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Incidence and predictors of severe anemia in Asian HIV-infected children using first-line antiretroviral therapy

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Abstract

Objective—There are limited data on treatment-related anemia in Asian HIV-infected children.

Methods—Data from Asian HIV-infected children aged <18 years on first-line highly active antiretroviral therapy (HAART) were used. Children who had preexisting severe anemia at baseline were excluded. Anemia was graded by using the DAIDS 2004 table. Potential risk factors of severe anemia were assessed by logistic regression.

Results—Data from 1,648 children (51.9% female, 62.8% WHO stage 3/4) were analyzed. Median (IQR) age was 6.8 (3.7–9.6) years, CD4% was 9 (3–16)% and plasma HIV-RNA was 5.2

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(4.7–5.6) $\log_{10}$ copies/ml at HAART initiation in those with available testing. The most common regimens were stavudine/lamivudine/nevirapine (42%) and zidovudine/lamivudine/nevirapine (25%). Severe anemia was identified in 47 (2.9%) children after a median time of 6 months after HAART initiation with an incidence rate of 5.4 per 100 child-years. Mild anemia or moderate anemia at baseline (p=0.024 and p=0.005, respectively), previous or current use of zidovudine (p<0.0001 and p=0.013, respectively), and male sex (p=0.008) were associated with severe anemia. Higher weight-for-age z-score (p=0.004) was protective.

Conclusions—The incidence of severe anemia in Asian HIV-infected children after HAART initiation was low and mainly occurred during the first few months after HAART initiation. Mild to moderate anemia at baseline and using AZT were independent risk factors of developing severe anemia.

Keywords

pediatric HIV; Asia; antiretroviral therapy; anemia

INTRODUCTION

Increasing access to potent antiretroviral therapy (ART) in resource-limited settings has transformed the prognosis of HIV infection, but adverse events may still occur after therapy initiation. Anemia is commonly seen after ART initiation, whether due to pre-existing HIV-related bone marrow suppression or as a side effect of antiretrovirals like zidovudine (AZT) (1, 2). Anemia in HIV-infected patients has been associated with worse quality of life, disease progression and increased risk of death (1, 3–6). However, there is a lack of data on post-ART anemia in HIV-infected children in Asia (1). We aimed to describe the incidence of severe anemia after the first 24 weeks of HAART initiation in a regional observational cohort of Asian children, and identify associated factors.

METHODS

Patients

The TREAT Asia Pediatric HIV Observational Database (TApHOD) is a longitudinal, multicenter, cohort study of HIV-infected children in Asia. TApHOD is a member cohort of the US National Institutes of Health (NIH) International Epidemiology Databases to Evaluate AIDS (IeDEA) program. Detailed information on the overall study design and description of the cohort has been published elsewhere (7). In brief, children eligible for inclusion in TApHOD must be ≤18 years and have been conclusively diagnosed with HIV, by age-appropriate testing or a presumptive clinical diagnosis of HIV infection defined as meeting World Health Organization criteria for initiating HAART (8).

Data collection

The study protocol was approved by the local ethics committees or institutional review boards of each participating clinical site, the data management and analysis center (Kirby Institute for Infection and Immunity in Society, University of New South Wales, Australia), and the coordinating center (TREAT Asia/amfAR, Thailand). For this analysis, we included

children from 18 clinics in six countries; Cambodia (n=3), India (n=1), Indonesia (n=2), Malaysia (n=4), Vietnam (n=3), and Thailand (n=5), that routinely provide pediatric HIV clinical care and treatment. The database includes information about demographic characteristics, and laboratory and treatment information. This information is collected from medical records and at clinic visits, and entered into computerized databases by trained staff. Data are transferred to the Kirby Institute twice yearly for cleaning and analysis.

Eligibility criteria and definitions

The present study includes information on children (≤18 years) who received HAART between November 1997 and March 2012, and had hemoglobin (Hgb) measurements at HAART initiation and at any time during the first six months of HAART. Children who had severe anemia at baseline were excluded. We defined severe anemia according to the US NIH Division of AIDS 2004 toxicity grading table (9) as; Hgb <10 g/dL for children <21 days; Hgb <8 g/dL for children between 22 and 35 days; Hgb <7 g/dL for children between 36 and 56 days; Hgb <7.5 g/dL for children ≥57 days. Baseline values at HAART initiation for laboratory and clinical measurements were defined as the values closest to HAART initiation that fell into a window of six months prior to and seven days after HAART initiation. Children were considered lost to follow-up if the time between their last visit and the date of last data transfer was more than one year.

Statistical analysis

Baseline categorical data are presented as frequencies (%) and continuous data as medians and interquartile ranges (IQR). The Wilcoxon signed-rank test was used to test the differences in medians and Chi-squared or Fisher's exact tests to compare frequencies. Follow-up started at HAART initiation and ended at the date of diagnosis of first severe anemia, death or six months after starting HAART. The incidence rates of severe anemia in the six months after HAART were calculated per 100 child-years. If anemia occurred more than once in a single patient, the earliest event was analyzed for both overall incidence and risk factor analyses. Potential risk factors for development of severe anemia were explored by univariate and multivariate Cox proportional hazards models. The variables and possible confounders investigated included: age (<1.5, 1.5–4, 5–11, 12–14, and ≥15 years), sex, WHO clinical stage (stage 1, 2, 3 and 4), CD4% (<10, 10–14, and ≥15%), HIV- RNA $\log_{10}$copies/ml (<5 and ≥5 $\log_{10}$copies/ml), anemia (mild, moderate and no anemia), weight, height, and exposure to AZT and nevirapine (NVP). Weight and height measurements were converted into age- and sex-standardized z scores. For height-for-age z score (HAZ) the WHO 2006/2007 Child Growth Standards were used (10). WHO 1977 Standards were used for weight-for-age z scores (WAZ), to allow for scoring children >10 years of age (11). AZT and NVP use as part of a HAART regimen were included as time-dependent variables and categorized as: current use (currently receiving it or stopped ≤60 days before starting a new regimen), ever used (had used it but stopped >60 days before starting new regimen), and never used. Countries were categorized as upper middle-income (Thailand, Malaysia), lower middle-income (Indonesia, India and Vietnam) and low-income (Cambodia) (12). Variables were included in the full model if they were associated with severe anemia in the univariate analysis with $p<0.10$. A final model was then created, by using a forward step-wise with a p-

value less <0.05 was considered statistically significant in the adjusted analysis. Analyses were done with STATA version 11.0 (Stata Corp, College Station, Texas).

RESULTS

By the end of March 2012, 3448 children who had been recruited into TApHOD received HAART when aged ≤18 years. We excluded 1099 (32%) children who did not have baseline Hgb values reported, 616 (18%) with no Hgb results in the first six months after HAART, and 85 (2.5%) who had severe anemia at baseline. The analysis was consequently based on 1648 children (Table 1), of whom 1123 (68.1%) had no anemia at HAART initiation, 407 (24.7%) had mild anemia and 118 (7.2%) had moderate anemia. About half (51.9%) of the children were girls. The median age was 6.8 (IQR: 3.7–9.6) years. The median pre-HAART CD4% was 9 (IQR: 3–16)%. Eleven percent of children had a history of prior mono- and/or dual-therapy with nucleoside reverse transcriptase inhibitors (NRTI). First-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART was used in 91.7% and protease inhibitor (PI)-based HAART in 7.8%. The initial NNRTI-based HAART regimens were stavudine (d4T)/lamivudine (3TC)/NVP in 42%, AZT/3TC/NVP in 25%, AZT/3TC/efavirenz (EFV) in 17%, and d4T/3TC/EFV in 13% of children. The most common ritonavir-boosted PI-based HAART regimens were AZT/3TC/lopinavir/ritonavir (LPV/r) in 47%, d4T/3TC/LPV/r in 40%, and others (e.g., saquinavir/3TC/LPV/r, indinavir/3TC/LPV/r) in 14% of children.

The 1800 children who were excluded from the study had similar median CD4 counts and CD4% from those included. However, they were younger (median age 5.4 vs. 6.8 years), and had lower median WAZ (−3.0 vs. −2.5; p<0.0001). Excluded children were more likely to be WHO stage 4 (21% vs. 12%; p<0.0001) and WHO stage 1–2 (49% vs. 37%; p<0.0001) at baseline.

Incidence rate and predictors of severe anemia

Forty-seven (2.9%) of 1648 children had severe anemia during the first six months of HAART start (incidence rate 5.4 per 100 child-years; 95% confidence interval [CI]: 4.1–7.2). The number (%) of children who developed severe anemia during month 0–2 was 26 (55.3%), during month 2–4 was 15 (31.9%), and during month 4–6 was 6 (12.8%). The incidence was 7.4 (5.2–10.6) per 100 child-years in boys and 3.5 (2.2–5.8) per 100 child-years in girls. Table 2 shows the incidence rate of severe anemia by baseline anemia status. A Kaplan–Meier analysis to estimate the probability of severe anemia categorized by baseline anemia status is shown in Figure 1. Results of the multivariate analyses showed increased risk of early severe anemia for children who had mild anemia or moderate anemia at baseline (p=0.024 and p=0.005, respectively), previous or current use of AZT (p<0.0001 and p=0.013, respectively), and male sex (p=0.008) (Table 3). However, higher WAZ (p=0.004) was protective.

Long-term outcomes

The 407 of children who had baseline mild anemia were followed for a median (IQR) of 5.4 years (2.5–6.8) years. Among these, 134 (33%) used AZT in their initial regimen. At their

last visit, the median (IQR) Hgb was 12.0 (11.1–12.8), CD4% was 27.0 (20.0–32.0), CD4 count was 737 (497–1032) cells/mm3, and of 344 with HIV-RNA testing, 80% had HIV-RNA <400 copies/ml.

The 118 children with baseline moderate anemia were followed for a median (IQR) of 4.7 (2.1–6.6) years, and had median (IQR) Hgb of 11.8 (10.7–12.7), CD4% of 27.3 (18.4–31.8), CD4 count of 780 (468–1219), and 76% of 84 tested had HIV-RNA <400 copies/ml. Twenty three (19%) of these children used AZT in their initial regimen.

The 47 children who developed severe anemia during the first six months of ART were followed for a median of 2.7 years (IQR: 1.0–5.1). At their last visit, the median (IQR) Hgb was 11.3 (7.2–12.7), CD4% was 23.5 (7.1–32.0), CD4 count was 509 (149–1000) cells/mm^3, and of 37 with available test results, 76% had HIV-RNA <400 copies/ml.

DISCUSSION

Anemia is a common complication in HIV-infected children and is associated with disease progression and poor outcomes (1, 13). In our report, the incidence of severe anemia after ART initiation in children without severe anemia at baseline was low at 2.9%. This may reflect the historically predominant use of d4T in first-line therapy regimens in our cohort. The incidence of post-HAART severe anemia in our cohort was comparable to reports of HIV-infected adults in Asia (2), and Africa (14).

In our study, mild to moderate pre-HAART anemia, and the use of AZT were associated with post-HAART severe anemia, and higher weight-for-age z-score was protective. Although WHO guidelines recommend to avoid AZT in children with severe anemia (15), it may be appropriate to extend that to children with mild or moderate anemia in the initial phase of their treatment when other options are available, particularly in the malnourished or severely immunosuppressed. Age younger than six years, advanced HIV disease stage and presence of stunting (HAZ < −2) were associated with anemia in a study of HIV-infected children in India (13). However, we failed to identify these associations in this cohort. In addition, Shet et al. reported no association of sex and anemia in Indian HIV-infected children (13), but we found that boys had more than twice the risk of severe early anemia. The reasons for this finding are unclear. Additional studies of childhood nutrition, use of vitamin and mineral supplements, and hemoglobinopathy in the cohort may help explain our results.

The limitations of the study are primarily reflective of the observational nature of these data and the availability of lab-based monitoring of children in our cohort on HAART. Around half of the children in our cohort were excluded from analysis as they were missing baseline pre-HAART Hgb levels. We performed an additional subgroup analysis for occurrence of severe anemia among 445 children who did not have baseline Hgb levels, but had test results reported during the first six months of HAART. Twenty two (4.9%) of these children had severe anemia, with a median Hgb level of 6.5 (5.3–6.8) g/dL. This was higher than in our analysis sub-cohort, and their exclusion may have biased our results towards children who were more likely to have Hgb measurements, whether due to disease progression,

malnutrition, or level of clinic resources. In addition, we did not have clinical information about other possible causes of anemia (e.g., history of hemoglobinopathy, iron deficiency anemia, concurrent bone marrow-suppressive medications), nor additional clinical management or outcomes data for the patients who developed severe anemia. Kosalaraksa et al. reported that mild to moderate anemia was common (around 50%) among 299 ART-naïve Thai and Cambodian children without advanced HIV (16). However, prevalence of iron deficiency anemia was low (2.7%) and the majority of cases were caused by carriage of a thalassemia trait (47%) and anemia of chronic disease (42%) (16). Therefore, iron supplementation in anemic HIV-infected Asian children without further assessment of red blood cell indices or iron levels may not necessarily be beneficial.

In conclusion, the incidence of severe anemia in Asian HIV-infected children was low (2.9%) during their initial period of HAART. However, mild to moderate anemia at baseline and use of AZT were independent risk factors for developing severe anemia. Monitoring of Hgb during the first few months of HIV treatment, either for children with baseline mild to moderate anemia or for children using AZT, is warranted and should be implemented more consistently in our region.

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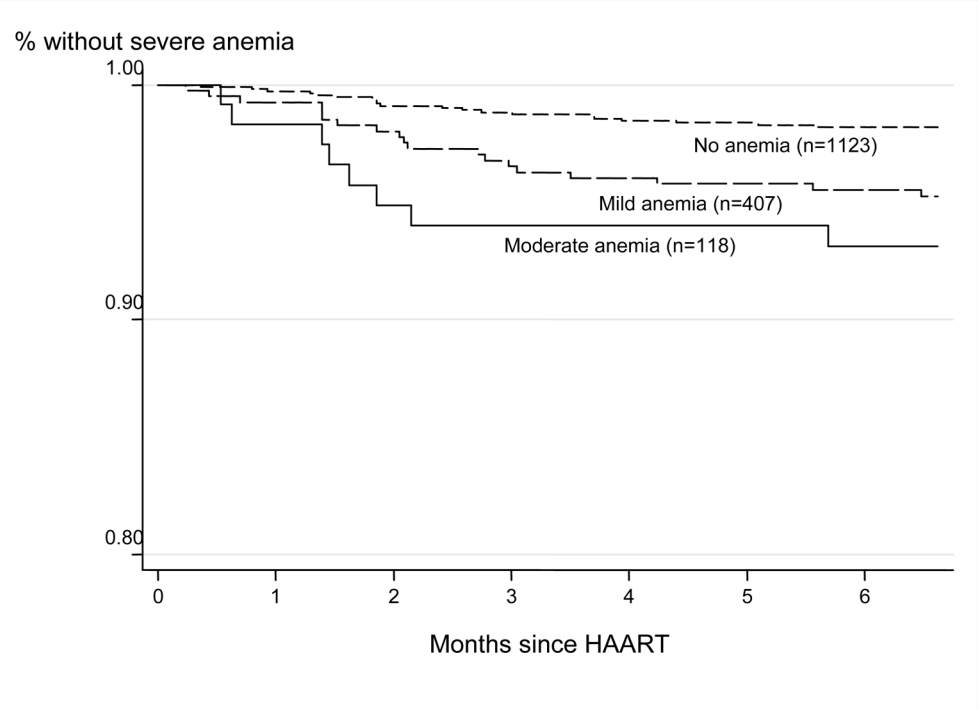

Figure 1.

Kaplan–Meier estimates of the probability of severe anemia in 1648 children in the first six months of HAART; by anemia status at baseline.

HAART, highly active antiretroviral therapy

Table 1

Patient characteristics at HAART initiation

Characteristics	All (N=1648)	No anemia (N=1123)	Mild anemia (N=407)	Moderate anemia (N=118)
Age in years – median (IQR)	6.8 (3.7–9.6)	7.3 (4.5–10.0)	5.9 (2.9–8.6)	5.1 (2.1–8.0)
Female sex – n (%)	51.9	52.8	49.4	51.7
Country by income level – n (%)				
Thailand/Malaysia	1087 (66.0%)	758 (67.5%)	256 (62.9%)	73 (61.9%)
Indonesia/India/Vietnam	304 (18.5%)	199 (17.7)	75 (18.4%)	30 (25.4%)
Cambodia	257 (15.6%)	166 (14.8%)	76 (18.7%)	15 (12.7%)
CD4% - median (IQR)	9 (3–16)	11 (5–17)	6 (2–13)	6 (2–11)
Missing data	123	82	34	7
CD4 count, cells/mm^3 – median (IQR)	228 (60–513)	273 (89–547)	115 (23–377)	122 (24–400)
Missing data	136	77	50	9
HIV-RNA (log_{10}copies/ml) – median (IQR)	5.2 (4.7–5.6)	5.0 (4.5–5.5)	5.4 (5.0–5.8)	5.5 (5.1–5.9)
Missing data	853	553	227	73
WHO clinical staging – n (%)				
Stage 1/2	612 (37.1)	495 (44.1)	152 (37.3)	26 (9.3)
Stage 3	846 (51.3)	499 (44.4)	145 (35.6)	42 (35.6)
Stage 4	190 (11.5)	129 (11.5)	110 (27.0)	50 (42.4)
Weight for age z-score – median (IQR)	−2.3 (−3.6 to −1.2)	−1.9 (−3.1 to −1.0)	−3.1 (−4.2 to −2.0)	−3.5 (−4.9 to −2.3)
Missing data	51	31	14	6
Height for age z-score – median (IQR)	−2.2 (−3.2 to −1.3)	−2.0 (−2.9 to −1.1)	−2.7 (−3.6 to −1.8)	−3.2 (−3.9 to −2.4)
Missing data	111	65	33	13
Hemoglobin (g/dL) – median (IQR)	10.6 (9.6–11.6)	11.2 (10.5–12.0)	9.3 (9.0–9.6)	8.1 (7.8–8.3)

HAART, highly active antiretroviral therapy.

Classification of anemia was based on the US NIH Division of AIDS 2004 toxicity grading table (9).

Table 2

Incidence of severe anemia in the first six months of HAART by baseline anemia status.

Anemia at baseline	Children (N=1648)	Severe anemia	Incidence per 100 child years (95% CI)	Hgb at HAART, gd/L median (IQR)	Hgb at severe anemia, gd/L median (IQR)
No anemia	1123	20	3.3 (2.2–5.2)	10.9 (10.3–11.3)	6.6 (5.4–7.1)
Mild anemia	407	19	9.0 (5.7–14.0)	9.4 (9.0–9.7)	6.3 (4.5–6.9)
Moderate anemia	118	8	13.3 (6.7–26.6)	8.1 (7.7–8.3)	6.4 (5.5–7.1)

HAART, highly active antiretroviral therapy; Hgb, hemoglobin.

Classification of anemia was based on the US NIH Division of AIDS 2004 toxicity grading table (9).

Table 3

Factors associated with the incidence of severe anemia within the first six months of HAART initiation.

Characteristics	Events	Person years	Univariate		Adjusted	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age, years[a]						
<1.5	8	81	2.33 (0.94–5.78)	0.069	1.10 (0.40–3.07)	0.852
1.5–4.9	17	212	1.89 (0.89–4.03)	1.00	1.56 (0.71–3.40)	0.264
5–11.9	11	320	0.81 (0.35–1.87)	0.626	0.78 (0.34–1.80)	0.559
>=12	11	259	1.0			
Sex						
Female	16	454	1.0	-	1.0	
Male	31	418	2.10 (1.15–3.84)	0.016	2.36 (1.25–4.48)	0.008
CD4% [a]						
0–9%	33	403	2.50 (1.15–5.40)	0.02	1.89 (0.79–4.48)	0.153
10–14%	3	160	0.58 (0.15–2.17)	0.415	0.68 (0.17–2.64)	0.576
≥15%	8	245	1.0		1.0	
Missing	3	64				
HIV-RNA at baseline[a]						
<5 $\log_{10}$	3	158	1.0			
≥5 $\log_{10}$	17	264	3.36 (0.98–11.4)	0.053	2.43 (0.70–8.40)	0.160
Missing	27	450				
WHO stage [a]						
1–2	13	430	1.0		1.0	
3	18	269	2.20 (1.08–4.49)	0.030	2.03 (0.94–4.39)	0.072
4	16	173	3.04 (1.46–6.31)	0.003	2.38 (1.03–5.49)	0.042
Weight-for-age z-score		-	0.77 (0.69–0.87)	<0.0001	0.80 (0.68–0.93)	0.004

Characteristics	Events	Person years	Univariate		Adjusted	
			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Height-for-age z-score[a]		-	0.82 (0.66–1.02)	0.075	1.25 (0.90–1.73)	0.185
Anemia at HAART						
No anemia	20	599	1.0		1.0	
Mild	19	212	2.67 (1.43–5.00)	0.002	2.16 (1.11–4.22)	0.024
Moderate	8	60	3.98 (1.75–9.03)	0.001	3.77 (1.49–9.54)	0.005
Zidovudine use						
Never used	13	498	1.0		1.0	
Ever used	33	367	3.44 (1.80–6.52)	<0.0001	5.30 (2.67–10.53)	<0.0001
Currently used	1	7	11.90 (1.47–96.53)	<0.020	14.72 (1.78–121.97)	0.013
Nevirapine[a]						
Never used	23	320	1.0			
Ever used	23	527	0.61 (0.34–1.08)	0.089	0.93 (0.50–1.71)	0.806
Currently used	1	25	0.84 (0.11–6.30)	0.867	1.27 (0.17–9.79)	0.816

[a]These variables were only significant in the univariate analysis. The hazard ratio was obtained by adding each to the final model.