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Brief communication (Original)

HIV-infected children in the Asia-Pacific region with baseline severe anemia: antiretroviral therapy and outcomes

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Background: Severe anemia is common among children infected with human immunodeficiency virus (HIV). The choice of antiretroviral (ART) regimen needs careful consideration. No information is available regarding the initial ART regimens used in the Asia–Pacific region and the rate of switch of ART regimens in HIV-infected children with severe anemia.

Objectives: To study the initial ART regimens and the rate of switch of ART regimens used during the first 36 months in HIV-infected children with severe anemia and to evaluate their clinical and laboratory outcomes.

Methods: We analyzed regional cohort data of 130 Asian children aged <18 years with baseline severe anemia (hemoglobin <7.5 g/dl) who started antiretroviral therapy (ART) between January 2003 and September 2013.

Results: At ART initiation, median age was 3.5 years old (interquartile range (IQR) 1.7 to 6.3) and median hemoglobin was 6.7 g/dL (IQR 5.9-7.1, range 3.0-7.4). Initial ART regimens included stavudine (85.4%), zidovudine (13.8%), and abacavir (0.8%). In 81 children with available hemoglobin data after 6 months of ART, 90% recovered from severe anemia with a median hemoglobin of 10.7 g/dL (IQR 9.6-11.7, range 4.4-13.5). Those starting AZT-based ART had a mortality rate of 10.8 (95% confidence interval (CI) 4.8-23.9) per 100 patient-years compared to 2.7 (95% CI 1.6-4.6) per 100 patient-years among those who started d4T-based ART.

Conclusions: With the phase-out of stavudine, age-appropriate non-zidovudine options are needed for younger Asian children with severe anemia.

Keywords: Antiretroviral therapy, Asia, HIV-infected children, severe anemia

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Anemia is common in human immunodeficiency virus (HIV)-infected individuals both before and during antiretroviral therapy (ART) and has multiple causes [1]. Because of its hematologic toxicity, use of zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI), is not recommended for children or adolescents with anemia [2, 3]. A suggested alternative to AZT is abacavir (ABC), but it has been inconsistently available because of its cost and non-procurement by national programs for pediatric HIV care in many low- and middle-income countries (LMIC) in Asia. Tenofovir (TDF) is now recommended for use in older children [2], but it is not approved for children younger than 2 years of age, and pediatric formulations have not been available in most LMICs. Stavudine (d4T) can be used in children with anemia for whom ABC and TDF are not options, whether because of access issues or ineligibility. However, d4T is associated with multiple long-term side effects (e.g., lipoatrophy, lipohypertrophy, and hyperlactatemia), and the World Health Organization (WHO) has recommended it be phased out globally [2, 3]. Pediatric ART outcome studies frequently exclude children with severe anemia from follow-up analyses [4-6]. We aimed to describe initial ART regimen use and rates of switch during the first 36 months treatment in HIV-infected children with pre-ART severe anemia, and to assess anemia and treatment outcomes classified by type of antiretroviral exposure.

Methods

Study population

The TREAT Asia Pediatric HIV Observational Database (TApHOD) is a longitudinal, multicenter, cohort study of HIV-infected children in Asia that has been described elsewhere [7]. For this analysis, we included children from 18 clinics in 6 countries: Thailand (n = 5), Malaysia (n = 4), Cambodia (n = 3), Vietnam (n = 3), Indonesia (n = 2), and India (n=1); these referral clinics routinely provide pediatric HIV clinical care and treatment. The database includes demographic characteristics, laboratory testing, and treatment information, which are collected from medical and clinical records and entered into computerized databases by trained staff. Data are transferred to the Kirby Institute twice yearly for cleaning and analysis.

For this report, we included children aged <18 years who initiated highly active ART (HAART; defined as a combination of ≥3 antiretrovirals) between January 2003 and September 2013, and who had available baseline pre-ART hemoglobin (Hb) data. We defined severe anemia in accordance with the United States National Institutes of Health Division of AIDS (DAIDS) 2004 toxicity grading table: Hb <7.5 g/ dL for children ≥57 days [8]. Baseline values for Hb measurements were defined as the values closest to a window of 6 months before and 7 days after HAART initiation. Children were considered lost to follow-up if the time between their last visit and the date of the last data transfer was ≥12 months without documentation of transfer or death.

The baseline data included: age (<1, 1-5, 6-10, and ≥11 years), sex, height- and weight-for-age *z*-scores (within ± 3months of baseline), CD4 cell percentage (within ± 3 months of baseline), HIV viral load (within 3 months before baseline up to 2 weeks after baseline), WHO stage, initial ART regimen, year of ART initiation and country income status as defined by The World Bank [9].

Statistical analyses

Baseline categorical data are presented as frequencies (%) and continuous data as medians and interquartile ranges (IQR). Height-for-age *z*-scores for children <61 months and for children ≥61 months old were calculated using the WHO 2006 child growth standards and macros (ages 6 months to 5 years) [10] and the WHO 2007 child growth standards and macros (age 5-19 years) [11], respectively. Weight-for-age z-scores were calculated using the WHO child growth standards and macros for 1977 to allow for inclusion of all age groups [12].

Recovery from severe anemia, CD4%, AZT-based regimen modification (change to a regimen not containing AZT), death, and loss to follow-up were compared between those initiated on AZT- and non-AZT-containing regimens. All longitudinal analyses were performed on an intention-to-treat basis. Median CD4 percentage and the proportions "severe anemia-free" were evaluated in 6 ± 3-monthly intervals up to 3 years of follow-up (i.e., 3-9, 9-15, 15-21, 21-27, 27-33, and 33-39 months). If, for any given time interval, multiple values were recorded for a patient, the value closest to the 6-monthly time point was used. Kaplan–Meier method was used to evaluate the probability of AZT modification, death, and loss to follow-up over time. Time-to-event was left-censored. Right censoring occurred at the date of the last clinic visit. Stata version 12.1 was used for all statistical analyses.

Ethical considerations

This study was approved by the Institutional Review Boards at all of the data-contributing sites, the data management and analysis center (Kirby Institute, University of New South Wales, Sydney, Australia), and the coordinating center (TREAT Asia/amfAR, Bangkok, Thailand). The requirement for informed consent was waived because only anonymized patient data collected during routine patient care were used for analysis.

Results

Of 3398 children in the database starting first-line ART between January 2003 and September 2013, 2365 (69.6%) had a documented baseline Hb measurement; of whom 130 (5.5%) met the definition for severe anemia (**Table 1**). Sixty-nine patients (53.1%) were male and the median age was 3.5 years old (IQR 1.7 to 6.3). The weight-for-age and height-for-age *z*-scores were < –2.5 in 82.5% and 71.0%, respectively. The CD4 was <15% in 75.9%, and 81.6% were in WHO stage 3 or 4. The HIV viral load was >100,000 copies/mL in 27 of 37 (73.0%) children with available data, median (IQR): 387,312 (1000 to 750,000). The median Hb level at ART initiation was 6.7 g/dL (IQR 5.9-7.1, range 3.0–7.4). The prevalence of severe anemia at ART initiation was 7.1% (40/561) between 2003-2005, 5.7% (49/864) between 2006-2008, and 4.4% (41/940) between 2009-2013.

The initial ART regimens included d4T in 111 children (85.4%), AZT in 18 children (13.8%), and ABC in one child (0.8%). d4T-containing regimens were used in 33 children (82.5%) between 2003-2005, 45 (91.8%) between 2006 and 2008, and 33 (80.5%) between 2009 and 2013. ABC was used in one patient with pre-ART severe anemia during the 2006-2008 period. Forty-four children (33.8%) were from upper middle-income countries and 86 (66.2%) were from low or low-middle-income countries.

Table 1. Baseline characteristics of HIV-infected children with severe anemia

Characteristics	Number (%)
Age (years)	
<1	19 (14.6%)
1 to 5	66 (50.8%)
6 to 10	32 (24.6%)
>10	13 (10.0%)
Median (IQR)	3.48 (1.67 to 6.32)
Height-for-age *z*-score n = 114	
> –1.5	9 (7.9%)
–1.5 to –2.5	24 (21.1%)
< –2.5	81 (71.0%)
Median (IQR)	–-3.2 (–4.2 to –2.3)
Weight-for-age *z*-score n = 126	
> –1.5	9 (7.1%)
–1.5 to –2.5	13 (10.3%)
< –2.5	104 (82.5%)
Median (IQR)	–4.3 (–6.4 to –2.9)
CD4 cell percentage n = 116	
≥25	7 (6.0%)
15 to 24	21 (18.1%)
10 to 14	18 (15.5%)
<10	70 (60.4%)
Median (IQR)	5.9 (1.0 to 13.9)
WHO category	
1 or 2	24 (18.5%)
3	63 (48.5%)
4	43 (33.1%)
Year of ART initiation	
2003 to 2005	40 (30.8%)
2006 to 2008	49 (37.7%)
2009 to 2013	41 (31.5%)

IQR = interquartile range; WHO = World Health Organization; ART = antiretroviral therapy; AZT = zidovudine; d4T = stavudine; ABC = abacavir

Outcomes at 36 months after ART initiation

The median Hb 6 months after ART initiation was 10.7 g/dL (IQR 9.6–11.7, range 4.4–13.5) in the 81 of 130 children (62.3%) with available data; severe anemia persisted in 9.9%. At 36 months, 48 children had Hb tested and severe anemia persisted in 4.2% (median 11.9, IQR 10.7–12.6, range 6.6–14.0 g/dL). Of 130 children, 116 (89.2%) had a baseline CD4%, with a median of 5.9% (IQR1.0–13.9). At 6 months after ART initiation, the median CD4% (n = 91) was 16.0% (IQR 10.0–26.9), and at 36 months, median CD4% (n = 68) was 29.6% (IQR 25.9–36.0). By 36 months, growth improved with the weight-for-age z-score (n = 65) of < –2.5 decreased from 82.5% to 30.8% and height-for-age z-score (n = 65) of < –2.5 decreased from 71.0% to 36.9%.

Current outcomes

By September 2013, 3 of the 18 children with severe anemia who started ART with an AZT-based regimen were switched off AZT at a rate of 6.3 (95% CI 2.0–19.6) switches per 100 patient-years. Two of these 3 children were switched at 1.6 months, and the other at 11.3 months (**Table 2**). By comparison, 60 of the 111 severely anemic children who started a d4T-based regimen were switched off d4T at a rate of 17.0 (95% CI 13.2-21.9) switches per 100 patient-years with a median time to d4T switch of 2.5 (IQR 1.5-4.2) years.

Twenty deaths occurred during the follow-up period at a rate of 3.5 (95% CI 2.3-5.5) per 100 patient-years. Those starting AZT-based first-line ART had a mortality rate of 10.8 (95% CI 4.8-23.9) deaths per 100 patient-years compared to 2.7 (95% CI 1.6-4.6) deaths per 100 patient-years among those who started d4T-based first-line ART. Loss to follow-up occurred in 15 children at a rate of 2.6 (95%CI 1.6-4.4) per 100 patient-years.

Discussion

The overall prevalence of severe anemia at ART initiation in our cohort was 5.5%, which is similar to the 6% among 2117 children in the pediatric West African Database on AIDS (pWADA) [13]. The findings that most of our patients with severe anemia had poor growth and advanced disease stages were also consistent with other studies [5, 14, 15]. The prevalence of severe anemia at ART initiation in our cohort decreased from 7.1% in 2003-2005 to 4.4% in 20092013, which were likely because of parallel increases in earlier HIV diagnosis and improved linkage to care within the region. However, the initial ART use in these children was mainly d4T-based (≥80%) across the 3 time periods and the time to switching off of d4T was prolonged, reflecting limited drug availability, the relatively slow pace of change of national pediatric treatment guidelines, and the ongoing procurement of d4T for children in the Asia–Pacific region as late as 2013.

Table 2. Outcomes of children initiated on (a) AZT-containing regimens (n = 18) and (b) d4T-containing regimens (n = 111) over 36 months of follow-up

Months of antiretroviral therapy	0	6	12	18	24	30	36
(a) Children on AZT, number	**18**	**9**	**8**	**7**	**6**	**6**	**6**
Cumulative AZT modifications	0	2	3	3	3	3	3
Deaths	0	4	4	5	5	5	5
Loss to follow-up*	0	2	2	2	2	2	2
Censored	0	1	1	1	2	2	2
(b) Children on d4T, number	**111**	**102**	**85**	**74**	**64**	**54**	**46**
Cumulative d4T modifications	0	0	9	16	22	30	36
Deaths	0	7	10	12	13	13	13
Loss to follow-up**	0	1	3	3	4	5	6
Censored	0	1	1	6	8	9	10

*3.6 (95% CI 0.9–14.4) per 100 patient-years
**2.6 (95% CI 1.5–4.4) per 100 patient-years
AZT = zidovudine, d4T = stavudine

After ART initiation, 90% of children with available follow-up Hb data recovered from their severe anemia by 6 months. The mortality rate was much higher among severely anemic children starting AZT-containing first-line regimens compared to d4T-containing regimens. Although it was not possible to compare these 2 groups because of the small sample sizes, this represents a concerning finding.

Our study has several limitations. In addition to small sample sizes, we did not have data on specific etiologies of anemia beyond the potential toxicities of individual antiretrovirals, nor did we have details on treatment of opportunistic infections (e.g., with medicines impacting bone marrow function), or documentation of blood transfusions. Moreover, because of the observational nature of our cohort, we had inconsistent Hb monitoring data in terms of the frequency and timing of testing. Because malaria is uncommon in the urban referral settings of our cohort, these data cannot be generalized to malarious areas.

Conclusion

This study provides useful insights into the impact of different ART regimens on outcomes of HIV-infected Asian children with severe anemia. Where ARV options are limited and when younger children are ineligible for TDF, it may be necessary to use AZT or short-course d4T for those with preexisting moderate-to-severe anemia, rather than to delay ART to treat with iron or other nutritional supplements and risk further morbidity and mortality. With the phase-out of d4T, age-appropriate non-AZT options are needed for younger children with severe anemia in this region.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

References

1. Calis JC, van Hensbroek MB, de Haan RJ, Moons P, Brabin BJ, Bates I. HIV-associated anemia in children: a systematic review from a global perspective. AIDS. 2008; 22:1099-112.
2. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. [online] 2011. [cited 2015 Feb 19]. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf
3. World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach 2010 revision. Geneva: WHO; 2010.
4. Leroy V, Malateste K, Rabie H, Lumbiganon P, Ayaya S, Dicko F, et al. Outcomes of antiretroviral therapy in children in Asia and Africa: a comparative analysis of the IeDEA pediatric multiregional collaboration. J Acquir Immune Defic Syndr. 2013; 62: 208-19.
5. Nyesigire Ruhinda E, Bajunirwe F, Kiwanuka J. Anaemia in HIV-infected children: severity, types and effect on response to HAART. BMC Pediatr. 2012; 31:12:170.
6. Bunupuradah T, Kariminia A, Chan KC, Ramautarsing R, Huy BV, Han N, et al. Incidence and predictors of severe anemia in Asian HIV-infected children using first-line antiretroviral therapy. Int J Infect Dis. 2013; 17:e806-10.
7. Kariminia A, Chokephaibulkit K, Pang J, Lumbiganon P, Hansudewechakul R, Amin J, et al. Cohort profile: the TREAT Asia pediatric HIV observational database. Int J Epidemiol. 2010; 40:15-24.
8. National Institute of Allergy and Infectious Disease. The division of AIDS table for grading the severity of adult and pediatric adverse events, version 1.0, December 2004; clarification August 2009.
9. The World Bank [online] 2015. [cited 2015 Feb 19]. Available from: *http://data.worldbank.org/country*
10. WHO child growth standards and macros (ages 6 months–5 years). [online] 2015. [cited 2015 Feb 19]. Available from: http://www.who.int/childgrowth/software/en
11. WHO child growth standards and macros (ages 5–19 years). [online] 2011. [cited 2015 Feb 19]. Available from: *http://www.who.int/growthref/en*
12. WHO child growth standards and macros, 1977.
13. Renner LA, Dicko F, Kouéta F, Malateste K, Gueye RD, Aka E, et al. Anaemia and zidovudine-containing antiretroviral therapy in paediatric antiretroviral programmes in the IeDEA Paediatric West African Database to evaluate AIDS. J Int AIDS Soc. 2013; 16: 18024.
14. Shet A, Arumugam K, Rajagopalan N, Dinakar C, Krishnamurthy S, Mehta S, et al. The prevalence and etiology of anemia among HIV-infected children in India. Eur J Pediatr. 2012; 171:531-40.
15. Shet A, Mehta S, Rajagopalan N, Dinakar C, Ramesh E, Samuel NM, et al. Anemia and growth failure among HIV-infected children in India: a retrospective analysis. BMC Pediatr. 2009; 9:37.