363 (98%) of the deaths.

The primary analyses were conducted among the 5523 who ever received cART, which included 84% of all deaths (Table 1). The total follow-up time available was 32 361 person-years; 16 482 person-years for males and 15879 for females. At cART start, median age was 5.4 (interquartile range 2.5–8.6) years, median $CD4^+$ percentage was 11% (4–18%), and 90% started cART with an NNRTI-based regimen (Supplemental Table 1). At the analysis

baseline, the overall median age was 6.7 (3.3–10.5) years, median weight-for-age *z*-score was 2.0 (3.2 to 1.0), height-for-age *z*-score was 2.1 (3.0 to 1.2), and 25% had a history of meeting WHO stage 3 or 4 criteria. Median $CD4^+$ was 510 (193–917) cells/ml, $CD4^+$ percentage was 18% (9–26%), and the median time on cART was 2.2 (1.0–4.2) years.

Causes of death among those with a history of combination antiretroviral therapy

Of the 5523 who had been on cART, 312 (5.6%) died during follow-up, representing a crude all-cause mortality rate of 9.6 per 1000 person-years (males 10.3; females 8.9). Over time, this decreased from 19.8 from 2008 to 2010, to 8.8 in 2011 to 2013, to 4.0 per 1000 person-years in 2014–2017 (Supplemental Fig. 2). The median age at death was 7.0 (2.9–13) years: males 6.4 (2.9–13) years, females 7.7 (2.8–13) years. This increased by calendar year from 3.9 (2.7–7.8) years in 2008 to 15 (10–20) years by 2017 (Supplemental Fig. 1). Of the 88% with an available $CD4^þ$ cell count at death, the median value was 73 (16–325) cells/ ml. The most common individual underlying causes of death were pneumonia due to unspecified pathogens (17%), tuberculosis (TB) (16%), sepsis (8.0%), and AIDS (6.7%); 12% of deaths were due to unknown causes, and 2.2% did not have CoDe forms to review (Table 2, Supplemental Table 2).

The underlying causes were grouped into AIDS-related infections (22%) and noninfection (5.8%) causes, and non-AIDS-related infections (47%) and noninfections (11%), with 12% due to unknown and 2.2% to unreviewed causes. Non-AIDS-related infections were consistently the most common underlying causes of death (Fig. 1). The cumulative incidence of non-AIDS, noninfection-related deaths exceeded that of AIDS, noninfection-related deaths during recent years of follow-up. Median time on cART at last visit prior to death was 5.7 (1.6–7.9) years for non-AIDS, noninfections, and ranged from 0.3 to 0.4 years for all other categories.

There were 228 contributing causes of death reported for 161 children (52%), of which the most common were wasting with or without severe malnutrition (n=114), anemia (n=36), and pneumonia (n=12). When the contributing causes of death were taken into account in the alternate classification, the proportions of AIDS-related deaths in those whose underlying causes were infections increased to 52%; the noninfection category remained stable.

Factors associated with AIDS-related and infection-related underlying causes of death

In multivariable analysis, higher $CD4^+$ cell count, and better weight-for-age *z*-score were protective against mortality, regardless of whether or not the underlying cause was AIDS-related (Table 3). Receiving care in mostly rural vs. urban settings and cART initiation between 2014 and 2017 compared with less than 2010 were protective against AIDS-related mortality. Across age subgroupings, increased hazard rates of AIDS-related death were associated with younger age compared with 5–9 years (asHR for <1 year 5.09, 95% CI 2.80–9.23; for 1–4 years 1.82, 95% CI 1.24–2.67), and increased hazard rates of non-AIDS-related death were associated with age less than 1 year (asHR 3.79, 95% CI 1.62–8.84) and age 15–19 years (asHR 2.03, 95% CI 1.06–3.91) compared with age 5–9 years.

CD4$^+$ cell count more than 200 cells/μl, weight-for-age *z*-score at least 3, and cART initiation during 2014– 2017 compared with less than 2010 were protective against infection-related mortality (Table 4). For noninfection-related mortality, CD4$^+$ cell count at least 500 cells/ml and weight-for-age *z*-score at least 2 were protective. In contrast, higher hazard rates of infection-related mortality were associated with age less than 5 years compared with 5–9 years (highest asHR for age <1 year 7.46, 95% CI 4.48–12.42), and being on second-line cART. A prior AIDS diagnosis was associated with infection-related [asHR 5.60 (3.30–9.30)] and noninfection-related mortality [asHR 4.13 (1.80–9.50)].

Underlying causes of death among those without prior antiretroviral therapy

Among 394 children (52% male) who did not receive cART during follow-up, 58 (15%) died (62% male); these deaths were not included in the detailed risk factor analyses. Deaths were due to underlying AIDS-related infections (17%) and noninfections (6.9%), and non-AIDS-related infections (60%) and noninfections (3.4%), with 10% of deaths due to unknown causes and one death not reviewed. When the contributing causes were taken into account for the alternate categorization, the proportion of those with AIDS-related deaths whose underlying causes were infections increased to 59%. The most common underlying causes of death overall were pneumonia (21%), sepsis (16%), and TB (16%).

Discussion

This analysis is the first conducted in Asia to systematically evaluate causes of death by applying standardized criteria to routinely collected clinical data among children and adolescents with HIV. By making minor, pediatric-specific modifications to the ‘adult’ CoDe process, we were able to extract and harmonize the available data to develop robust characterizations of morbidity and mortality in our network of primarily urban, public referral centers in LMIC contexts. Our results represent a valuable benchmark for this population that can be used to guide prioritization of diagnostic testing and clinical care interventions in the region.

In the late 2000s, early infant diagnostic testing and cART were not widely available across our cohort [19], as evidenced by the median age of over 5 years at treatment initiation. Notably, severe malnutrition and wasting were associated with 40% of all deaths, outcomes that developing infants and children are especially vulnerable to. Although subsequent widespread HIV program scale-up, changes in global cART guidelines to higher CD4$^+$ based thresholds and ultimately universal treatment, and improvements in care quality have led to lower mortality among those recently starting cART, infections continue to represent the most common causes of death (68%). Our crude mortality rates substantially declined over time as access to cART and diagnostic testing expanded. These trends were also seen earlier in cohorts in the United States and Europe [20], such as in the PACTG 219 study, in which deaths fell from 72 to eight per 1000 person-years from 1994 to 2004 [21], the CHIPS study in which deaths fell from 82 to six per 1000 person-years from 1997–2006 [22], and the EPPICC cohort, in which deaths peaked at 17.7 per 1000 person-years in 2003 and fell to 3.6 per 1000 person-years by 2006 [23].

We did observe increasing numbers of noninfection causes of death with age and over time, as more children and adolescents survived beyond the immediate postcART period. This has been reported in the US pediatric-to-adolescent HIV cohort studies PHACS and IMPAACT P1074, in which deaths due to HIV related kidney and cardiac disease have become more common than opportunistic infections in older youth [24,25]. In our study, the most common non-AIDS, noninfection causes of death were related to trauma; largely due to drowning (six of 10) and head injuries (three of 10), which are major causes of pediatric death worldwide, and reflect that those with HIV additionally face the main risks of mortality experienced by other children [2]. However, we were unable to determine whether these deaths could have been related to mental health or neurodevelopmental issues known to be more common among those with perinatally acquired HIV [26–28]. Data from cohorts with longer term follow-up in the United States and United Kingdom have emphasized that mental healthcare must be part of comprehensive HIV care for youth [29,30].

In these and other high-income countries, detailed data on causes of death are often available through registries and insurance databases. Although these resources are available in some LMICs [31,32], deaths among those with HIVare more often attributed only to HIVor AIDS [3]. Although such data are useful on a population level [2,33,34], broad generalizations are insufficient to guide local clinicians or policy makers to understand how health interventions or systems can be implemented and improved to prevent deaths. For example, pneumonias and sepsis of unknown cause represented 25% of underlying reasons why children in our cohort died. Limited laboratory capacity is likely to have impacted microbiologic confirmation of pathogens that could have been more effectively targeted. Improving laboratory infrastructure could reduce empiric treatment and improve clinical outcomes. In addition, whereas severe malnutrition and wasting represented 3.5% of underlying causes of death, they were noted as contributing causes in 36% of deaths, and represent easily diagnosable and treatable conditions [35].

We found that hallmarks of advanced HIV disease (e.g. immunodeficiency, wasting) were associated with higher risk of infection-related deaths. However, there were more similarities between factors associated with AIDS and non-AIDS deaths than we anticipated, which may have been due to misclassification of the non-AIDS underlying causes, such as if comprehensive diagnostic testing was not available. In fact, when contributing causes of individual deaths were considered in our alternate categorization, the proportion of overall deaths that were AIDS-related in the context of underlying infectious cases increased from 21 to 52%. There was an unexpected protective association between sites in mostly rural settings and AIDS-related death. This may be because sites in that category are referral centers with higher levels of resources and lower patient volumes, despite having a majority of patients who live in rural areas.

In addition to the potential for misclassification of causes of death, a key limitation of our study was that the CoDe method was not developed nor validated for use in children. Although we added pediatric-specific variables to improve the utility of the report forms and instituted an adjudication process to review all deaths, the process was still reliant on medical records and provider reports. It did not include formal interviews with families or caregivers, which could be especially valuable in contexts that have limited diagnostic

capacity. Although the CoDe review process uses the US CDC staging system, our cohort tracks clinical disease progression using WHO staging, which is reflected in our risk factor analyses. The risk of subjectivity in the clinical categorization of the causes of death for the purposes of our analysis could have increased the risk of misclassification. Incomplete data on HIV-related parameters (e.g. HIV viral load) and the predominance of patients in care at urban referral centers also could have biased our risk factor analysis, limiting the generalizeability of our findings.

Conclusion

The standardized assessment of causes of death in children with HIV in Asia highlights emerging challenges to pediatric and adolescent care, and the continued importance of infections as causes of death in those with and without AIDS. To maintain public health gains, we must adjust to the needs of our 'aging' populations who have survived beyond childhood. Using rigorous methods like the CoDe process to assess deaths in adolescents and young adults would provide useful data around chronic treatment failure leading to pre-ART levels of immunodeficiency and opportunistic infections, as well as emerging mental health concerns like suicide. Greater emphasis on surveillance of noninfection-related causes of morbidity and mortality will also better prepare national programs to integrate HIV care within models of chronic disease management and guide prioritization of limited clinical resources and targeted interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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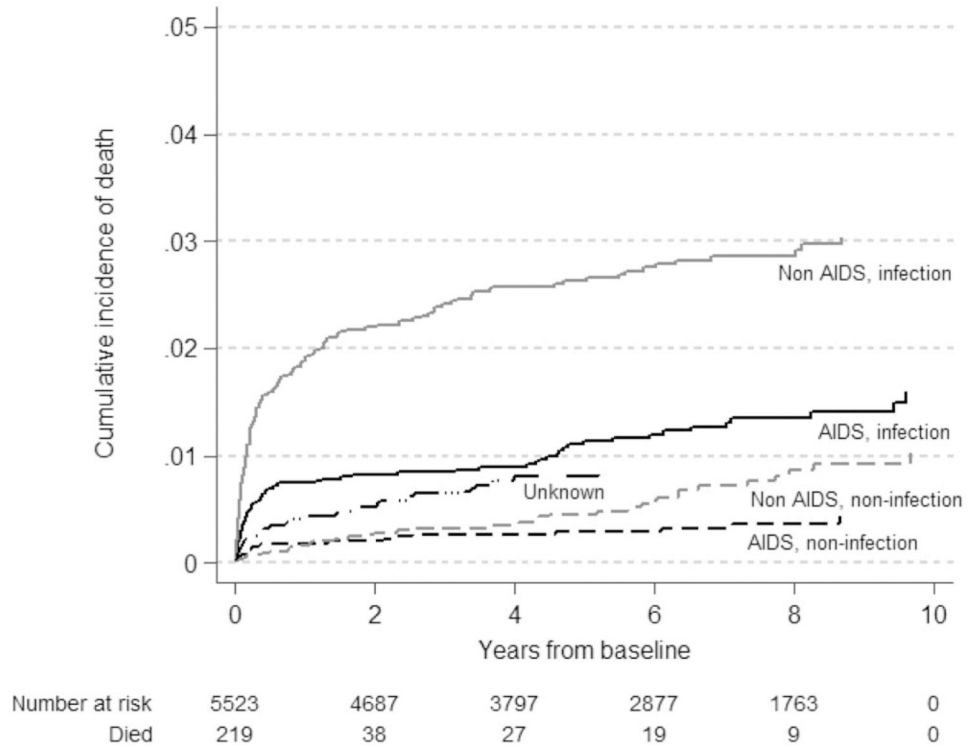

Fig. 1.

Cumulative incidence of death by underlying causes using competing risk regression for children and adolescents with a history of combination antiretroviral therapy ($N = 312$).

Table 1.

Characteristics of children and adolescents with a history of starting combination antiretroviral therapy at analysis baseline[a], by vital status and underlying cause of death.[b]

	Alive, *N* = 5211	Deaths, *N* = 305[a]				
		AIDS, infection, *N* = 66	AIDS, noninfection, *N* = 18	Non-AIDS, infection, *N* = 148	Non-AIDS, noninfection, *N* = 35	Unknown, *N* = 38
Sex, female	2532 (49)	28 (42)	8 (44)	74 (50)	11 (31)	16 (42)
Age (years)						
<1	469 (9.0)	10 (15)	1 (5.6)	23 (16)	5 (14)	6 (16)
1–4	1471 (28)	20 (30)	6 (33)	56 (38)	6 (17)	14 (37)
5–9	1793 (34)	20 (30)	6 (33)	43 (29)	11 (31)	6 (16)
10–14	1231 (24)	11 (17)	2 (11)	21 (14)	9 (26)	11 (29)
≥15	247 (4.7)	5 (7.6)	3 (17)	5 (3.4)	4 (11)	1 (2.6)
Median (IQR)	6.8 (3.4, 10.6)	5.6 (2.7, 9.9)	5.4 (1.8, 10.9)	4.6 (1.9, 8.6)	7.0 (3.5, 12.5)	4.7 (1.9, 10.2)
$CD4^+$ cell count (cells/μl)						
<200	1034 (20)	38 (58)	7 (39)	93 (62)	10 (29)	15 (39)
200–349	561 (11)	3 (4.6)	1 (5.6)	7 (4.7)	2 (5.7)	6 (16)
350–499	515 (9.9)	4 (6.1)	-	11 (7.4)	4 (11)	3 (7.9)
≥500	2339 (45)	8 (12)	4 (22)	15 (10)	15 (43)	4 (11)
Unknown	762 (15)	13 (20)	6 (33)	22 (15)	4 (11)	10 (26)
Median (IQR)	534 (217, 934)	36 (10, 246)	96 (35, 530)	47 (12, 220)	486 (64, 846)	189 (36, 369)
HIV viral load (copies/ml)						
<50	793 (15)	7 (11)	3 (16)	3 (2.0)	6 (17)	2 (5.3)
50–399	275 (5.3)	1 (1.5)	0	2 (1.4)	1 (2.9)	0
400–999	45 (0.9)	0	0	1 (0.7)	0	0
1000–9999	128 (2.5)	1 (1.5)	0	2 (1.4)	2 (5.7)	0
>10 000	779 (15)	16 (24)	2 (11)	18 (12)	8 (23)	8 (21)
Unknown	3191 (61)	41 (62)	13 (72)	122 (82)	18 (51)	28 (74)
Median log 10 (IQR)	2.4 (1.7, 5.0)	4.7 (1.7, 5.4)	1.7 (1.7, 4.2)	4.9 (3.2, 5.4)	3.8 (1.7, 5.5)	5.0 (4.0, 6.9)
Weight-for-age *z*-score						
<−3	1178 (23)	35 (53)	10 (56)	83 (56)	13 (37)	20 (53)

	Alive, *N* = 5211	Deaths, *N* = 305[a]				
		AIDS, infection, *N* = 66	AIDS, noninfection, *N* = 18	Non-AIDS, infection, *N* = 148	Non-AIDS, noninfection, *N* = 35	Unknown, *N* = 38
≤−3 to <−2	1008 (19)	11 (17)	0	25 (17)	7 (20)	7 (18)
≤−2 to <−1	1160 (22)	6 (9.1)	3 (17)	7 (4.7)	4 (11)	7 (18)
≥−1	1163 (22)	4 (6.1)	1 (5.6)	8 (5.4)	4 (11)	1 (2.6)
Unknown	702 (13)	10 (15)	4 (22)	25 (17)	7 (20)	3 (7.9)
Median (IQR)	−1.9 (−3.1, −1.0)	−3.9 (−5.6, −2.4)	−5.1 (−5.7, −1.7)	−3.8 (−6.4, −2.6)	−2.9 (−4.0, −1.5)	−3.2 (−4.4, −2.1)
Height-for-age *z*-score						
<−3	982 (19)	23 (35)	6 (33)	49 (33)	11 (31)	17 (45)
≤−3 to <−2	1157 (22)	13 (20)	2 (11)	25 (17)	6 (17)	8 (21)
≤−2 to <−1	1173 (23)	6 (9.1)	2 (11)	14 (9.5)	3 (8.6)	5 (13)
≥−1	950 (18)	3 (4.6)	1 (5.6)	8 (5.4)	6 (17)	2 (5.3)
Unknown	949 (18)	21 (32)	7 (39)	52 (35)	9 (26)	6 (16)
Median (IQR)	−2.0 (−2.9, −1.3)	−3.1 (−3.7, −2.3)	−3.0 (−3.4, −1.6)	−3.1 (−4.3, −2.2)	−2.5 (−3.5, −1.20)	−3.0 (−3.8, −2.3)
WHO clinical stage						
Stage 1	494 (9.5)	1 (1.5)	0	2 (1.4)	1 (2.9)	2 (5.3)
Stage 2	555 (11)	7 (11)	1 (5.6)	6 (4.1)	0	5 (13)
Stage 3	824 (16)	17 (26)	3 (17)	60 (41)	7 (20)	5 (13)
Stage 4	337 (6.5)	14 (21)	7 (39)	42 (28)	9 (26)	8 (21)
Unknown	3001 (58)	27 (41)	7 (39)	38 (26)	18 (51)	18 (47)
Age at cART (years)						
<1	612 (12)	12 (18)	1 (5.6)	23 (16)	6 (17)	8 (21)
1–4	1793 (34)	21 (32)	7 (39)	66 (45)	9 (26)	12 (32)
5–9	1935 (37)	26 (39)	6 (33)	42 (28)	11 (31)	9 (24)
10–14	784 (15)	7 (11)	4 (22)	15 (10)	8 (23)	8 (21)
≥15	87 (1.7)	0	0	2 (1.4)	1 (2.9)	1 (2.6)
Median (IQR)	5.5 (2.6, 8.6)	5.0 (2.6, 7.4)	5.4 (1.8, 8.5)	3.6 (1.9, 7.5)	5.5 (2.9, 10.1)	4.7 (1.6, 9.1)
Year of cART start						
<2008	2270 (44)	24 (36)	7 (39)	34 (23)	18 (51)	15 (39)
2008–2010	1304 (25)	36 (55)	9 (50)	73 (49)	14 (40)	19 (50)
2011–2013	1002 (19)	6 (9.1)	2 (11)	36 (24)	2 (5.7)	3 (7.9)

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	Alive, *N* = 5211	Deaths, *N* = 305[a]				
		AIDS, infection, *N* = 66	AIDS, noninfection, *N* = 18	Non-AIDS, infection, *N* = 148	Non-AIDS, noninfection, *N* = 35	Unknown, *N* = 38
2014–2017	635 (12)	0	0	5 (3.4)	1 (2.9)	1 (2.6)
$CD4^+$ cell count at cART (cells/μl)						
<200	1713 (33)	46 (70)	10 (56)	89 (60)	14 (40)	20 (53)
200–349	688 (13)	5 (7.6)	0	10 (6.8)	3 (8.6)	5 (13)
350–499	448 (8.6)	4 (6.1)	0	8 (5.4)	4 (11)	1 (2.6)
≥500	1376 (26)	3 (4.6)	2 (11)	12 (8.1)	9 (26)	3 (7.9)
Unknown	986 (19)	8 (12)	6 (33)	29 (20)	5 (14)	9 (24)
Median (IQR)	288 (72, 644)	39 (10, 117)	40 (11, 138)	40 (11, 208)	276 (27, 508)	98 (12, 257)
Type of therapy						
cART-NNRTI	4711 (90)	58 (88)	18 (100)	134 (91)	28 (80)	36 (95)
cART-PI	377 (7.2)	6 (9.1)	0	5 (3.4)	4 (11)	1 (2.6)
cART-NNRTI/PI	40 (0.8)	0	0	0	0	1 (2.6)
cART-other	83 (1.6)	2 (3.0)	0	9 (6.1)	3 (8.6)	0
Duration on cART, years[c]						
<1	632 (26)	6 (23)	2 (25)	13 (33)	2 (10.5)	7 (47)
1–2	900 (36)	8 (31)	2 (25)	12 (30)	11 (58)	6 (40)
≥3	945 (38)	12 (46)	4 (50)	15 (38)	6 (32)	2 (13)
Median (IQR)	2.2 (1.0–4.2)	2.7 (1.2, 4.0)	2.8 (1.4, 4.5)	1.5 (0.9, 3.8)	1.9 (1.4, 4.6)	1.2 (0.9, 1.9)
Facility level						
Health center	907 (16)	11 (17)	1 (5.6)	26 (18)	5 (14)	6 (16)
Regional, provincial or University hospital	4616 (84)	55 (83)	17 (94)	122 (82)	30 (86)	32 (84)
Facility setting						
Urban	3444 (62)	41 (62)	13 (72)	111 (75)	17 (49)	33 (87)
Mostly urban	1682 (31)	23 (35)	4 (22)	24 (16)	13 (37)	4 (11)
Mostly rural	397 (7.2)	2 (3.0)	1 (5.6)	13 (8.8)	5 (14)	1 (2.6)

cART, combination antiretroviral therapy;IQR, interquartile range;NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Analysis baseline is defined as 1 January 2008, first clinic visit, or date of first cART, whichever occurred later. Data on the seven deaths without review forms are not presented.

[b]Values are *N*(%) unless otherwise specified.

[c]Duration was given for 2585 patients who started cART before baseline.

Table 2.

Underlying causes of death and mortality rates of children and adolescents with a history of combination antiretroviral therapy, 2008–2017.

	Numbers (%) of deaths	Rates of death[a], all patients (95% CI)	Rates of death[a], males (95% CI)	Rates of death[a], females (95% CI)
Total deaths	**312 (100%)**	**9.64 (8.63–10.77)**	**10.31 (8.87–11.99)**	**8.94 (7.59–10.54)**
AIDS-related infections[b]	**66 (21.8)**	**2.04 (1.60–2.60)**	**2.31 (1.68–3.17)**	**1.76 (1.22–2.55)**
AIDS	21 (6.7)	0.65 (0.42–1.00)	0.85 (0.50–1.43)	0.44 (0.21–0.92)
TB	11 (3.5)	0.34 (0.19–0.61)	0.49 (0.24–0.97)	0.19 (0.06–0.59)
Cytomegalovirus	6 (1.9)	0.19 (0.08–0.41)	0.12 (0.03–0.49)	0.25 (0.09–0.67)
Cryptococcal infection	8 (2.6)	0.25 (0.12–0.49)	0.30 (0.13–0.73)	0.19 (0.06–0.59)
Pneumocystis pneumonia	8 (2.6)	0.25 (0.12–0.49)	0.24 (0.09–0.65)	0.25 (0.09–0.67)
Penicilliosis	5 (1.6)	0.15 (0.06–0.37)	0.06 (0.01–0.43)	0.25 (0.09–0.67)
Pneumonia	3 (1.0)	0.09 (0.03–0.29)	0.18 (0.06–0.56)	–
Mycobacteria avium complex	2 (0.6)	0.06 (0.02–0.25)	–	0.13 (0.02–0.25)
Other[c]	2 (0.6)	0.06 (0.02–0.25)	0.06 (0.01–0.43)	0.06 (0.01–0.45)
AIDS-related noninfections	**18 (5.8)**	**0.56 (0.35–0.88)**	**0.61 (0.33–1.13)**	**0.50 (0.25–1.00)**
Severe malnutrition/wasting	11 (3.5)	0.34 (0.19–0.61)	0.30 (0.13–0.73)	0.38 (0.17–0.84)
Encephalopathy	4 (1.3)	0.12 (0.05–0.33)	0.18 (0.06–0.56)	0.06 (0.01–0.45)
Other[d]	3 (1.0)	0.09 (0.03–0.29)	0.12 (0.03–0.49)	0.06 (0.01–0.45)
Non-AIDS-related infections	**148 (47.4)**	**4.57 (3.89–5.37)**	**4.49 (3.58–5.64)**	**4.66 (3.71–5.85)**
Pneumonia	49 (15.7)	1.51 (1.14–2.00)	1.21 (0.78–1.88)	1.83 (1.27–2.63)
TB	40 (12.8)	1.24 (0.91–1.69)	1.46 (0.98–2.17)	1.01 (0.62–1.64)
Sepsis	25 (8.0)	0.77 (0.52–1.14)	0.61 (0.33–1.13)	0.94 (0.57–1.57)
Diarrhea	13 (4.2)	0.40 (0.23–0.69)	0.42 (0.20–0.89)	0.38 (0.17–0.84)
Meningitis/encephalitis	11 (3.5)	0.34 (0.19–0.61)	0.49 (0.24–0.97)	0.19 (0.06–0.59)
Cytomegalovirus	2 (0.6)	0.06 (0.02–0.25)	0.06 (0.01–0.43)	0.06 (0.01–0.45)
Other[e]	8 (2.6)	0.25 (0.12–0.49)	0.24 (0.09–0.65)	0.25 (0.09–0.67)
Non-AIDS-related noninfections	**35 (11.2)**	**1.08 (0.78–1.51)**	**1.46 (0.98–2.17)**	**0.63 (0.34–1.17)**
Physical trauma	10 (3.2)	0.31 (0.17–0.57)	0.49 (0.24–0.97)	0.13 (0.03–0.50)
Cancer	5 (1.6)	0.15 (0.06–0.37)	0.24 (0.09–0.65)	0.06 (0.01–0.45)
Hematologic	4 (1.3)	0.12 (0.05–0.33)	0.24 (0.09–0.65)	–

	Numbers (%) of deaths	Rates of death[a], all patients (95% CI)	Rates of death[a], males (95% CI)	Rates of death[a], females (95% CI)
Other central nervous system	3 (1.0)	0.09 (0.03–0.29)	0.12 (0.03–0.49)	0.06 (0.01–0.45)
Other cardiovascular	3 (1.0)	0.09 (0.03–0.29)	0.06 (0.01–0.43)	0.06 (0.01–0.45)
Renal failure	2 (0.6)	0.06 (0.02–0.25)	–	0.13 (0.03–0.50)
Other[f]	8 (2.6)	0.25 (0.12–0.49)	0.30 (0.13–0.73)	0.19 (0.06–0.59)
Unknown/not reviewed[g]	**45 (14.4)**	**1.39 (1.04–1.86)**	**1.46 (0.98–2.17)**	**1.32 (0.86–2.03)**

95% CI, 95% confidence interval; CDC, Centers for Disease Control and Prevention; TB, tuberculosis. Text in bold represents major categories.

[a]AIDS-related clinical diagnoses were defined by US CDC clinical staging criteria [16,18]. Some diagnoses meet AIDS criteria by the age at diagnosis, level of invasiveness, or chronicity, and may appear in both AIDS and non-AIDS categories (e.g. pulmonary tuberculosis in children <13 years of age is considered a non-AIDS diagnosis).

[b]Death rate per 1000 person-years.

[c]Includes: brain abscess (1), progressive multifocal leukoencephalopathy (1).

[d]Includes: bronchiectasis (1), non-Hodgkin lymphoma (2).

[e]Includes: cryptococcal pneumonia (1), disseminated mycosis (1), disseminated sporotrichosis (1), invasive aspergillosis (1), mastoiditis (1), necrotizing fasciitis (1), toxoplasmosis (1), unknown infection (1).

[f]Includes: aspiration (1), asthma (1), drug side effect (1), glomerulonephritis (1), lactic acidosis (1), neurogenic bladder (1), psychiatric disease (suicide by poisoning; 1), systemic lupus erythematosus (1).

[g]Seven of the 45 did not have a completed cause of death form.

Table 3.

Factors associated with AIDS-related and non-AIDS-related underlying causes of death among children and adolescents who received combination antiretroviral therapy.

		AIDS-related			Non-AIDS-related		
Characteristics	**Follow-up time (32 361 person-years)**	**Deaths, *n* = 183**	**asHR (95% CI)**	***P* value**	**Deaths, *n* = 84**	**asHR (95% CI)**	***P* value**
Sex							
Male	16 482	95	–	–	51		
Female	15 879	88	–	–	33	0.75 (0.48–1.17)	0.207
Current age (years)[a]				<0.001			0.002
<1	173	18	5.09 (2.80–9.23)	<0.001	7	3.79 (1.62–8.84)	0.002
1–4	3894	64	1.82 (1.24–2.67)	0.002	18	1.15 (0.63–2.11)	0.647
5–9	10 031	46	1.00		23	1.00	
10–14	10 982	29	0.89 (0.56–1.41)	0.609	14	0.67 (0.34–1.31)	0.244
15–19	6201	20	1.62 (0.92–2.84)	0.094	20	2.03 (1.06–3.91)	0.034
20–24	10 788	6	2.17 (0.88–5.34)	0.093	2	1.04 (0.20–5.51)	0.959
Current $CD4^+$ cell count (cells/μl)[a]				<0.001			0.005
<200	1629	116	1.00		23	1.00	
200–349	1478	11	0.20 (0.10–0.38)	<0.001	13	1.27 (0.62–2.61)	0.519
350–499	7223	20	0.15 (0.09–0.26)	<0.001	19	0.59 (0.29–1.19)	0.141
≥500	17 628	4	0.02 (0.01–0.05)	<0.001	20	0.35 (0.17–0.73)	0.005
Missing	4403	32			9		
Current weight-for- age *z*-score[a]				0.029			<0.001
<−3	4327	127	1.00		41	1.00	
≤−3 to <−2	6005	17	0.23 (0.14–0.39)	<0.001	11	0.36 (0.18–0.73)	0.005
≥−2	17 636	20	0.14 (0.08–0.24)	<0.001	21	0.29 (0.17–0.52)	<0.001
Missing	4392	19			11		
History of AIDS diagnosis[a]							
No	14 796	14	1.00		10	1.00	
Yes	17 565	169	5.35 (3.04–9.42)	<0.001	74	4.67 (2.35–9.25)	<0.001
Currently on second-line cART[a]							

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		AIDS-related			Non-AIDS-related		
Characteristics	**Follow-up time (32 361 person-years)**	**Deaths, *n* = 183**	**asHR (95% CI)**	***P* value**	**Deaths, *n* = 84**	**asHR (95% CI)**	***P* value**
No	27 453	158	1.00		67	1.00	
Yes	4908	25	1.41 (0.87.2.30)	0.163	17	1.75 (1.00–3.09)	0.051
Facility setting				0.021			0.145
Urban	19 909	136	1.00		46	1.00	
Mostly urban	10 436	37	0.74 (0.52–1.07)	0.106	27	1.43 (0.88–2.32)	0.146
Mostly rural	2016	10	0.43 (0.22–0.85)	0.015	11	1.73 (0.90–3.31)	0.101
Year of first cART				<0.001			0.101
<2008	17 409	48	1.00		35	1.00	
2008–1010	8898	96	1.49 (1.02–2.18)	0.041	36	1.42 (0.80–2.50)	0.230
2011–2013	4696	35	0.90 (0.56–1.45)	0.665	11	0.77 (0.37–1.60)	0.479
2014–2017	1358	4	0.26 (0.09–0.76)	0.014	2	0.36 (0.08–1.62)	0.182

Deaths due to non-AIDS-related underlying causes ($n = 84$) and those for which causes were unknown or not reviewed ($n = 45$) were competing events for deaths due to AIDS-related underlying causes ($n = 183$). Similarly, deaths due to AIDS-related underlying causes and those for which causes were unknown or not reviewed were competing events for death due to non-AIDS-related causes. 95% CI, 95% confidence interval; asHR, adjusted sub distribution hazard ratio; cART, combination antiretroviral therapy of three or more antiretrovirals.

[a]Current age, $CD4^+$ cell count, weight-for-age *z*-score, second-line, and AIDS were considered time-dependent variables.

Table 4.

Factors associated with infection and noninfection causes of death in children and adolescents who received combination antiretroviral therapy.

		Infection-related			Noninfection-related		
Characteristics	**Follow-up time (32 361 person-years)**	**Deaths, *n* = 214**	**asHR (95% CI)**	***P* value**	**Deaths, *n* = 53**	**asHR (95% CI)**	***P* value**
Sex							
Male	16 482	112	–		34	1.00	
Female	15 879	102	–		19	0.64 (0.36–1.13)	0.125
Current age (years)[a]				<0.001			0.049 0.050
<1	173	24	7.46 (4.48–12.42)	<0.001	1	0.91 (0.12–6.88)	0.925
1–4	3894	70	1.73 (1.21–2.47)	0.003	12	1.56 (0.71–3.46)	0.271
5–9	10 031	57	1.00		12	1.00	
10–14	10 982	34	0.77 (0.50–1.18)	0.234	9	0.80 (0.33–1.94)	0.628
15–19	6201	24	1.36 (0.81–2.31)	0.246	16	2.79 (1.26–6.22)	0.012
20–24	1079	5	1.22 (0.45–3.36)	0.695	3	2.51 (0.62–10.24)	0.198
Current $CD4^+$ cell count (cells/μl)[a]				<0.001			0.033
<200	1629	124	1.00		15	1.00	
200–349	1478	18	0.31 (0.18–0.53)	<0.001	6	0.84 (0.33–2.19)	0.731
350–499	7223	28	0.18 (0.11–0.29)	<0.001	11	0.47 (0.20–1.14)	0.095
≥500	17 628	11	0.05 (0.02–0.09)	<0.001	13	0.29 (0.13–0.67)	0.004
Missing	4403	33			8		
Current weight-for-age *z*-score[a]				<0.001			0.020
<−3	4327	146	1.00		22	1.00	
≤−3 to <−2	6005	19	0.21 (0.13–0.34)	<0.001	9	0.56 (0.25–1.29)	0.173
≥−2	17 636	26	0.15 (0.10–0.24)	<0.001	15	0.38 (0.19–0.75)	0.005
Missing	4392	23			7		
History of AIDS diagnosis[a]							
No	14 796	17	1.00		7	1.00	
Yes	17 565	197	5.60 (3.30–9.30)	<0.001	46	4.13 (1.80–9.50)	<0.001
Currently on second-line cART[a]							
No	27 453	182	1.00		43	1.0	

		Infection-related			Noninfection-related		
Characteristics	**Follow-up time (32 361 person-years)**	**Deaths, *n* = 214**	**asHR (95% CI)**	***P* value**	**Deaths, *n* = 53**	**asHR (95% CI)**	***P* value**
Yes	4908	32	1.64 (1.08–2.50)	0.020	10	1.21 (0.56–2.62)	0.624
Facility setting			0.212				
Urban	19 909	152	1.00		30	–	
Mostly urban	10 436	47	0.89 (0.64–1.23)	0.476	17	–	
Mostly rural	2016	15	0.61 (0.35–1.09)	0.096	6	–	
Year of first cART				<0.001			0.100
<2008	17 409	58	1.00		25	1.00	
2008–1010	8898	109	1.51 (1.05–2.18)	0.028	23	1.58 (0.82–3.06)	0.171
2011–2013	4696	42	1.01 (0.66–1.55)	0.978	4	0.52 (0.17–1.60)	0.256
2014–2017	1358	5	0.27 (0.10–0.71)	0.008	1	0.37 (0.05–2.84)	0.280

Deaths due to noninfection underlying causes ($n = 53$) and those for which causes were unknown or not reviewed ($n = 45$) were competing events for deaths due to infection-related underlying causes ($n = 214$). Similarly, deaths due to infection-related underlying causes and those for which causes were unknown or not reviewed were competing events for deaths due to noninfection causes. 95% CI, 95% confidence interval; asHR, adjusted sub distribution hazard ratio; cART, combination antiretroviral therapy of three or more antiretrovirals.

[a]Current age, $CD4^+$ cell count, weight-for-age *z*-score, second-line, and AIDS were considered time-dependent variables.

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