

Original Research Article

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

ABSTRACT

Aims: To determine the frequency and severity of zidovudine-induced anaemia in HIV-infected children on anti-retroviral therapy in Jos, Nigeria.

Study Design: This was an observational cohort study.

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 treatment-naive HIV-infected children initiated on highly active anti-retroviral therapy (HAART) for 12 months. We compared the haemoglobin level of those on zidovudine (ZDV) and stavudine (d4T)-containing regimens at baseline, 3 months, 6 months and 12 months after initiation of HAART.

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 ± 2.06 g/dl for the ZDV group and 6.9 ± 1.33 g/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 were switched to d4T with 16 (4.6%) of them requiring blood transfusion. The mean Hb level of ZDV group decreased from 10.8 ± 2.06 g/dl to 9.3 ± 1.79 g/dl while that of d4T group increased from 6.9 ± 1.33 g/dl to 11.2 ± 1.46 g/dl.

24 **Conclusion:** ZDV-induced anaemia was common in HIV-infected children on HAART in this
25 study. Regular clinical and laboratory monitoring is necessary for early detection in order to
26 mitigate the harmful effect anaemia has on the health and survival of such children.

27 Keywords: HIV, anaemia, haemoglobin, zidovudine, stavudine, cotrimoxazole, Jos, Nigeria.

28

29 1. INTRODUCTION

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

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

49 dose-dependent fashion. [9, 10] This haematological toxicity is observed in most of the
50 patients within 3-6 months and is reversible. [10]

51 The World Health Organization and Nigerian guidelines on paediatric ART recommend that
52 children with haemoglobin levels <8g/dl should not be placed on ZDV. [11, 12] Anaemia has
53 been reported in 5.4-34.5% of patients on ZDV-containing regimen. [13-17] Anaemia may
54 however not be attributable to ZDV alone; other causes of anaemia in HIV-infected children
55 include changes in cytokine production with subsequent effects on haematopoiesis,
56 decreased erythropoietin concentrations, opportunistic infections, malnutrition and
57 micronutrient deficiency, and administration of other chemotherapeutic agents such as
58 cotrimoxazole. [18-25] This study therefore aimed to compare the haemoglobin level of HIV-
59 infected children on ZDV-containing regimen with those that were on stavudine-containing
60 regimen in order to have a better insight into the true burden of ZDV-induced anaemia.

61 **2. MATERIAL AND METHODS**

62 **2.1 Background of study area**

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

67 **2.2 Study Design**

68 This was an observational cohort study.

69 **2.3 Ethical Consideration**

70 A written informed consent was obtained from parents/guardians for use of data for
71 research. Ethical clearance was obtained from the Ethical committee of Jos University
72 Teaching Hospital.

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76 **2.4 Patient Selection and Data Collection**

77 Treatment-naïve HIV-infected children enrolled in the Paediatric ART program and initiated
78 on ART between April 2008 and March 2013 were the subjects of the study. HIV was
79 confirmed by either deoxyribonucleic acid Polymerase Chain Reaction (PCR) for children
80 <18 months or Western blot for children ≥18 months. They were initiated on ART based on
81 WHO and Nigerian guidelines. [7, 11, 12] Haemoglobin levels, CD4⁺T cell count and CD4⁺T
82 cell percent were determined at baseline before initiation of ART. The haemoglobin levels
83 were measured with Mindray 3200 Auto Haematology Analyzer (Shenzhen Mindray Bio-
84 Medical, Shenzhen, China). Flow cytometry was used to determine CD4⁺T cell count
85 (Partec, GmbH Munster, Germany) and the CD4⁺T percent.

86 Based on recommended guidelines, [7, 11, 12] those with haemoglobin level ≥8g/dl at
87 baseline were initiated on ZDV-containing regimen while those with haemoglobin level
88 <8g/dl were initiated on stavudine (d4T)-containing regimen. All the children with sickle cell
89 disease were initiated on d4T-containing regimen but were excluded from the study.
90 Cotrimoxazole (CTX) was commenced for all the children <1 year, those aged 12-59 months
91 with CD4⁺T % <25%, and those aged ≥5 years with CD4⁺T <350 cells/μL. Those with WHO
92 clinical stages 3 and 4 were also placed on CTX according to WHO recommendation. [7] To
93 make analysis easier, those on ZDV and CTX were assigned to group 1, those on ZDV but
94 not on CTX were assigned to group 2, while those on d4T and CTX were assigned to group
95 3. Group 4 was supposed to include patients on d4T but not on CTX, however no patient
96 met the criteria.

97 All the children on ART were reviewed on each scheduled monthly visits and on any event-
98 triggered visit and checked for pallor. Those that were found to be pale had their
99 haemoglobin levels checked. The laboratory evaluations were repeated 3 months, 6 months
100 and 12 months after initiation of ART in accordance with monitoring guidelines. [12] Any

patient on ZDV with a haemoglobin of <8g/dl in the course of the study was switched to d4T. Those that were switched to d4T or were transfused were excluded from further 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 associations. Linear regression analyses were used to determine whether haemoglobin level was associated with the independent variables. *P* value <.05 was considered significant.

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 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%), 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.

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	335 (87.7)
2	17 (4.4)
3	30 (7.9)
4	0 (0.0)

122

123 The mean age of those on ZDV-containing regimen was 4.83±5.08 years while that of those
 124 on d4T-containing regimen was 4.71±3.85 years ($P = .87$). The mean haemoglobin level at
 125 baseline was 10.07±1.77g/dl, there was no difference in the mean haemoglobin level of
 126 males and females (males 10.01±1.53g/dl, females 10.14±1.99g/dl; $P = .22$). The mean
 127 haemoglobin level at baseline was 10.8±2.06g/dl for the ZDV group and 6.9±1.33g/dl for the
 128 d4T group ($P < .001$). At baseline, 232 (60.7%) had anaemia while 26 (6.8%) had severe
 129 anaemia. Seven (18.0%) of those aged 11-15 years had severe anaemia compared to 6

130 (6.5%) of those aged <1 year, 9 (5.9%) of those aged 1-5 years, and 4 (4.0%) of those aged
131 6-10 years ($P = .02$).

132 At 3 months evaluation, 36 (10.2%) patients in the ZDV group had Hb level <8g/dl and were
133 switched to d4T. This consisted of 33 (9.9%) of group 1 and 3 (17.7%) of group 2. In
134 addition, 12 (33.3%) of those that were switched to d4T required blood transfusion. The
135 mean Hb level of group 1 decreased from 10.9 ± 2.11 g/dl to 9.8 ± 1.66 g/dl, Hb level of group 2
136 decreased from 10.54 ± 2.03 g/dl to 8.97 ± 1.77 g/dl while Hb level of group 3 increased from
137 6.9 ± 1.33 g/dl to 8.4 ± 1.43 g/dl.

138 At 6 months, additional 19 (5.4%) patients in the ZDV group were switched to d4T. This was
139 made up of 17 (5.1%) of group 1 and 2 (11.8%) of group 2. Four (21.1%) of them required
140 blood transfusion. The mean Hb level of group 1 decreased further from 9.8 ± 1.66 g/dl to
141 8.70 ± 1.84 g/dl, Hb level of group 2 also decreased from 8.97 ± 1.77 g/dl to 8.53 ± 1.62 g/dl, while
142 Hb level of group 3 increased from 8.4 ± 1.43 g/dl to 10.6 ± 1.89 g/dl.

143 At 12 months, 4 (1.1%) patients in the ZDV group were switched to d4T, they were all in
144 group 1 and none of them required blood transfusion. The mean Hb level of group 1
145 increased from 8.70 ± 1.84 g/dl to 9.4 ± 1.42 g/dl while that of 2 increased from 8.53 ± 1.62 g/dl to
146 9.0 ± 1.58 g/dl. The mean Hb of group 3 also increased from 10.6 ± 1.89 to 11.2 ± 1.46 g/dl.

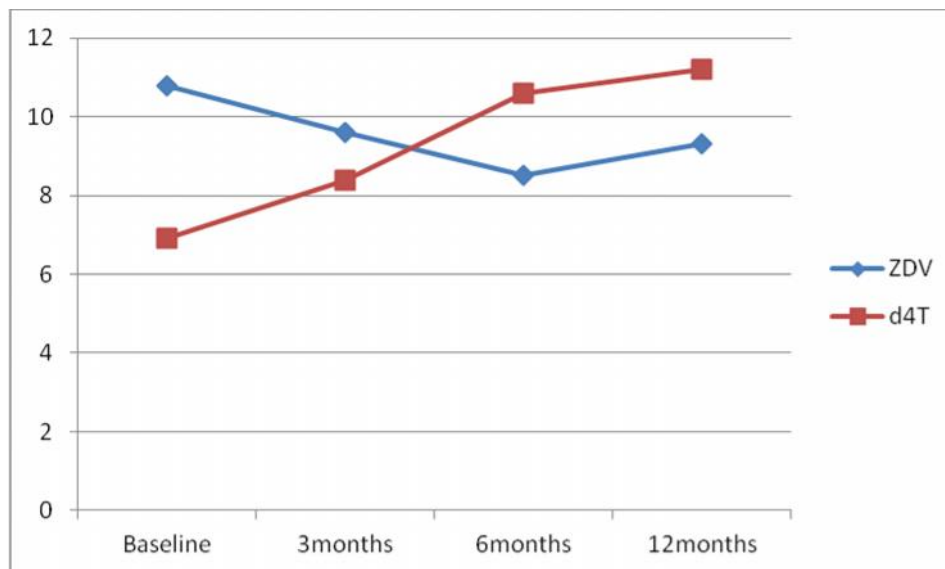
147 At the end of the 12 months evaluation period, fifty-nine (16.8%) of the patients on ZDV were
148 switched to d4T with 16 (27.1%) of them requiring blood transfusion. The number of patients
149 on d4T increased from 30 (7.9%) at baseline to 89 (23.3%). The mean Hb level of ZDV
150 group decreased from 10.8 ± 2.06 g/dl at baseline to 9.3 ± 1.79 g/dl at 12 months while that of
151 d4T group increased from 6.9 ± 1.33 g/dl at baseline to 11.2 ± 1.46 g/dl at 12 months. Table 2
152 shows the relationship between the 2 groups and mean Hb levels while figure 1 shows the
153 trend in Hb levels of the 2 groups.

154 Table 2: Relationship between the 2 groups and mean Hb level

Haemoglobin level	ZDV group n = 352	d4T group n = 30	P value
Mean Hb at baseline (g/dl)	10.8±2.06	6.9±1.33	<.001
Mean Hb at 3 months (g/dl)	9.6±1.98	8.4±1.43	.08
Mean Hb at 6 months (g/dl)	8.6±1.84	10.6±1.89	.02
Mean Hb at 12 months (g/dl)	9.3±1.79	11.2±1.46	.03

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156 Figure 1: Trend in haemoglobin levels in the 2 groups



157

158 DISCUSSION

159 Anaemia was observed in 60.7% of HIV-infected children in this cohort while severe
 160 anaemia was observed in 6.8% before initiation of HAART. This is similar to previous reports
 161 in both developed and developing countries. [4-6, 26-29] Clarke et al [6] reported a very high
 162 baseline prevalence rate of 91.7% in HIV-infected children in Uganda. Causes of anaemia in
 163 HIV-infected children include changes in cytokine production with subsequent effects on
 164 haematopoiesis, decreased erythropoietin concentrations, opportunistic infections,
 165 malnutrition and micronutrient deficiency, and administration of other chemotherapeutic
 166 agents such as zidovudine and cotrimoxazole.

The prevalence rate of anaemia was similar in both males and females. We however observed that older children infected with HIV had a higher rate of severe anaemia at baseline compared to the younger ones. 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 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 sulphamethoxazole 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.

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

204 **CONCLUSION**

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

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