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Survival of HIV-infected children: A cohort study from the Asia-Pacific region

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Abstract

Background—Combination antiretroviral therapy (ART) has been used for HIV-infected children in many Asian countries since 2002. This study describes survival outcomes among HIV-infected children in a multicenter regional cohort in Asia.

Patients and Methods—Retrospective and prospective data collected through March 2009 from children in five countries enrolled in TREAT Asia's Pediatric HIV Observational Database (TApHOD) were analysed. Multivariate Cox proportional hazard models were used to assess factors associated with mortality in children who received ART.

Results—Among 2280 children, 1752 (77%) had received ART. During a median follow up of 3.1 years after ART, 115 (6.6%) deaths occurred, giving a crude mortality rate of 1.9 per 100 child-years (95% CI, 1.6-2.4). The mortality rate was highest in the first three months of ART (10.2 per 100 child-years; 95% CI, 7.5-13.7) and declined after 12 months (0.9 per 100 child-years; 95% CI, 0.7-1.3). Those with a low recent CD4 percentage, who started ART with lower baseline weight-for-age z-score, or with WHO clinical stage 4 had an increased risk of death. Of 528 (23%) children who never received ART, 36 (6.8%) died after presenting to care, giving a crude mortality rate of 4.1 per 100 child-years (95% CI 3.0-5.7), with a lost-to-program rate of 31.5 per 100 child-years (95% CI, 28.0-35.5).

Conclusion—The high mortality during the first three months of ART and in those with low CD4 percentage support the implementation of early diagnosis and ART initiation.

Keywords

pediatric HIV; antiretroviral therapy; survival; mortality; Asia

Introduction

Since the introduction of triple-drug, combination antiretroviral therapy (cART), survival of HIV-infected children in resource-rich countries has substantially improved.¹⁻⁴ The mortality of perinatally HIV-infected children in the United Kingdom and Ireland has declined from 9.3 deaths per 100 child-years at risk before 1997 to 2.0 deaths per 100 child-years in 2001-2002¹ and to 0.6 per 100 child-years during 2003-2006.² An analysis based on data collected as part of the PACTG 219 and 219C cohort studies, which enrolled HIV-exposed and -infected children in the United States, demonstrated a decline in mortality from 7.1 per 100 child-years in 1994 to 0.6 per 100 child-years in 2006.³ In many resource-limited countries in Asia, ART use for HIV-infected children began around 2002 but was not scaled up consistently across the region.⁵ Before that time, drug access was largely limited to mono- or dual-therapy with nucleoside reverse transcriptase inhibitors (NRTI). Although, responses to cART have been reported to be comparable to Western cohorts,⁶⁻¹³ the impact of frequent mono- or dual-therapy use in the past and survival outcomes of perinatally HIV-infected children across the region has not been reported.

In 2005, TREAT Asia's Pediatric Program was initiated by amfAR, The Foundation for AIDS Research, to provide the first platform from which pediatric HIV clinical providers

and researchers in Asia could conduct regional-level observational research. In 2007, the group established the TREAT Asia Pediatric HIV Observational Database (TApHOD), a project designed to provide insights into improving treatment access and outcomes for HIV-positive children in Asia.^{14,15} In this analysis we describe survival and factors related with mortality in HIV-infected children managed in this regional network.

Patients and Methods

Study population

TApHOD is a multicenter, observational cohort study of infants and children living with HIV in Asia. TApHOD is a member cohort of the US National Institutes of Health's International Epidemiologic Databases to Evaluate AIDS (IeDEA). Data collection for TApHOD began in 2008, the methods of which have been described elsewhere.¹⁵ Participating sites are largely public referral hospitals based in urban settings. All eligible HIV-infected children receiving care at participating clinical sites are enrolled into the database. Inclusion criteria include: 1) age at the first clinic visit of ≤ 18 years; and 2) confirmed diagnosis of HIV using age-appropriate tests; or 3) presumptive diagnosis according to World Health Organization criteria until confirmation.¹⁶

Institutional Review Board approval was obtained at participating sites, and the data management and coordinating centers (University of New South Wales, Sydney; TREAT Asia, Bangkok). Since data are anonymously collected, informed consent was waived, unless locally required.

Data collection

Data are extracted from the existing clinic databases or medical records, and put into a standardized Microsoft Access database or Excel file before being transferred electronically to the data management center for quality control and aggregation. Core variables include sociodemographic data, clinical history, dates and outcomes of clinic visits and hospitalizations, laboratory monitoring, ART history, and vital status. The cohort was prospectively constituted in 2008; retrospective clinical data were provided from the date of first entry into the clinic. Sites also provided data for those who died and were lost to follow-up (LTFU) during the retrospective period where available, thus allowing for complete site-level data ascertainment.

Data included in this analysis were transferred to TApHOD through March 2009, from children at 12 sites in five countries, including five sites in Thailand, four in Malaysia and one each in India, Indonesia and Cambodia. For the purpose of this analysis, children were excluded if they enrolled in the clinic during a time period for which complete treatment data could not be ascertained for those who died or were LTFU at their site.

Statistical analysis

Continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. The incidence rates of mortality, the primary endpoint of interest, were calculated by dividing the number of deaths by the total number of person-years. For each member of the cohort, person-years at risk were measured from the start date of ART, or the date of first clinic visit for children who were ART-naïve until the date of death or the date of the most recent clinic visit. LTFU was defined as having had no documented clinic visit for >12 months. We used an 'intent-to-continue-treatment' approach and thus did not take into account changes to treatment, including treatment interruptions and termination of treatment after ART initiation. Kaplan-Meier methods were used to assess the cumulative probability of survival after the start of ART.

Univariate and multivariate Cox proportional hazard models were used to assess factors associated with mortality in children who received ART. Baseline covariates included in the univariate analysis were: ethnicity, weight-for-age and height-for-age z scores, body mass index (BMI), WHO clinical staging (i.e., the most advanced stage documented prior to ART), hemoglobin level, and initial ART regimens. For height-for-age z score, the WHO 2006/2007 Child Growth Standards¹⁷ were used. WHO 1977 Standards were used for weight-for-age z scores, to allow for scoring children >10 years of age.¹⁸ CD4 cell percentage was treated as a time-dependent covariate (i.e., the individual values were continually updated throughout the follow-up period). Laboratory values from within three months before (all tests) and one month after ART initiation (except for CD4) were used as baseline values. ART was classified as mono- or dual-therapy, or cART. Due to concerns about the inconsistent HIV viral load data collection across the cohort, it was not included in the model. We considered demographic and clinical characteristics that met the criterion of p value <0.10 in univariate analysis to be potential risk factors in multivariate analysis. Multivariate models were then developed using a stepwise forward selection procedure. The significance of each variable was assessed with the likelihood ratio test. Statistical analyses were performed using Stata version 10 (StataCorp, College Station, Texas, USA).

Results

Characteristics of the study population

Of the 2280 children included in this analysis, 1752 (77%) had been initiated on some level of ART, including cART in 1480 (84%) and mono- or dual-NRTI therapy in 272 (16%); 528 children were ART-naïve (Table 1). Most children initiated on cART (97%) presented for care from 2002 onwards, whereas 70% of children initiated with mono- or dual-therapy presented for care before this date. The median age at the time of ART initiation was 6.5 years; 7.0 years for those initiated on cART and 2.1 years for those initiated on mono- or dual-therapy. In more than half of the children on cART and a fourth of those on mono- or dual-therapy, the baseline CD4 percentage was under 15 percent. The most commonly used first-line cART regimen was non-nucleoside reverse transcriptase (NNRTI)-based (93%), while 6% received protease inhibitor (PI)-based regimens. Among the NNRTI-based regimens, 67% were nevirapine-based (NRTI backbone: 65% with stavudine, 35% with zidovudine), 33% were efavirenz-based (NRTI backbone: 56% with zidovudine, 42% with stavudine).

Duration of follow-up and mortality rate

By the end of March 2009, the median follow-up time for the 1752 children who had ever received ART was 3.1 (IQR, 1.5-4.8) years; 2.9 (IQR, 1.4-4.6) years for those who initiated cART; and 5.1 (IQR, 2.7-8.7) years for those who initiated mono- or dual-therapy. A total of 155 (8.8%) children were LTFU and 119 (6.8%) were transferred to other hospitals, giving a combined lost-to-program rate of 4.6 per 100 child-years (95% CI, 4.1-5.2). Among these 1752 children, 115 (6.6%) died, giving a crude mortality rate of 1.9 per 100 child-years (95% CI, 1.6-2.4); 37% of deaths occurred during the first three months of ART. The median age at death for children who had ever received ART was 7.7 (IQR, 4.7-10.9) years; 7.8 (IQR, 4.8-10.9) years for those who initiated cART; and 5.8 (IQR, 2.7-7.9) years for those who initiated mono- or dual-therapy. The mortality rate decreased by half from 10.2 per 100 child-years (95% CI: 7.5-13.7) during the first three months of ART to 4.2 per 100 child-years (95% CI, 2.6-6.8) during the fourth to sixth months (Table 2). The rate fell further to 2.0 per 100 child-years (95% CI, 1.2-3.3) from 6-12 months, and was 0.9 per 100 child-years (95% CI, 0.7-1.3) after 12 months. The Kaplan-Meier estimate of 5-year survival from the time of ART initiation was 91.7% (95% CI, 90.0-93.2%). Survival curves by baseline CD4 category are shown in Figure 1. Half of deaths in children with a baseline CD4

<5% occurred within six months after ART initiation and all of the reported deaths occurred within the first two years. The two most common causes of death reported were serious bacterial infections or pneumonia and opportunistic infections (Table 3). The baseline characteristics of children who died in each period are shown in Table 4. The median weight for age z score in children who died during the first three months of ART was -5.1 (-6.9 to -3.4), which was much lower than those who died in other periods, but significant differences were not found between the four groups.

The 528 (23%) children who never received ART (Table 1) had a median follow-up time of 0.9 years (IQR 0.1-2.5); 49 of them attended the clinic only once. Thirty-six children (6.8%) died after presenting to care, giving a crude mortality rate of 4.1 per 100 child-years (95% CI 3.0-5.7). Their causes of death are described in Table 3. In the ART-naïve group, 241 (46%) children were LTFU and 34 (6%) were transferred to other clinical care programs, resulting in a combined lost-to-program rate of 31.5 per 100 child-years (95% CI, 28.0-35.5).

Predictors of death after ART initiation

The risk of death showed a significant decreasing trend as CD4 percentage increased (Table 5). The hazard ratio dropped from 33.85 (95% CI: 14.96-76.59) in children with a CD4 <5% to 4.02 (95% CI: 1.53-10.57) in children with a CD4 of 15-19%, when compared with the reference category (CD4 ≥20%). The risk of death decreased by 10% for each unit increase in weight-for-age z score (95% CI 0.81-0.98). Mortality risk was significantly higher for those with WHO clinical stage 4 at baseline (HR 4.78, 95% CI, 1.84-12.41).

Current ART outcomes

By the end of March 2009, 1580 of 2280 children (69%) were still on active follow-up at the participating sites. A total of 1363 (86%) were on ART, of whom 1041 (76%) were on NNRTI-based regimens and 7 (0.5%) were on mono- or dual-NRTI. The median age was 10.7 years (IQR, 7.4-13.5, range 8 months to 25.7 years). There were 217 (13%) children who had not yet started ART with a median age of 8.1 years (IQR 5.7-10.7; range 1-21.7 years). The most recent CD4 was ≥15% in 85% of those on ART and 83% of ART-naïve children and adolescents.

Discussion

We found a mortality of 6.6% with 8.8% LTFU, giving an overall mortality rate of 1.9 per 100 child-years among Asian children who received any level of ART in this regional cohort. The 5-year survival rate from the time of ART initiation was 91.7% (95% CI 90.0-93.2%). Mortality was highest in the first three months after ART initiation and fell with time on ART, and was frequently caused by bacterial infections, *Pneumocystis carinii* pneumonia, and tuberculosis.

In comparison to our results, the KIDS-ART-LINC collaboration reported 6.9% mortality after ART initiation and 10.3% LTFU after two years in West Africa.¹⁹ Reduction in mortality with the availability of ART has been shown in several studies from developed countries^{1-4, 20-22} as well as from resource-limited settings.^{19, 23-24} Before ART became available to children in this region, survival of HIV-infected children with advanced stage disease was low. In a study of 353 symptomatic HIV-infected children cared for at Chiang Mai University Hospital, Thailand between 1989 and 1994, 42% of them died during their first hospital admission.²⁵ In a study at a tertiary-care hospital in northeastern Thailand between 1989 and 1997, among 90 HIV-infected children with AIDS, 50% of them died

with 30% LTFU. The 1-year survival rate from the time of first symptom was 75.3% (95% CI 65.8%-84.7%).²⁶

In our study, the predictors of mortality in ART-experienced children included WHO clinical stage 4, low CD4% (as a time-dependent variable), and low weight-for-age Z score. Children who died in the first three months of ART had very low baseline weight-for-age z-score (i.e., median -5.1), although not significantly lower than those who died during other periods. Malnutrition can play a critical role in HIV infection, as it impairs both humoral and cell-mediated immunity, while infection itself also contributes to malnutrition.^{27,28} The type of initial ART regimen (i.e., cART vs. mono- or dual-NRTI) was not associated with increased mortality. This may be related to subsequently switching from mono- or dual-NRTI regimens to cART during the follow-up period; as only 0.5% children who were previously initiated on mono- or dual-NRTIs remained on those regimens. Unlike studies from sub-Saharan Africa, we did not find baseline severe anemia as an independent risk factor for mortality.¹⁹

Excess early mortality in the first three months on ART has been reported both in children and adults.^{19,24,29-30} In a prospective cohort study of 135 HIV-infected Kenyan children initiating cART between August 2004 and December 2008 and followed for a median of 21 months, 20 (13%) children died; the overall mortality was 8.4 per 100 child-years.²⁹ However, the mortality rate was 46 per 100 child-years in the first four months and dropped to 1.0 per 100 child-years from four to 24 months.²⁹ A Medecins sans Frontières study including 3936 children <5 years of age in Africa and Asia reported 6.3% mortality at a median follow-up time of 10.5 months. The survival rate at one year was 93% (95% CI 92-94%), and 55% of deaths and LTFU occurred during the first three months of ART.³⁰

This study has several limitations. The data were both retrospectively and prospectively collected, therefore specific causes of death and outcomes of children LTFU were not fully ascertainable. In addition, although there were at least three patients with suspected immune reconstitution syndrome, we were unable to assess the impact of immune reconstitution on mortality. The lack of data on adherence and viral load are other factors that limited our analysis. The children in our cohort were seen at regional pediatric referral centers, so results may not be generalizable to children receiving care in primary care centers or rural areas. Their acuity was high, as they frequently presented late to care and may have been transferred from centers less equipped to manage complicated opportunistic infections. However, some of these factors are challenging to control in the analysis of observational databases from a resource-limited setting. As the largest analysis of survival and mortality in HIV-infected children across Asia, these findings contribute important evidence on which to consider future management strategies.

Survival of HIV-infected children in Asia has improved substantially as ART has become more widely available in the region. The findings that advanced clinical and immunologic disease predicted mortality emphasize the urgent need for early identification of HIV-infected infants and children and access to cART before disease progression. The frequent association of low weight-for-age with poor outcomes in pediatric cohorts further highlights the importance of integrating nutritional interventions into ART programs to reduce early mortality.

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Figure 1.
Kaplan-Meier survival estimates after ART initiation, by baseline CD4 percentage.
Note: Values outside the brackets show the number at risk at the beginning of each year and values inside the brackets are number of deaths.

Table 1Baseline^a characteristics of children enrolled in TApHOD

Characteristics	cART as the first ART regimen (n=1480)	Mono- or dual-therapy as the first ART regimen (n=272)	No ART (n=528)
Age, years			
<1	112 (7.6)	92 (33.8)	36 (6.8)
1-4	360 (24.3)	109 (40.1)	239 (45.3)
5-12	930(62.8)	64(23.5)	233(44.2)
≥13	78 (5.3)	7 (2.6)	20 (3.8)
Median (IQR)	7.0 (3.9-9.9)	2.1 (0.8-5.0)	4.8 (2.7-7.8)
Male	748 (50.5)	141 (51.8)	269 (51.0)
Perinatal infant antiretroviral prophylaxis	136 (9.2)	28 (10.3)	51 (9.7)
Unknown	500 (33.8)	154 (56.6)	357 (67.6)
Maternal antiretroviral prophylaxis	119 (8.0)	17 (6.3)	46 (8.7)
Unknown	490 (33.1)	154 (56.6)	360 (68.2)
CD4 percentage			
≤4	452 (30.5)	30 (11.0)	16 (3.1)
5-14	427 (28.9)	39 (14.3)	44 (8.3)
15-24	191 (12.9)	64 (23.5)	101 (19.1)
≥25	68 (4.6)	35 (12.9)	69 (13.1)
Median (IQR)	7.0 (3.9-9.9)	17.0 (9.0-24.0)	20.7 (14.0-26.0)
Unknown	342 (23.1)	104 (38.2)	298 (56.4)
Median HIV RNA log ₁₀ copies/ml (IQR; percent available)	5.3 (4.8-5.8; 38.1)	5.8 (5.4-6.2; 14.3)	5.1 (4.7-5.9; 6.6)
WHO clinical staging ^b			
Stage I	100 (6.8)	10 (3.7)	28 (5.3)
Stage II	306 (20.7)	40 (14.7)	89 (16.9)
Stage III	411 (27.8)	85 (31.3)	140 (26.5)
Stage IV	404 (27.3)	38 (14.0)	28 (5.3)
Unknown	259 (17.5)	99 (36.4)	243 (46.0)
Severe anemia ^c	54 (3.7)	11(4.0)	15 (2.8)
Unknown	403 (27.2)	145 (53.3)	233 (44.1)
Mean hemoglobin, g/dl (SD)	10.4 (1.7)	10.1 (1.8)	10.6 (1.8)
Weight-for-age z score, ^d median (IQR) (n=1121)	-2.7 (-4.0 to -1.5)	-2.1 (-3.6 to -1.1)	-2.2 (-3.6 to -1.2)
Height-for-age z score, ^e median (IQR) (n=1026)	-2.4 (-3.4 to -1.5)	-2.2 (-3.0 to -1.0)	-1.8 (-2.9 to -0.7)
BMI, median (IQR) (n=1010)	14.4 (13.2-15.6)	15.1(13.5-16.4)	14.1 (12.8-15.4)

ART – antiretroviral therapy; cART – combination ART; IQR – interquartile range; BMI – body mass index

^f Refers to the first ART regimen.^a Baseline was defined as date of ART initiation or date of enrollment if no ART was received. Data provided as n (%) unless otherwise noted.

^b Maximum stage at baseline was used.

^c Severe anemia was defined according to US guidelines (see Methods): hemoglobin <10 g/dL <21 days; <8 g/dL 22-35 days; <7 g/dL 36-56 days; <7.5 g/dL ≥57 days.

^d The 2000 US CDC growth curve was used.

^e The 2007 WHO growth curve was used.

Table 2

Short-term and overall mortality in children who started ART (n=1752)

Time on ART	Deaths n=115 n (%)	Child-years	Rate per 100 child-years (95% CI)
≤3 months	43 (37.3)	422.9	10.2 (7.5-13.7)
4-6 months	17 (14.8)	401.1	4.2 (2.6-6.8)
7-12 months	15 (13.0)	755.4	2.0 (1.2-3.3)
>12 months	40 (34.8)	4337.9	0.9 (0.7-1.3)

ART – antiretroviral therapy

Table 3
Most commonly reported causes of death since ART initiation or date of first clinic visit in ART-naïve children

Cause of death	Timeframe in months, n				Total n (%)
	≤3	4-6	7-12	>12	
Children who received ART	43	17	15	40	115 (100)
-Pneumonia/sepsis	15 ^a	4	6	9	34 (29.6)
- Other opportunistic infection ^b	12	8 ^a	1 ^a	5	26 (22.6)
-AIDS	7	4	2	8	21 (18.3)
-Serious adverse events	2		1		3 (2.6)
-Others ^c	2	-	1	4	7 (6.0)
-Unknown	5	1	4	14	24 (20.9)
Children who were ART-naïve	14	6	5	11	36 (100)
-Pneumonia/sepsis	5	2	-	3	10 (27.8)
- Other opportunistic infections ^b	5	-	1	1	7 (19.4)
-AIDS	1	1	-	1	3 (8.3)
-Others ^c	1	1	-	1	3 (8.3)
-Unknown	2	2	4	5	13 (36.1)

ART – antiretroviral therapy

^aincluding one patient with suspected immune reconstitution syndrome

^bincluding Pneumocystis carinii pneumonia, tuberculosis, cytomegalovirus infection, toxoplasmosis, penicilliosis.

^cincluding trauma, lymphoma, glomerulonephritis, malnutrition, stroke.

Table 4

Baseline characteristics of children who died by time of death after ART

Characteristics	≤3 months n=43	4-6 months n=17	7-12 months n=15	>12 months n=40
Age, years				
<1	6 (14.0)	0	2 (13.3)	5 (12.5)
1-4	11 (25.6)	4 (23.5)	4 (26.7)	7 (17.5)
5-12	25 (58.1)	13 (76.5)	8 (53.3)	24 (60)
≥13	1 (2.3)	0	1 (6.7)	4 (10.0)
Median (IQR)	7.1 (2.9-9.4)	8.3 (6.3-11.3)	6.2 (1.9-8.7)	6.0 (4.0-9.2)
Baseline CD4%				
<5	19 (44.2)	10 (58.8)	5 (33.3)	11 (27.5)
5-14	6 (14.0)	1 (5.9)	5 (33.3)	6 (15.0)
15-24	4 (9.5)	0	0	0
≥25	1 (2.3)	0	1 (6.7)	2 (5.0)
Unknown	13 (30.2)	6 (35.3)	4 (26.7)	21 (52.5)
Median (IQR)	2.0 (1.0-7.0)	1.0 (0-1.3)	5.0 (1.0-13.0)	3.0 (1.5-12.0)
WHO stage				
Stage 1/2	2 (4.7)	1 (5.9)	0	3 (7.5)
Stage 3	15 (34.9)	1 (5.9)	2 (13.3)	16 (40.0)
Stage 4	23 (53.5)	12 (7.6)	9 (60.0)	11 (27.5)
Unknown	3 (7.0)	3 (17.7)	4 (26.7)	10 (25.0)
HIV-RNA				
<10,000	0		0	0
10,000-99,999	1 (2.3)	3 (17.7)	0	1 (2.5)
≥100,000	5 (11.6)	1 (5.9)	2 (13.3)	5 (12.5)
Unknown	37 (86.1)	13 (76.5)	13 (86.7)	34 (85.0)
Severe anemia				
Yes	3 (7.0)	1 (5.9)	3 (20.0)	2 (5.0)
No	31 (72.1)	10 (58.8)	9 (60.0)	20 (50.0)
Unknown	9 (20.9)	6 (35.3)	3 (20.0)	18 (45.0)
Median (IQR)	9.7 (7.6-10.6)	8.9 (8.1-10.2)	8.7 (7.2-10.0)	9.3 (8.2-2.8)
Weight for age z median (IQR)	-5.1 (-6.9 to -3.4)	-3.8 (-6.4 to -2.0)	-3.7 (-4.7 to -2.5)	-3.5 (-4.4 to -2.4)
BMI Median (IQR)	11.9 (10.5-14.1)	12.7 (12.0-14.4)	14.0 (12.9-14.8)	13.5 (12.3-15.5)

ART – antiretroviral therapy; IQR – interquartile range; BMI – body mass index

Table 5

Univariate and multivariate analyses of risk factors for death for children who received ART (n=1752)

Characteristics	Incidence rate	Univariate		Multivariate	
		RR (95% CI)	p value	RR (95% CI)	p value
Age, years					
<1	1.60 (0.93-2.76)	1.0			
1-4	1.54 (1.05-2.27)	0.87 (0.45-1.70)	0.69		
5-9	2.16 (1.65-2.84)	1.13 (0.62-2.08)	0.69		
10-13	2.20 (1.39-3.49)	1.06 (0.52-2.16)	0.88		
≥13	3.02 (1.36-6.72)	1.28 (0.49-3.38)	0.61		
Male	2.32 (1.82-2.94)	1.41 (0.98-2.05)	0.07		
Perinatal infant antiretroviral prophylaxis					
Yes	0.63 (0.20-1.96)	1.0			
No	2.44 (1.95-3.07)	4.08 (1.29-12.95)	0.02	NS	
Maternal antiretroviral prophylaxis					
Yes	0.27 (0.04-1.94)	1.0			
No	2.35 (1.87-2.95)	9.49 (1.32-68.27)	0.03	NS	
CD4 percentage ^a					
0-4	15.96 (12.03-21.18)	27.80 (15.10-51.17)	<0.0001	33.85 (14.96-76.59)	<0.0001
5-9	3.26 (1.85-5.73)	5.20 (2.36-11.43)	<0.0001	5.87 (2.18-15.84)	<0.0001
10-14	2.13 (1.21-3.75)	4.03 (1.84-8.81)	<0.0001	5.33 (2.05-13.84)	0.001
15-19	1.05 (0.54-2.01)	2.35 (1.01-5.46)	0.05	4.02 (1.53-10.57)	0.005
≥20	0.37 (0.22-0.63)	1.0		1.0	
WHO clinical stage					
Stage I/II	0.46 (0.22-0.97)	1.0		1.0	
Stage III	2.05 (1.46-2.89)	4.46 (1.97-10.08)	<0.0001	2.55 (0.96-6.75)	0.06
Stage IV	3.75 (2.88-4.88)	8.23 (3.75-18.08)	<0.0001	4.78 (1.84-12.41)	<0.001
Severe anemia					
No	1.97 (1.56-2.49)	1.0			
Yes	5.04 (2.62-9.68)	2.48 (1.24-4.96)	0.01	NS	

Characteristics	Incidence rate	Univariate		Multivariate	
		RR (95% CI)	p value	RR (95% CI)	p value
Weight for age z score		0.74 (0.68-0.81)	<0.0001	0.89 (0.81-0.98)	0.02
Height for age z score		0.69 (0.58-0.81)	<0.0001	NS	
Mono/dual-NRTI	1.05 (0.65-1.72)	1.0			
cART	2.25 (1.85-2.74)	1.35 (0.79-2.30)	0.27	-	

ART – antiretroviral therapy; NRTI – nucleoside reverse transcriptase inhibitor; cART – combination antiretroviral therapy

^a treated as time-dependent variable