Background: Data are scarce on the long-term clinical outcomes of perinatally HIV-infected children and adolescents receiving antiretroviral therapy (ART) in low/middle-income countries. We assessed the incidence of mortality before (early) and after (late) 6-month of ART and of the composite outcome of new/recurrent AIDS-defining-event or death >6 months after ART start (late AIDS/death) and their associated factors.

Methods: Study population was perinatally HIV-infected children (≤18 years) initiating ART within the Program for HIV Prevention and Treatment observational cohort (NCT00433030). Factors associated with late AIDS/death were assessed using competing risk regression models accounting for loss-to-follow-up, and included baseline and time-updated variables.

Results: Among 619 children, "early" mortality incidence was 99 deaths per 1000-PYFU (95%CI; 69-142) and "late" mortality 6 per 1000-PYFU (95%CI; 4-9). Of the 553 children alive >6 months after ART initiation, median age at ART initiation was 6.4 years, CD4% 8.2% and HIV-RNA 5.1 log10 copies/mL. 38 (7%) children developed late AIDS/death after median time of 3.3 years: 24 died and 24 experienced new/recurrent AIDS-defining-events (10 subsequently died). Factors independently associated with late AIDS/death were: current age ≥13 years (adjusted sub-distribution hazard-ratio 4.9; 95%CI; 2.4-10.1), HIV-RNA always ≥400 copies/mL (12.3; 4.0-37.6), BMI-z-score always <-2 SD (13.7; 3.4-55.7), and hemoglobin <8g/dL at least once (4.6; 2.0-10.5).

Conclusions: After the initial 6 months of ART, being an adolescent, persistent viremia, poor nutritional status and severe anemia were associated with poor clinical outcomes. This supports the need for novel interventions that target children, particularly adolescents with poor growth and uncontrolled viremia.

TITLE PAGE

Title: AIDS-defining events and deaths in HIV-infected children and adolescents on antiretrovirals: a 14-year study in Thailand

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Abstract

Background: Data are scarce on the long-term clinical outcomes of perinatally HIV-infected children and adolescents receiving antiretroviral therapy (ART) in low/middle-income countries. We assessed the incidence of mortality before (early) and after (late) 6-month of ART and of the composite outcome of new/recurrent AIDS-defining-event or death >6 months after ART start (late AIDS/death) and their associated factors.

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Conclusions: After the initial 6 months of ART, being an adolescent, persistent viremia, poor nutritional status and severe anemia were associated with poor clinical outcomes. This supports the need for novel interventions that target children, particularly adolescents with poor growth and uncontrolled viremia.

Keywords: Mortality; AIDS; HIV; Thailand; Children; Adolescents

Introduction

In low and middle-income countries, a growing number of perinatally infected children are reaching adolescence and adulthood as the result of the scale-up of ART programs during the last decade. However, few pediatric cohorts have been sufficiently followed to investigate clinical outcomes during adolescence[1-3]. Maintaining ART adherence throughout adolescence is challenging[4,5] and poor outcomes during this vulnerable period have been reported[6-8].

Using data from a cohort of HIV-infected children receiving ART over a 14-year period within a network of 39 public hospitals throughout Thailand, we estimated the incidence of mortality before ("*early*") and after ("*late*") 6-month of ART initiation and of a composite outcome defined as new/recurrent AIDS-defining-events or death after 6 month of ART start (late AIDS/death). We also studied factors associated with the risk of *late* AIDS/death.

Methods

Study Population

We included data on all perinatally HIV-infected children (≤18 years) who initiated ART between January 1, 1999 and June 30, 2013 and were followed until July 31, 2014, as part of the Program for HIV Prevention and Treatment (PHPT) prospective observational cohort (NCT00433030)[9,10]. Children were enrolled with parental/caregiver consent, and personal assent if age ≥8 years. ART and laboratory monitoring were provided free of charge.

The study protocol was approved by the ethics committees at the Thai Ministry of Public Health, local hospitals and the Faculty of Associated Medical Sciences, Chiang Mai University, Thailand.

Follow-up

Clinical visits were scheduled at ART initiation, at 2 weeks, 1, 3 and 6 months, and then every 6 months thereafter. CD4 and virology testing was performed at start of ART and every 6 months thereafter. HIV-genotyping was performed in case of virological failure using the Agence Nationale de Recherches sur le SIDA (ANRS) in-house technique (AC11-Resistance Study Group PCR and Sequencing Procedures)[11]. Loss-to-follow-up (LTFU) was defined as a missed scheduled visit and no contact for at least 9 months since last appointment. Attempt to contact LTFU children were made with telephone calls and home visits. Voluntary withdrawal was defined as notified exit from study, including notified transfer to adult care.

Antiretroviral treatment

Nucleoside reverse-transcriptase inhibitor (NRTI) dual therapy was provided from 1999, mostly zidovudine and didanosine. Protease inhibitor (PI) became available in 2002 and non-nucleoside reverse-transcriptase inhibitors (NNRTI) in 2003. Children initially on dual NRTIs could be switched to triple therapy when it became available. Children who experienced drug toxicity or treatment failure received alternative regimens as needed.

Outcomes and analysis of the risk factors

Events occurring during the first 6 months after ART start were defined as "early", and those occurring after 6 months were defined as "late". The outcomes of interest were *early* deaths, *late* deaths, and a composite outcome defined as *late* new/recurrent AIDS-defining-events or death (*late* AIDS/death). All events were documented by the responsible site physicians. Clinical records were reviewed by 2 independent physicians, and causes of death classified according to the International Classification of Diseases 10.

Factors associated with mortality within this cohort after median follow-up of 4.5 years have been previously described[9]. We assessed here factors associated with the risk of occurrence of *late* AIDS or death. Children were considered at risk from 6 months after ART start and their follow-up time was censored at the earliest date of first AIDS event, death or at last visit.

Analysis of factors associated with late AIDS/death included baseline characteristics at ART start and time-updated variables. Baseline characteristics were based on the closest assessment available within one year before ART start, or if not available, within 15 days after. Weight-for-age and height-for-age z-scores were computed based on Thai references[12] and BMI-for-age z-scores based on WHO curves[13,14]. For time-

updated variables, all measurements after 6 months of ART were used and dichotomized as follow: adolescent (current age ≥13 years, corresponding to the age at puberty in this population[15]), BMI-for-age z-score always <-2 standard deviations (SD) and ever severely anaemic (hemoglobin <8 g/dL). HIV-RNA viral load was categorized in 3 categories: always suppressed (<400 copies/mL), occasional viremia (≥1 viral load measurement ≥ 400 copies/mL), and never suppressed (all viral load measurements ≥400 copies/mL).

Statistical analysis

Crude mortality rates are provided with their 95% confidence intervals (CIs) based on Poisson distribution. Incidences are reported in events per 1000 person-years of follow-up (PYFU).

Factors associated with the late composite outcome of AIDS or death used Fine-Gray competing risk regression models accounting for LTFU as a competing event[16], with a backward stepwise selection. In the multivariable analysis, only time-updated variables were considered if baseline and time-updated variables were collinear and both were associated with the outcome (P<0.20) in the univariable analysis. Associations were reported using subdistribution hazard-ratio (SHR)[17].

To avoid loss of information and biased estimates because of missing data, we imputed missing values with linear interpolation for time-updated variables[18]. Sensitivity analyses on complete cases and with adjustment on age and calendar year at ART initiation, and using HIV-RNA ≥1000 copies/mL threshold instead of 400 copies/mL, were also performed. All tests were two-sided and P<0.05 was considered statistically significant. Analyses were performed using STATA-Version 13.

Results

Overall incidence of mortality

Over the 14-year study period, 619 children ≤18 years initiated ART within the cohort. The median (IQR) follow-up duration was 7.7 years (3.5-9.8) corresponding to 4,320 PYFU. Overall, 53 (9%) children died during follow-up, 144 (23%) were LTFU and 152 (25%) voluntarily withdrew, most often due to notified self-referral to another hospital. The median follow-up duration among children who died was 0.4 years (0.1-2.2), 6.5 years (2.2-8.5) for those LTFU, and 4.9 years (1.5-8.7) for those who withdrew. The crude incidence (95%CI) of death was 12 (9-16) per 1000-PYFU, Table 1.

Early deaths

A total of 29 deaths occurred within the first 6 months after ART initiation corresponding to an incidence of early death of 99 (69 to 142) per 1000-PYFU (Table 1).

For the analysis of *late* events, 553 (89%) children were included, 66 children were excluded due to <6 months follow-up after ART start (29 deaths, 15 LTFU and 22 withdrawals). Characteristics at ART initiation are described in Table 2, 302 (55%) were female, median age 6.4 years [IQR, 2.2-9.6], and BMI-for-age z-score -0.8 [-1.9 to 0.1]. Their median follow-up was 8.1 years [4.9-9.9]. Half of the children were CDC stage B or C, median CD4% was 8.2% [2.5-16.3] and HIV-RNA load 5.1 $\log_{10}$ copies/mL [4.7-5.6]. The majority, 441 (80%) children initiated NNRTI-based ART, 56 (10%) PI and 56 (10%) a dual NRTI regimen.

Late deaths

A total of 24 (4%) children died after a median time of 2.6 years (1.3-6.3). Crude incidence (95%CI) of late death was 6 (4-9) per 1000-PYFU (Table 1). Of these deaths, 14 (58%) occurred in hospitals, 8 (33%) at home, and 2 (8%) elsewhere. The median age at death was 11.9 years (IQR, 2.6-14.4). Causes of death were mostly HIV-related: wasting syndrome (5) cryptococcal meningitis (4), septic shock (3), respiratory failure (3), cerebral hemorrhage (2), bacterial pneumopathy (1), brain abscess (1), complete heart block (1) and congestive heart failure (1). Three external causes of death included drowning (2) and suicide (1).

Late new/recurrent AIDS defining event.

Twenty-four patients experienced a total of 45 new/recurrent AIDS-defining-events (Table 1). Median time to first new/recurrent AIDS-defining-event was 5.1 years after ART initiation (1.7-7.2). Crude incidence (95%CI) of new/recurrent AIDS-defining-events 6 (4 to 8) per 1000-PYFU. First AIDS-defining-events were: tuberculosis (6), pneumonia (6), penicilliosis (4), cryptococcal meningitis (2), septic shock (2) and one each of the following: brain abscess, meningitis, encephalopathy, and pneumocystosis.

Late composite outcome: new/reccurent AIDS-defining-event or death

A total of 38 (7%) children met the *late* composite outcome of AIDS/death, the first event was AIDS in 24 children (10 went on to subsequently die) and 14 died without a preceeding AIDS event. Median time to the first composite outcome was 3.3 years (1.3-6.3) after ART start, with a crude incidence 9 (7 to 12) per 1000-PYFU (Table 1).

Factors associated with the late AIDS/deaths are presented in Table 2. In multivariable analysis, after adjustment on time-updated variables, factors independently associated with the composite outcome were: current age ≥13 years (adjusted SHR [aSHR], 4.9; 95%CI; 2.4-10.1), HIV-RNA load always ≥400 copies/mL (aSHR=12.3; 4.0-37.6), BMI-z-score always below -2 SD (aSHR=13.7; 3.4-55.7), and ever experiencing severe

anemia (aSHR=4.6; 2.0-10.5). There was no interaction between current age and HIV-RNA load. Results of sensitivity analyses were similar when using complete case analysis, or with adjustment on age and calendar year at ART initiation, or when using HIV-RNA ≥1,000 threshold instead of 400 copies/mL (data not shown).

HIV genotypic resistance testing was performed at least once in 30% (167/553) of children, 47% (18/38) of those who reached the composite outcome vs. 29% (149/515) of those who did not (p=0.026). Median time from ART initiation to first genotyping was 3.3 years (2.0-5.1) among those who reached the composite outcome versus 2.0 years (1.3-4.7) in the others (p=0.200). At the time of first HIV genotyping, 80% of children had NRTI mutations, 77% NNRTI mutations and 3% PI mutations with no difference whether they met the composite outcome or not (p=0.758). However, there was a trend suggesting children with the composite outcome were more likely to carry resistance mutations to at least 2 ART classes (32%, 12/38) than the others (20%, 103/515), (p=0.099).

Discussion

Our study indicates that the incidence of mortality in HIV-infected children and adolescents dramatically decreased after the first 6 months of ART as it was 16 times lower than during the first 6 months. It emphasizes the importance of splitting *early* and *late* mortality analyses. After adjustment, being an adolescent, having persistent severely low BMI, never achieving viral suppression<400 cps/mL and one or more episode of severe anemia 6 months after ART start were independently associated with *late* new/recurrent AIDS-defining-events or deaths.

The overall mortality incidence in our study was low at 12 per 1000-PYFU, within the range 6–15 per 1000-PYFU reported in other pediatric cohorts in developed countries[2,19], but lower than the 17–144 per 1000-PYFU in developing countries[3,20-26]. Also, the dramatic decrease in mortality after a few months of ART is consistent with previous studies[19-22.] Yet, rates are difficult to compare since mortality depends on age at ART initiation which varies across cohorts. Indeed, several studies indicate lower mortality in children initiating ART at older ages, a selected population of long-term survivors[3,19,21,25,26]. In a previous assessment within the same cohort after 4.5-year follow-up, the *late* mortality incidence was similar than in this updated analysis, reflecting a stable mortality trend over time among those on long-term ART[9].

Children meeting the composite outcome had their first HIV genotypic resistance test later than those who did not reach the outcome, which may reflect delayed detection of treatment failure leading to the accumulation of resistance mutations to ART classes.

As in any cohort, unreported AIDS-events or mortality among children LTFU may lead to an underestimation of events[27]. Taking into account LTFU as a competing risk should limit this bias.

Since the number of deaths was relatively small and deaths were mainly related to AIDS-defining-events, we used a combined outcome of AIDS-defining-events or deaths to increase the statistical power in identifying most at-risk children.

In previous studies over shorter follow-up periods, baseline characteristics at ART initiation such as young age, advanced disease stage, poor immunological status, anemia and poor nutritional status were associated with mortality[3,9,19-23,28]. However, as follow-up lengthens, the significance of baseline characteristics fades while the relative contribution of time-updated variables increases. In our study, using time-updated variables, we found that children experiencing persistent poor nutritional status or severe anemia were at higher risk of adverse outcome. These factors are easily accessible to clinicians, even with limited laboratory facilities.

Our analysis clearly shows that adolescence was an independent predictor of *late* new/recurrent AIDS-defining-event or death with a risk nearly 5 times higher than in younger children. This association remained even after adjustment on viral load, suggesting the potential role of unadjusted confounders related to poor adherence. In a cohort-study in Uganda, over a median 28-month follow-up, the crude mortality rate was higher for adolescents than for younger children[6]. Also, an increasing trend in mortality has been described among perinatally HIV-infected adolescents reaching adulthood in England[29]. Maintaining ART adherence is challenging especially when children stop relying on their caregivers for their daily medication[4,30,31]. In a context where third-line ART is not readily available, this may result in adverse outcomes, including death[32,33].

Our results emphasize factors that should trigger closer follow-up and highlight the need for novel interventions to support the increasing group of adolescents at risk of poor clinical outcomes.

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Table 1. Number of events, median time to events and incidence

Outcomes	Number of events	Number of children	Time to events Median (IQR)	PYFU	Incidence (95%CI) per 1000-PYFU
Overall mortality	53	619	0.4 years (0.1 to 2.2)	4320	12 (9 to 16)
"Early"[a] deaths	29	619	0.2 years (0.1 to 0.3)	293	99 (69 to 142)
"Late"[b] deaths	24	553	2.6 years (1.3 to 6.3)	4027	6 (4 to 9)
"Late"[b] AIDS-defining-events (new or recurrent)	45[c]	553	5.1 years (1.7 to 7.2)	4027	6 (4 to 8)
"Late"[b] new AIDS-defining-events or deaths	38[d]	553	3.3 years (1.3 to 6.3)	4027	9 (7 to 12)

Abbreviations: IQR, Interquartile range; CI, confidence interval; PYFU, Person-years of follow-up.

[a] < 6 months of ART initiation. [b] ≥ 6 months of ART initiation

[c] 45 AIDS-defining-events in 24 children, children were censored at time of first AIDS event.

[d] 24 children died and 24 experienced at least one AIDS-defining-event, of whom 10 subsequently died

Table 2. Factors associated with AIDS-defining-events or death after 6 months of ART: univariable and multivariable analysis.

Characteristics	Children who survived without AIDS-defining event (n=515)	AIDS-defining events or death (n=38)*	Univariable analysis		Multivariable analysis† (N=539)	
			SHR (95%CI)	*P*	aSHR (95%CI)	*P*
At ART initiation						
Sex, Female	279/515 (54%)	23/38 (61%)	1.3 (0.7, 2.4)	0.488		
Age						
< 2 years (ref.)	117/515 (23%)	12/38 (32%)	1	0.018		
2 ≤ age < 6 years	130/515 (25%)	2/38 (5%)	0.2 (<0.1, 0.7)			
6 ≤ age < 11 years	204/515 (40%)	14/38 (37%)	0.6 (0.3, 1.4)			
age ≥ 11 years	64/515 (12%)	10/38 (26%)	1.4 (0.6, 3.3)			
CDC stage, B or C	256/494 (52%)	21/36 (58%)	1.3 (0.7, 2.6)	0.405		
CD4%, <10%	260/498 (52%)	26/38 (32%)	1.9 (0.9, 3.6)	0.079		
HIV-RNA load, ≥ 5 $\log_{10}$ copies/mL	263/438 (60%)	20/32 (63%)	1.1 (0.6, 2.3)	0.700		
Height-z-score, < -2 SD	241/515 (47%)	20/36 (56%)	1.3 (0.7, 2.4)	0.489		
Weight-z-score, < -2 SD	73/515 (14%)	8/38 (21%)	1.7 (0.8, 3.8)	0.178		
BMI-z-score, < -2 SD	107/490 (22%)	16/36 (44%)	2.8 (1.5, 5.5)	0.002		
Hemoglobin, <8 g/dL	26/481 (5%)	3/38 (8%)	1.6 (0.5, 5.4)	0.436		
ART regimen						
NNRTI-based (ref.)	413/515 (80%)	28/38 (74%)	1	0.186		
PI-based	50/515 (10%)	6/38 (16%)	2.3 (0.9, 5.5)			
NRTIs only	52/515 (10%)	4/38 (11%)	1.1 (0.4, 3.1)			
Year of ART initiation, before 2003**	430/515 (84%)	30/38 (79%)	1.2 (0.6, 2.7)	0.629		
***Time-varying variables*‡**						
Current age ≥13 years	320/512 (63%)	20/35 (57%)	4.1 (2.0, 8.4)	< 0.001	4.9 (2.4, 10.1)	< 0.001
CD4% per unit increase			0.9 (0.8, 0.9)	< 0.001		
CD4% always below 10%	5/511 (1%)	6/35 (17%)	25.9 (9.3, 72.7)	< 0.001		
HIV-RNA						
Always <400 copies/mL (ref.)	261/503 (52%)	9/34 (26%)	1	< 0.001	1	< 0.001
At least once ≥ 400 copies/mL	221/503 (44%)	16/34 (48%)	1.8 (0.8, 4.1)		2.2 (0.9, 5.1)	
Always ≥ 400 copies/mL	21/503 (4%)	9/34 (26%)	11.5 (4.4, 30.0)		12.3 (4.0, 37.6)	
Height-z-score per unit increase			0.8 (0.6, 1.0)	0.081		
Weight-z-score per unit increase			0.3 (0.2, 0.4)	< 0.001		
BMI-z-score per unit increase			0.5 (0.4, 0.6)	< 0.001		
BMI-z-score, always below -2 SD	6/511 (1%)	2/35 (6%)	7.9 (1.6, 38.1)	0.010	13.7 (3.4, 55.7)	< 0.001
Experienced anemia <8g/dL at least once	27/509 (5%)	10/35 (29%)	6.3 (3.1, 12.9)	< 0.001	4.6 (2.0, 10.5)	< 0.001

Abbreviations: SHR, subhazard ratio; aSHR, adjusted subhazard ratio; CI, confidence interval; CDC, Centers for Disease Control and Prevention.

* 24 children (4%) died and 24 (4%) experienced at least one AIDS-defining event, 10 of whom who subsequently died.

† Variables included in the multivariable analysis were: current age ≥13-years, HIV-RNA (always <400 copies/mL, at least once > 400 copies/mL and always ≥ 400 copies/mL), BMI-z-score always below -2 SD, and experienced of anemia <8g/dL at least once.

** Median duration of follow-up for children initiated on ART before 2003 was 10.9 (IQR, 4.5-12.6) and 7.8 (IQR, 4.9-9.3) for those initiated thereafter.

‡ Time-varying variables only included data available after 6 months of follow-up (6 children were excluded).