DOI: 10.1111/j.1468-1293.2008.00560.x
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HIV Medicine (2008), **9**, 317–321

SHORT COMMUNICATION

Haematological changes after switching from stavudine to zidovudine in HIV-infected children receiving highly active antiretroviral therapy

L Aurpibul,[1] T Puthanakit,[1] T Sirisanthana[1] and V Sirisanthana[2]

[1]*Research Institute for Health Sciences and* [2]*Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Objective

In resource-limited countries, stavudine (d4T) is commonly used as part of the initial highly active antiretroviral therapy (HAART) regimen. Many patients who subsequently develop lipodystrophy switch from d4T to zidovudine (ZDV), a drug that can be myelotoxic. We aimed to study the spectrum and severity of haematological changes following this substitution.

Methods

This was a retrospective cohort study. The inclusion criteria were as follows: HIV-infected children were included who (1) were 2–15 years old at the time of HAART initiation, (2) had not been diagnosed as having haematological diseases, (3) had been receiving a first HAART regimen consisting of either nevirapine or efavirenz, together with lamivudine and d4T, for at least 48 weeks and (4) had switched from d4T to ZDV at least 48 weeks previously.

Results

Seventy-eight children were included in the study. Thirty-six (46%) were male. The mean age was 10.3 years (standard deviation 3.1 years). The switch had been made a median time of 65 weeks (range 48–97 weeks) previously. There was no significant change in CD4 lymphocyte count or percentage, or HIV RNA level, after the switch. There was a statistically significant decrease in haemoglobin level (12.6 *vs.* 12.1 g/dL; $P<0.001$), total white blood cell (WBC) count (8088 *vs.* 6910 cells/μL; $P<0.001$) and absolute neutrophil count (ANC) (4320 *vs.* 3448 cells/μL; $P<0.001$). However, the decreases never reached Division of AIDS grade 3 or 4 severity, and none of the patients had clinical symptoms or signs of anaemia, leukopenia, or neutropenia. No participant had to discontinue ZDV during the 48-week follow-up period.

Conclusion

In a paediatric population, statistically significant decreases in haemoglobin level, WBC count and ANC occurred following the substitution of d4T with ZDV, but the magnitudes of the decreases were small and not clinically significant.

Keywords: anaemia, children, HIV, stavudine, zidovudine

Received: 31 October 2007, accepted 22 January 2008

Introduction

HIV infection is a major global health challenge, with 33.2 million people currently infected world-wide, including 2.5 million children [1]. Highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality of HIV-infected adults and children in developed countries and certain developing countries, including Thailand [2–4]. As first-line HAART in resource-limited countries, the World Health Organization (WHO) has recommended regimens consisting of a nonnucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs), lamivudine (3TC) together with either zidovudine (ZDV) or stavudine (d4T) [5].

Correspondence: Dr Virat Sirisanthana, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand 50200. Tel: + 66-53-946471; fax: + 66-53-894138; e-mail: vsirisan@mail.med.cmu.ac.th

Most HIV-infected children in developing countries present to the health care system late in the course of their illnesses and, as concurrent malnutrition is common, they are frequently anaemic [6–8]. ZDV is not therefore usually prescribed because it may further suppress the bone marrow. Thus, the first-line HAART regimen in Thai HIV-infected children almost always consists of d4T, 3TC and an NNRTI. d4T can cause lipodystrophy, the incidence of which correlates with the duration of treatment [9]. In a recent study, we found that 9, 47 and 65% of HIV-infected children taking d4T as part of their HAART regimen developed lipodystrophy at weeks 48, 96 and 144 respectively after the initiation of HAART [10]. WHO guidelines recommend switching d4T to abacavir (ABC) in children who develop lipodystrophy [5]. As ABC is not widely available in resource-limited countries because of its high cost, ZDV, which is associated with a lower incidence of lipodystrophy [11], is used as an alternative. The objective of this study was to determine the spectrum and severity of haematological changes after switching from d4T to ZDV in children who had been on a d4T-containing regimen.

Patients and methods

We performed a retrospective chart review as a substudy of a prospective longitudinal cohort study to assess HAART treatment outcomes [2,4]. The inclusion criteria were as follows: HIV-infected children were included who (1) were 2–15 years old at the time of HAART initiation, (2) had not been diagnosed as having haematological diseases (including haemolytic anaemia, thrombocytopenia, and haemoglobinopathy), (3) had been receiving their first HAART regimen consisting of either nevirapine (NVP) or efavirenz (EFV), together with 3TC and d4T, for at least 48 weeks, and (4) had switched from d4T to ZDV at least 48 weeks previously. The clinical stage of disease was determined according to the 1994 US Centers for Disease Control and Prevention (CDC) revised classification [12]. In children who had initially started with an NVP-containing regimen, switching was carried out using a fixed-dose combination tablet (GPOvir Z250®, containing 250, 150 and 200 mg of ZDV, 3TC and NVP, respectively; Thai Government Pharmaceutical Organization, Bangkok, Thailand). In those who had initially started with an EFV-containing regimen, substitution was carried out using a tablet containing a fixed-dose combination of ZDV and 3TC (Zilavir®, containing 300 mg of ZDV and 150 mg of 3TC; Thai Government Pharmaceutical Organization) and another tablet of EFV. The fixed-dose combination tablets were prescribed according to the child's body weight, delivering a ZDV dose of 137–300 mg/m^2/dose.

At the time of switching, parents or guardians were informed of the reason for the switch and the benefits and potential side effects of ZDV. Patients were followed at 12-week intervals as stipulated in the main study. All patients were followed for at least 48 weeks after switching to ZDV. During each visit, we reviewed the patient's medical history and performed a physical examination. Blood collection for haematological tests, blood chemistry tests, CD4 lymphocyte count and percentage, and plasma HIV RNA level were routinely performed at 24-week intervals in the main study. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0 (December 2004) was used to assess the severity of haematological changes [13]. Briefly, grade 1 and 2 decreased haemoglobin levels were defined as haemoglobin levels of 8.5–10.0 and 7.5–8.4 g/dL, respectively. Grade 1 and 2 decreased white blood cell (WBC) counts were defined as WBC counts of 2000–2500 and 1500–1999 cells/μL, respectively. Grade 1 and 2 decreased absolute neutrophil counts (ANCs) were defined as ANCs of 1000–1300 and 750–999 cells/μL, respectively.

CD4 lymphocyte counts and percentages, HIV RNA levels, and haematological parameters (haemoglobin level, WBC count, ANC and platelet count) were compared using the paired-sample *t*-test at weeks 0 and 48 of d4T-containing HAART, and at two time-points after switching to ZDV. Data were analysed with SPSS software version 11.5 (SPSS Inc., Chicago, IL, USA). A two-sided *P*-value of <0.05 was considered significant.

The study was approved by the research ethics committee of Chiang Mai University. Informed consent for participation in this study was obtained from each child's parent or legal guardian.

Results

Seventy-eight children were included in the study. Thirty-six (46%) were male. The mean age at the time of HAART initiation was 7.4 years [standard deviation (SD) 2.8 years]. The mean time on a d4T-containing regimen prior to switching to ZDV was 144 weeks (range 48–192 weeks). At the time of switching from d4T to ZDV, almost all children were in immune recovery (defined as a CD4 lymphocyte percentage $\geq 25\%$) and had complete viral suppression. They had no concurrent illnesses and were not taking any concomitant medications that could cause bone marrow suppression. The switch had been made a median of 65 weeks (range 48–97 weeks) previously. The median times from the switch to the first and second blood collections were 15 weeks (range 3–26 weeks) and 39 weeks (range 27–50 weeks), respectively. Haematological parameters, CD4 lymphocyte count and percentage, and HIV RNA levels at specified time-points are shown in Table 1.

At the time of switching to ZDV, all but one child had normal haemoglobin levels. The one exception had a grade

Table 1 Haematological parameters of 78 HIV-infected children who switched to zidovudine

Time-point	Haemoglobin (g/dL)	Total white blood cell count (cells/μL)	Absolute neutrophil count (cells/μL)	Platelet count (cells/μL)	CD4 lymphocyte count (cells/μL)	CD4 lymphocyte percentage	HIV RNA PCR (log_{10} copies/mL)
Baseline (week 0) ($n = 78$)	10.1 (1.6)	8069 (3345)	4487 (2539)	291 201 (134 485)	200 (236)	6 (6)	5.3 (0.4)
During treatment with stavudine							
Week 24 ($n = 78$)	11.4 (1.3)	8721 (3272)	4534 (2694)	381 372 (123 308)	480 (423)	14 (7)	1.8 (0.4)
Week 48 ($n = 78$)	12.1 (1.1)	8494 (2670)	4145 (1866)	364 180 (107 311)	569 (319)	17 (7)	1.8 (0.4)
P-value*	<0.01	0.32	0.28	<0.01	<0.01	<0.01	<0.01
At the time of switching	12.6 (1.3)	8088 (1962)	4320 (1642)	352 680 (82 817)	688 (298)	26 (7)	1.9 (0.6)
After switching to zidovudine							
First blood collection ($n = 78$)	12.1 (1.5)	6910 (1957)	3448 (1566)	358 436 (101 495)	716 (316)	27 (7)	1.9 (0.7)
P-value**	<0.01	<0.01	<0.01	0.54	0.27	0.04	0.36
Second blood collection ($n = 78$)	12.2 (1.3)	6947 (1933)	3377 (1703)	371 892 (113 905)	760 (313)	27 (7)	1.9 (0.7)
P-value**	<0.01	<0.01	<0.01	0.09	0.01	0.01	0.25

Data are mean (standard deviation).
**P*-value: comparing week 48 of treatment with baseline.
***P*-value: compared with values at the time of switching.

1 decreased haemoglobin level. At the first time-point after switching from d4T to ZDV, 54 children (69%) had a decrease in haemoglobin relative to the time of switching. The mean decrease was 1.0 g/dL (SD 0.8 g/dL). The child with a grade 1 anaemia became more anaemic, at grade 2 severity. No other child had grade 2, 3 or 4 decreased haemoglobin levels.

All but one child had a normal WBC count at the time of switching to ZDV, the exception having a grade 1 decreased WBC count. At the first time-point following switching from d4T to ZDV, 59 children (76%) had a WBC count lower than that at the time of switching. The mean decrease in WBC count was 2002 cells/μL (SD 1448 cells/μL). The child with pre-existing grade 1 leukopenia recovered, but one other child developed a grade 1 decreased WBC count after switching. No child had a grade 2, 3 or 4 decreased WBC count.

At the time of switching to ZDV, all but one child had a normal ANC; the exception had a grade 1 decreased ANC. At the first time-point following switching from d4T to ZDV, 55 children (71%) had an ANC lower than that at the time of switching. The mean ANC decrease was 1801 cells/μL (SD 1550 cells/μL). The child with pre-existing grade 1 neutropenia continued to have a grade 1 decreased ANC following switching to ZDV. Five other children (6%) developed a new grade 1 or 2 decreased ANC. No child had a grade 3 or 4 decreased ANC.

At the second time-point, there were no further significant decreases in any haematological parameters compared with the first time-point. No child developed thrombocytopenia. The children with haematological changes did not have any abnormal clinical symptoms or signs. No child had to discontinue ZDV during the 48 weeks of follow-up.

At baseline, 43 children were in CDC clinical category N or A, and 35 were in category B or C. We compared the haematological parameters of these two groups of children at various time-points as indicated in Table 1. At baseline, there was a significant difference in haemoglobin level between children in CDC category N or A when compared with those in category B or C (10.6 *vs.* 9.5 g/dL; $P = 0.004$); there was no significant difference in WBC count, ANC or platelet count between these two groups. There was no significant difference in haematological parameters at any other time-point between the two groups of children (data not shown). The child who had a grade 1 decreased haemoglobin level at the time of switching to ZDV was in CDC clinical category C at baseline. Of the five children who developed a grade 1 or 2 decreased ANC after switching, two, one and two were in CDC clinical categories A, B and C, respectively.

Discussion

In this study, 78 HIV-infected children started a first HAART regimen consisting of d4T, 3TC, and either NVP or EFV. Each child was on the regimen for at least 48 weeks. At week 48 of treatment, their mean haemoglobin level and mean platelet count were significantly higher than at baseline, while almost all of them were in immune recovery and had complete viral suppression (Table 1). These findings are similar to results from previous studies in HIV-infected adults [14–17].

In February 2006, when it became clear that most of the children would eventually suffer from lipodystrophy, a major adverse event of d4T [10], we decided to switch from d4T to ZDV in these 78 children. ZDV may cause bone marrow suppression, resulting in anaemia and neutropenia. Anaemia may occur within 4–6 weeks and neutropenia is usually seen after 12–24 weeks of treatment with ZDV [18]. Thus, we measured the haemoglobin level, WBC count, ANC and platelets of these 78 children at two time-points,

15 and 39 weeks, after switching from d4T to ZDV. We found that, although the switch resulted in a statistically significant decrease in haemoglobin level, WBC count or ANC, the changes were small and were clinically not significant. There was no clinically or statistically significant change in platelet counts.

Our study has several limitations, the most significant of which is that it is a retrospective study, subject to the possible effects of confounders. Thus, although we assume that the statistically significant decreases in haemoglobin level, WBC count and ANC after switching from d4T to ZDV were the result of the myelotoxic effects of ZDV, other potential causes could not be excluded. In addition, blood specimens were not drawn at fixed time-points after the switch. However, data on switching strategies because of toxicity in HIV-infected children are scarce and this study included a large enough number of patients and had a 1-year follow-up time.

In a recent study from Cambodia, 259 HIV-infected adults were studied after switching from d4T to ZDV for a median time of 6.9 months. The median haemoglobin level dropped from 13.2 to 12.0 g/dL within 4 months after switching and remained at 12.1 g/dL at months 7–12 [19]. This stabilization of haemoglobin level 4 months after switching was similar to the findings in our present study. ZDV had to be discontinued in 5.8% of the Cambodian patients, and grade 4 anaemia and grade 3–4 neutropenia occurred in 4.2 and 7.7% of the patients, respectively [19]. The more severe haematological changes in the Cambodian study may have been a result of many of their patients not being in immune recovery at the time of switching to ZDV. The mean time on HAART prior to switching was 7.4 months [19] compared with 36 months in our study. Furthermore, 22.4% of the Cambodian patients had a decrease in CD4 lymphocyte count after switching to ZDV and 3.5% had immunological failure [19], whereas all of the children in our study continued to be in immune recovery after the switch.

In another study using data from the TREAT Asia HIV Observational Database (TAHOD), a multicentre prospective observational study of an HIV-infected cohort in the Asia-Pacific Region, prior antiretroviral (ARV) therapy had a protective effect against ZDV-related anaemia (6 *vs.* 16% in ARV-naïve patients) [20].

These findings, coupled with the results of the present study, suggest that initiating therapy with a d4T–containing HAART regimen and then switching from d4T to ZDV may diminish the risk of developing ZDV-related bone marrow suppression. In addition, the switch may decrease the incidence of d4T-related lipodystrophy. This treatment strategy would be useful in resource-limited countries with limited choices of ARV agents. A controlled clinical trial is needed to further evaluate this strategy.

Acknowledgements

This study was supported by the Thai Government Pharmaceutical Organization and the Thailand Research Fund. The authors thank Voravit Suwanvanichkij, MPH, MD for his help with the English revision of the manuscript.

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