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Zidovudine-Induced Anaemia in Human Immunodeficiency Virus Infected Children on Highly Active Anti-Retroviral Therapy in Jos, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author EUE designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors SO and AOE managed the analyses of the study. Authors EUE and PU performed the statistical analysis. Authors SEO and ESY managed the literature searches. Authors OI, MOO, CD, LO, OOA and PO reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the incidence and severity of zidovudine-induced anaemia in HIV-infected children initiated on anti-retroviral therapy in Jos, Nigeria.
Study Design: This was an observational cohort study.

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Place and Duration of Study: AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Nigeria between April 2008 and March 2013.
Methodology: We followed up HIV-infected children initiated on highly active anti-retroviral therapy (HAART) for 12 months. We compared the haemoglobin level at baseline, 3 months, 6 months and 12 months after initiation of HAART. We also compared the haemoglobin level of those on zidovudine (ZDV) and stavudine (d4T)-containing regimens.
Results: Three hundred and fifty-two (92.1%) patients were on zidovudine-containing regimen while 30 (7.9%) were on stavudine-containing regimen. Three hundred and sixty-five (95.6%) were on cotrimoxazole while 17 (4.4%) were not on cotrimoxazole. The mean haemoglobin level at baseline was 10.8±2.1g/dl for the ZDV group and 6.9±1.3g/dl for the d4T group (P = .001). At baseline, 232 (60.7%) of the patients had anaemia while 26 (6.8%) had severe anaemia. At the end of the 12 months evaluation period, fifty-nine (16.8%) of the patients on ZDV had Hb <8g/dl and were switched to d4T while 16 (4.6%) received blood transfusion. The mean Hb level of ZDV group decreased from 10.8±2.1g/dl to 9.3±1.8g/dl (P = .03) while that of d4T group increased from 6.9±1.3g/dl to 11.2±1.5g/dl (P <.001).
Conclusion: ZDV-induced anaemia was common in HIV-infected children on HAART in this study. Regular clinical and laboratory monitoring is necessary for early detection in order to mitigate the harmful effect anaemia has on the health and survival of such children.

Keywords: HIV; anaemia; haemoglobin; zidovudine; stavudine; cotrimoxazole; Jos; Nigeria.

1. INTRODUCTION

The Human Immunodeficiency Virus (HIV) has become one of the major social and medical issues of our time since it was discovered. HIV is contributing substantially to the rising child mortality rates in many areas of sub-Saharan Africa, reversing years of hard won gains in child survival [1]. UNAIDS estimated that 3.3 million children <15 years were infected with HIV at the end of 2012 [1]. In Nigeria, 260,000 children were estimated to be living with HIV at the end of 2011 [2].

The World Health Organization (WHO) defined anaemia as haemoglobin (Hb) level <11g/dl in children aged 6-59 months, <11.5g/dl in children aged 5-11 years, and <12g/dl in children aged 12-14 years [3]. Severe anaemia is defined as haemoglobin level <7g/dl in children aged 6-59 months and <8g/dl in children aged 5-14 years [3]. Anaemia is common among HIV-infected children all over the world [4-6]. Anaemia may impair physical and neuro-physiological functioning and hence decrease survival [5,6]. With the recommendation of highly active anti-retroviral therapy (HAART) as the standard of care for children infected with HIV, [7] their quality of life has improved dramatically as ART regimens suppress viral replication, provide significant immune reconstitution, and have resulted in a substantial and dramatic decrease in AIDS related opportunistic infections and deaths. Unfortunately the drugs used in HAART regimens are often associated with adverse drug reactions, one of which is zidovudine (ZDV)-induced anaemia [8]. The mechanism of ZDV-induced anaemia is mainly attributable to inhibition of proliferation of blood cell progenitor cells in a time-and dose-dependent fashion [9,10]. This haematological toxicity is observed in most of the patients within 3-6 months and is reversible [10]. ZDV is commonly used as a component of

the nucleoside reverse transcriptase inhibitors (NRTI) backbone of ART regimens in children [11,12].

Anaemia has been reported in 5.4-34.5% of patients on ZDV-containing regimen [13-17]. Anaemia may however not be attributable to ZDV alone; other causes of anaemia in HIV-infected children include changes in cytokine production with subsequent effects on haematopoiesis, decreased erythropoietin concentrations, opportunistic infections, malnutrition and micronutrient deficiency, and administration of other chemotherapeutic agents such as cotrimoxazole. [18-25] this study therefore aimed to determine the incidence and severity of ZDV-induced anaemia in HIV-infected children initiated on ART in Jos, Nigeria.

2. MATERIALS AND METHODS

2.1 Background of Study Area

The study was carried out at AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Plateau State, Nigeria. The program cares for patients in and outside Plateau state in the North-central zone of Nigeria. HIV care, treatment and support services are free for all patients enrolled in the program.

2.2 Study Design

This was an observational cohort study.

2.3 Ethical Consideration

A written informed consent was obtained from each parent/guardian for use of data for research. Ethical clearance was obtained from the Ethical committee of Jos University Teaching Hospital.

2.4 Patient Selection and Data Collection

Treatment-naïve HIV-infected children enrolled in the Paediatric ART program and initiated on ART between April 2008 and March 2013 were the subjects of the study. HIV was confirmed by either deoxyribonucleic acid Polymerase Chain Reaction (PCR) for children <18 months or Western blot for children ≥18 months. They were initiated on ART based on WHO and Nigerian guidelines [7,11,12]. Haemoglobin levels, $CD4^+T$ cell count and $CD4^+T$ cell percent were determined at baseline before initiation of ART. The haemoglobin levels were measured with Mindray 3200 Auto Haematology Analyzer (Shenzhen Mindray Bio-Medical, Shenzhen, China). Flow cytometry was used to determine $CD4^+T$ cell count and the $CD4^+T$ percent (Partec, GmbH Munster, Germany).

Based on recommended guidelines, [7,11,12] those with haemoglobin level ≥8g/dl at baseline were initiated on ZDV-containing regimen while those with haemoglobin level <8g/dl were initiated on stavudine (d4T)-containing regimen. All the children with sickle cell disease were initiated on d4T-containing regimen but were excluded from the study. Cotrimoxazole (CTX) was commenced for all children <1 year, those aged 12-59 months with $CD4^+T$ <25%, and those aged ≥5 years with $CD4^+T$ <350 cells/μL. Those with WHO clinical stages 3 and 4 were also placed on CTX according to WHO recommendation [7] .To

make analysis easier, those on ZDV and CTX were assigned to group 1, those on ZDV but not on CTX were assigned to group 2, while those on d4T and CTX were assigned to group 3. Group 4 was supposed to include patients on d4T but not on CTX, however no patient met the criteria.

All the children on ART were reviewed on each scheduled monthly visits and on any event-triggered visit and checked for pallor. Those that were found to be pale had their haemoglobin levels checked. The laboratory evaluations were repeated 3 months, 6 months and 12 months after initiation of ART in accordance with monitoring guidelines [12]. Any patient on ZDV with a haemoglobin level <8g/dl in the course of the study was switched to d4T. Those that were switched to d4T before 3 months were included in the ZDV column for the 3 months analysis, those switched between 3 months and 6 months were included in the ZDV column for the 6 months analysis while those that were switched after 6 months were included in the ZDV column for the 12 months analysis. We did not include switched patients in the d4T column for subsequent analysis.

2.5 Statistical Analysis

Data obtained was analyzed using EpiInfo version 3.5.1. The independent variables examined included sex, age, ART regimen, and cotrimoxazole while the outcome was the haemoglobin level. The Kruskal-Wallis test was used for continuous variables while chi-square test was used to test significance of association between each independent variable and the outcome. Linear regression analyses were used to determine whether haemoglobin level was associated with the independent variables. *P* value <.05 was considered significant.

3. RESULTS

Three hundred and eighty-two patients were enrolled in the study within the stated period. There were 190 (49.7%) males and 192 (50.8%) females. The mean age was 4.72±3.95 years. The mean age for the males was 4.46±3.86 years and for the females 4.97±4.03 years (*P* = .20). ART regimens consisted of Zidovudine (ZDV) + Lamivudine (3TC) + Nevirapine (NVP) 268 (70.1%), ZDV + 3TC + Lopinavir/ritonavir (LPV/r) 8 (2.1%), ZDV + 3TC + Efavirenz (EFV) 76 (19.9%), Stavudine (d4T) + 3TC + NVP 24 (6.3%), and d4T + 3TC + EFV 6 (1.6%). Three hundred and fifty-two (92.1%) were on ZDV-containing regimen while 30 (7.9%) were on d4T-containing regimen. Three hundred and sixty-five (95.6%) were on cotrimoxazole while 17 (4.4%) were not on cotrimoxazole. Three hundred and thirty-five (95.2%) of those on ZDV were on cotrimoxazole while all the patients on d4T were on cotrimoxazole. Table 1 shows the characteristics of the patients.

The mean age of those on ZDV-containing regimen was 4.83±5.08 years while that of those on d4T-containing regimen was 4.71±3.85 years (*P* = .87). The mean haemoglobin level at baseline was 10.1±1.77g/dl. The mean baseline Hb for age group <1 year is 9.4±1.72g/dl compared to 10.1±1.86g/dl for 1-5 years, 10.2±1.80g/dl for 6-10 years, and 8.2±1.63g/dl for 11-15 years (*P* = .03). Those aged 11-15 years had significantly lower mean baseline Hb level compared to other age groups. There was no difference in the mean haemoglobin level of males and females (males 10.0±1.53g/dl, females 10.1±1.99g/dl; *P* = .22). The mean haemoglobin level at baseline was 10.8±2.06g/dl for the ZDV group and 6.9±1.33g/dl for the d4T group (*P* <.001). At baseline, 232 (60.7%) had anaemia while 26 (6.8%) had severe anaemia. Table 2 shows the incidence of anaemia based on age stratification.

Table 1. Characteristics of the patients

Characteristics	Total (%)
Sex	
Males	190 (49.7)
Females	192 (50.3)
Age group	
<1year	92 (24.1)
1-5years	152 (39.8)
6-10years	99 (25.9)
11-15years	39 (10.2)
Regimen	
ZDV + 3TC + NVP	268 (70.1)
ZDV + 3TC + LPV/r	8 (2.1)
ZDV + 3TC + EFV	76 (19.9)
d4T + 3TC + NVP	24 (6.3)
d4T + 3TC + EFV	6 (1.6)
ZDV-containing regimen	
Yes	352 (92.1)
No	30 (7.9)
Groups	
1 (ZDV + CTX)	335 (87.7)
2 (ZDV only)	17 (4.4)
3 (d4T + CTX)	30 (7.9)
4 (d4T only)	0 (0.0)

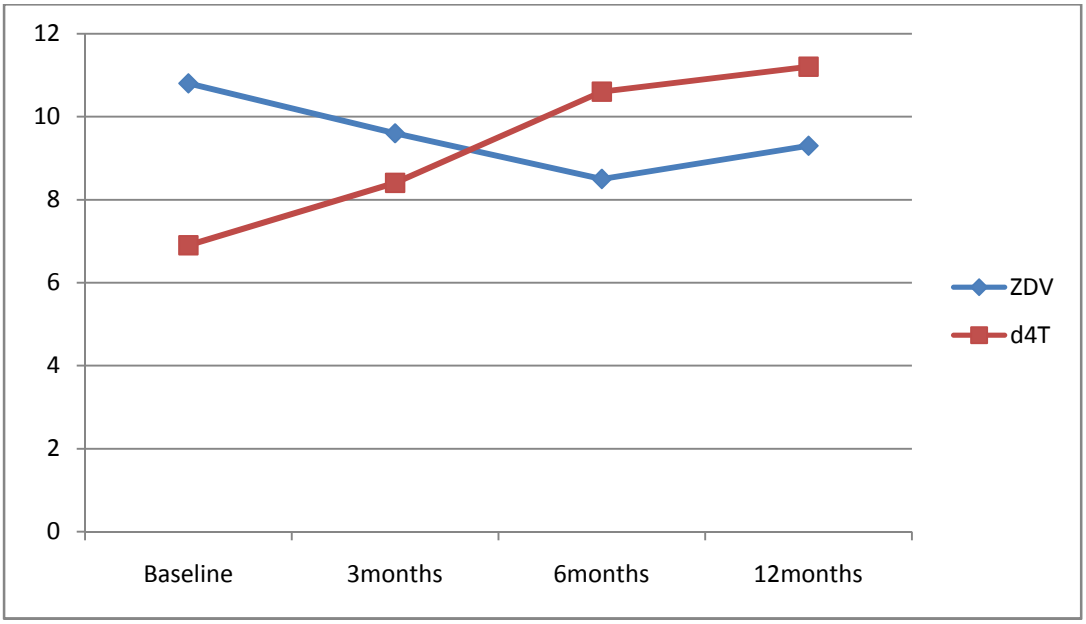

Fig. 1. Trend in haemoglobin levels between the ZDV and d4T groups

Table 2. Incidence of anaemia based on age stratification

Age	Baseline		3 months		6 months		12 months	
	Anaemia	**Severe anaemia**	**Anaemia**	**Severe anaemia**	**Anaemia**	**Severe anaemia**	**Anaemia**	**Severe anaemia**
<1 year	57	6	17	11	12	6	3	2
1-5years	90	9	20	12	11	8	5	1
6-10years	59	4	12	8	7	3	4	0
11-15years	26	7	9	4	2	2	1	1
Total	**232**	**26**	**58**	**36**	**32**	**19**	**13**	**4**

At 3 months evaluation 36 (10.2%) patients in the ZDV group had Hb level <8g/dl and were switched to d4T, 12 (33.3%) of them required blood transfusion. The mean Hb level at 3 months was 9.6±1.98g/dl for ZDV group compared to 8.4±1.43g/dl for d4T group (*P* = .08). At 6 months 19 (5.4%) additional patients in the ZDV group were switched to d4T, four (21.1%) of them required blood transfusion. The mean Hb level at 6 months was 8.6±1.84g/dl for ZDV group compared to 10.6±1.89g/dl for d4T group (*P* = .02). At 12 months 4 (1.1%) additional patients in the ZDV group were switched to d4T, none of them required blood transfusion. The mean Hb level at 12 months was 9.3±1.79g/dl for ZDV group compared to 11.2±1.46g/dl for d4T group (*P* = .03). Table 3 shows the evolution of Hb in the different groups.

At the end of the evaluation period, fifty-nine (16.8%) of the patients on ZDV were switched to d4T with 16 (27.1%) of them requiring blood transfusion. The mean Hb level of ZDV group decreased from 10.8±2.06g/dl at baseline to 9.3±1.79g/dl at 12 months (P = .03) while that of d4T group increased from 6.9±1.33g/dl at baseline to 11.2±1.46g/dl at 12 months (P <.001). Above Fig. 1 shows the trend in Hb levels of the 2 groups.

Table 3. Evolution of Hb in the different groups based on age stratification

	Baseline mean Hb (g/dl)	**3 months mean Hb (g/dl)**	**6 months mean Hb (g/dl**	**12 months mean Hb (g/dl)**
Group 1	**10.9±2.1**	**9.8±1.7**	**8.70±1.8**	**9.4±1.4**
<1 year	10.7±1.9	9.4±1.6	8.5±1.6	9.1±2.0
1-5 years	11.6±2.3	10.1±1.8	8.9±2.2	9.8±2.2
6-10 years	11.8±1.8	10.6±1.4	8.8±1.8	9.5±1.7
11-15 years	9.2±1.7	9.0±1.5	8.6±1.6	9.3±1.7
Group 2	**10.5±2.0**	**8.9±1.8**	**8.5±1.6**	**9.0±1.6**
<1 year	10.6±2.3	8.9±1.5	8.0±1.7	8.6±1.5
1-5 years	11.4±1.9	9.3±1.6	9.0±1.8	9.2±1.8
6-10 years	11.9±1.7	9.4±1.8	8.9±1.9	9.3±1.6
11-15 years	9.1±1.6	8.6±1.4	8.4±1.5	8.9±1.6
Group 3	**6.9±1.3**	**8.4±1.4**	**10.6±1.9**	**11.2±1.5**
<1 year	6.9±1.2	8.1±1.3	9.8±1.8	10.4±1.6
1-5 years	7.2±1.3	8.7±1.4	11.3±1.7	11.4±1.8
6-10 years	7.0±1.3	8.8±1.3	11.1±1.9	11.5±1.8
11-15 years	6.3±1.1	8.0±1.2	10.5±1.8	11.3±1.7

Group 1 (ZDV + CTX) Group 2 (CTX only) Group 3 (d4T + CTX)

4. DISCUSSION

Anaemia was observed in 60.7% of HIV-infected children in this cohort while severe anaemia was observed in 6.8% before initiation of HAART. This is similar to previous reports in both developed and developing countries [4,5,26-29]. Clarke et al. [6] however reported a very high baseline prevalence rate of 91.7% in HIV-infected children in Uganda.

The prevalence rate of anaemia was similar in both males and females. We however observed that children aged 11-15 years had a significantly lower mean Hb level at baseline compared to the younger children. This could be as a result of longer duration of HIV infection in this group of children which could have resulted in more severe changes in cytokine production and erythropoietin production, the two major factors that are implicated

in anaemia in HIV-infected patients before initiation of ART. Ninety-seven percent of HIV-infected children at our centre acquired the infection through the vertical route.

In this study, 16.8% of the patients developed ZDV-induced anaemia that necessitated switching to d4T. This is similar to a previous report from India, [14] but higher than what was reported elsewhere in Lagos, Nigeria, [13] India [15,30] and Cambodia. [31] The mean Hb level of patients on ZDV was observed to have progressively decreased from baseline to 6 months, and then started increasing gradually. This was accentuated in patients that were also on CTX. In contrast the mean Hb level of patients on d4T increased progressively from baseline. This is similar to previous reports that showed that the haematological effects of ZDV were maximal in the first 6 months of treatment and was more marked in those that were also on CTX. ZDV causes anaemia by bone marrow suppression and inhibition of proliferation of blood cell progenitor cells in a time-and dose-dependent fashion [9,10]. CTX is used for prophylaxis against most opportunistic infections in HIV-infected individuals. The two components of the drug, trimethoprim and sulphametoxazole interfere with folic acid and purine metabolism leading to megaloblastic changes in the bone marrow. The combination of ZDV-induced bone marrow suppression and CTX-induced megaloblastic bone marrow changes could worsen the severity of anaemia.

Stavudine-containing regimen on the other hand increases the Hb level by suppressing viral replication and reversing some of the mechanisms that cause anaemia in HIV-infected patients. We could not determine whether CTX slowed the rate of bone marrow recovery in patients on d4T-containing regimen as there were no patients on d4T but not on CTX for comparison.

About 5% of HIV-infected children on ZDV in this study were transfused. Indications for transfusion were Hb level <6g/dl and cardiac decompensation. The high rate of ZDV-induced anaemia and the need for blood transfusion in some patients in this study makes close monitoring of patients on ZDV very necessary. With the scaling up and decentralization of ART services in sub-Saharan African countries, healthcare workers should be trained and retrained on the potential side effects of drugs used in the management of HIV-infected patients. Apart from routine laboratory monitoring, patients on ZDV should be assessed for anaemia clinically and with Hb estimation or packed cell volume (PCV) estimation during each visit especially in the first 6 months of treatment. This will help in early detection and appropriate management of HIV-infected patients with ZDV-induced anaemia.

5. CONCLUSION

We observed that ZDV-induced anaemia was common in HIV-infected children in this study. Regular clinical and laboratory monitoring is necessary for early detection in order to mitigate the harmful effect anaemia has on the health and survival of such children.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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