ORIGINAL ARTICLE

Prevalence of Anaemia in HIV-Infected Children at the University of Abuja Teaching Hospital, Gwagwalada

***Okechukwu A A** *FMC Paed* ***Gambo D** *MBBS* ****Okechukwu I O** *MPH, Adherence Counsellor*,

*Department Of Paediatrics, **Paediatric Outpatient Special Treatment Clinic,
University Of Abuja Teaching Hospital,Gwagwalada

Abstract

Background: *Use of highly active antiretroviral therapy (HAART) has remained the only regimen potent enough to reduce viral replication in HIV-infected individuals. Its combination with co-trimoxazole has also been recommended in those with CD4% of less than 15%. The use of HAART containing zidovudine (ZDV) in combination with co-trimoxazole carries the risk of anaemia in already anaemic predisposed individuals from HIV infections, opportunistic infections, parasitic infestations, sickle cell anaemia, and malnutrition. The aim of the study is to document the effect of use of combination of HAART containing ZDV with co-trimoxazole in haemoglobin profile of HIV-infected children after one year of its administration at the University of Abuja Teaching Hospital (UATH), Gwagwalada. It is also aimed at comparing the result obtained with those on stavudine containing HAART with co-trimoxazole.*

Method : *A two year prospective study of HIV-infected children on treatment with HAART in combination with co-trimoxazole, and attending the paediatric outpatient special treatment clinic (POSTC) for HIV infected children at the UATH, Gwagwalada from November 2006 to October 2008, was carried out to determine effect of these drug combinations in the haemoglobin profile of infected children. Three monthly PCV level was carried out using haematocrit centrifuge and reader.*

Results: *A total of 173 patients were started on HAART during the first year recruitment period, 90 (52.0%) were males, while 83 (48.0%) females, giving a male to female ratio of 1.1:1. One hundred and seventeen (67.7%) of patients were on ZDV containing HAART, while 56 (32.3%) were on stavudine containing combination. All patients were started on co-trimoxazole prophylaxis with the exception of 6 (3.5%) patients because of drug reaction. The mean PCV of patients on ZDV containing combination with co-trimoxazole decreased from 30.2 ± 5.5% to 29.0 ± 2.3%, with a net decrease of 1.2% after one year treatment, those on stavudine containing combination with co-trimoxazole instead showed an increased from initial PCV of 28.3 ± 4.2% to 34.2 ± 3.0% with a net increase of 5.9% after the same duration of treatment, (p>0.05). While patients on ZDV combination alone without co-trimoxazole prophylaxis had a minimal decrease of 0.9% in their PCV level after one year treatment, those on stavudine combination alone without any prophylaxis instead showed an increase of 6.8% in their PCV after the same duration of treatment.*

Conclusion: *A combination of HAART containing ZDV plus co-trimoxazole carries risk of anaemia than that of stavudine containing combination with co-trimoxazole. Such combination should therefore not be given to anaemic patients. Regular check in PCV of patients on HAART combination with ZDV and additional co-trimoxazole prophylaxis is required for early detection of significant drop in PCV level.*

Key words: *Highly active antiretroviral therapy, zidovudine, stavudine, co-trimoxazole, anaemia.*

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Correspondence to **Dr Adline A Okechukwu**, P M B 228, FCT – Abuja

Introduction

Anaemia is a common condition in HIV infected children and contributes significantly to its morbidity and mortality.[1,2] Its prevalence is determined to a large extent to the prevailing conditions that cause anaemia in the environment like malaria, sickle cell anaemia, helminthiasis, malnutrition and micro-nutrient deficiencies.[4-6] The basic pathology in the anaemia of HIV infection appears to be related to the release of inflammatory cytokines during the chronic disease process which not only inhibits erythropoiesis by blunting the erythropoietin response, but also reduces the red blood cell survival via the haemo-phagocytic mechanism as well as preventing the release of iron from the reticuloedothelial system.[2-6]

Despite the survival benefits of antiretroviral drugs (ARD) in patients living with HIV, the clinical management of the disease presents a major challenge for both clinicians and patients.[7-11] Treatment of HIV infection with ARD is aimed at preventing progression of the disease to AIDS and death by reducing the plasma HIV ribonucleic acid (RNA) to as low levels as possible.[9,10] The eradication of HIV from an individual is not considered possible with the a single ARD, [10] and people undergoing treatment for HIV disease must take a daily regimen of at least three ARD combinations otherwise known as highly active antiretroviral therapy (HAART).[11]

HAART is the only regimen potent enough to drastically reduce viral replication, prevent the emergence of resistance, restore immune status, slows HIV disease progression, has durable therapeutic responses, improve quality of life and promotes normal growth and development in children.[11-13] Zidovudine or stavudine is commonly paired with lamivudine or abacavir as the nucleoside components of HAART regimen.[6,10,13] Zidovudine is well known for its bone marrow suppressive effect.[6,10,13] The suppression being related to marrow reserve, dosage of the drug, duration of treatment and the stage of HIV disease.[6,10,13] Anaemia is one of the major bone marrow suppressive effect of ZDV and is commonly seen 4 to 6 weeks of its commencement.[10,13]

HIV infected children are saddled with problem of opportunistic infections for which co-trimoxazole (combination of trimethoprim and sulphametoxazole) is commonly given as prophylaxis. The trimethoprim component of co-trimoxazole is an anti-foliate metabolite that inhibits the enzymic reduction of folate to folinic acid via the dihydro-reductase pathway. This inhibitory process eventually leads to loss of purine and hence poor synthesis of deoxyribonucleic acid (DNA) in the human cell, with subsequent megaloblastic changes in the marrow and manifestation of megaloblastic anaemia.[14,15]

This singular effect is expected to worsen the anaemia of patients on ZDV. Thus HIV infected children in this environment and on treatment with HAART containing ZDV plus co-trimoxazole, are saddled with problems of anaemia from nutritional causes, micro-nutrient deficiencies, chronic HIV disease and other infections/infestations, bone marrow suppressive effect of ZDV, as well as anti-folate activity of co-trimoxazole. The aim of the present study is to document the prevalence of anaemia in HIV/AIDS in children on treatment with HAART. It is also aimed at determining the effect of HAART containing ZDV plus co-trimoxazole on haemoglobin profile of infected children, and comparing the result with those on HAART containing stavudine (whose major side effect is not anaemia) plus co-trimoxazole.

Method

The prospective study was conducted at the paediatric outpatient special treatment clinic (POSTC) for HIV/AIDS children at the UATH, Gwagwalada over a two year period, from November 2006 to October 2008. The subjects were paediatric HIV/AIDS patients on HAART with or without co-trimoxazole. Patients were aged between two months to 15 years and positive for HIV infection either by serology method or by deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) test. For children 18 months of age and above, the sera were screened for the presence of HIV-I or 2 using commercially

available recombinant antigen based double rapid test (STATPAK by Chembio-Diagnostic System Inc, New York, and DETERMINE by Abbot laboratories Japan), with sensitivity and specificity of 100%. For those less than 18 months of age diagnosis was based on use of DNA PCR test. DNA PCR test amplifies and detects the HIV pro-viral DNA sequences within the mono-nuclear cells in the blood, and is 100% sensitive after 4 to 6 weeks of life.[6]

Blood for PCV was collected for all patients by the medical officer attached to the POSTC at recruitment, and subsequently at a three monthly intervals for the one year follow up period. Samples were collected at the dorsum of the right or left hand with 5 ml syringe after wiping the area with 2% alcohol spirit swab. The collected sample was centrifuged using a haematocrit centrifuge (Hawksley micro-haematocrit centrifuge, made in England by Hawksley & sons Limited) at 2,000 rovers per minute for 5 minutes. The PCV value was read with haematocrit reader (Hawksley micro-haematocrit reader).

Information collected at recruitment includes age of the patient, sex and body weight. CD4 cell count and its percentage, WHO clinical staging of the patients and their intial PCV level were also collected at recruitment. First line HAART regimens used for the patients were combinations of ZDV or stavudine plus lamivudine and nevirapine (NVP) or efevarenz (EFZ) depending on whether the patient was receiving anti-tuberculous therapy. Those on anti-tuberculous medication with rifampicin were given EFV instead of NVP when age is greater than 3 years or weight >10kg. When age is less than 3 years or weight <10kg, NVP was replaced with abacavir. Second line HAART regimen used were combination of ZDV or stavudine, plus lamivudine and lopinavir/ ritonavir.

University of Abuja Teaching Hospital is a 350 bed capacity referral centre sub serving FCT and neighbouring states like Nassarawa, Kogi, Benue, Niger, and parts of Kaduna. It is one of the centers in the country that offers free medical services to HIV/AIDS patients courtesy of United State government.

The study was carried out after approval from the ethics committee of the hospital, and informed written down consent obtained from the parents/ guardian of the patients following explanation on the implication of the study, in the language they understands most.

Paediatric patients who met the World Health Organization (WHO)/ National guideline for paediatric HIV and AIDS commencement on HAART were started on the drugs. They include patients greater than 3 years whose CD4 cell percentage were less than 15%, those between 1-3 years with CD4 percentage of less than 20%, and those less than one year whose CD4 percentage is less than 25%.[6,10]

All infected infants, older children with symptomatic HIV disease or an AIDS defining illness or those with CD4 of less than 20% for age 1-3years, or less than 15% for older children were all started on co-trimoxazole prophylaxis.[6,10,13] On recruitment of patients which lasted for one year, clinical, immunological and haematological assessments were carried out. This included general physical examination, anthropometric measurements (body weight, recumbent length or height and head circumference), immunological assessment (CD4 cell count and its percentages), haematological profile (full blood count and differential, packed cell volume), and blood chemistry (liver function test, urea/creatinine, and lipid profile).

For the purpose of the study, the patients were grouped into four based on the type of nucleoside reverse transcriptase inhibitors (NRTIs) component of HAART used, the PCV results at recruitment, as well as use or non- use of co-trimoxazole prophylaxis. The summary of the groups were as follows:

***Group 1** - HAART (ZDV) patients without co-trimoxazole.

***Group 11** - HAART (ZDV) with co-trimoxazole.

***Group 111** - HAART (stavudine) patients without co-trimoxazole.

***Group 1V** – HAART (stavudine) with co-trimoxazole.

Patients were assigned to ZDV or stavudine group based on the recruitment PCV level.

When PCV was found to be greater than 30%, patients were assigned to ZDV group, but when less than 30% they will be assigned to stavudine group. 30% PCV level was chosen because this is the level that signifies moderate anaemia.[23] Patients with moderate to severe anaemia were not assigned to ZDV group because of possibility of ZDV worsening the anaemia from its bone marrow suppressive effect.[6,13] They were instead assigned to stavudine group. Because all infants were expected to be on co-trimoxazole prophylaxis irrespective of CD4 cell count and its percentage, they were not assigned to groups 1 & 111. Data entry and analysis was carried out using SPSS programme version 7.5 that provided frequency distribution, means, standard deviations, and correlation coefficient.

Results

A total of 173 patients were stared on HAART during the one year recruitment period, 90 (52.0%) were males and 83 (48.0%) females giving a male to female ratio of 1.1:1. One hundred and sixty seven (167) of 173 recruited patients (96.5%) were on co-trimoxazole prophylaxis, while 6 (3.5%) were not because of drug reaction, and alternative drug (dapsone) was used instead. Significant number of recruited patients 117 (67.6%) were also on ZDV combination as against 56 (32.3%) on stavudine ($p< 0.05$). Of the 117 patients on ZDV, 113 (96.6%) were also on additional co-trimoxazole prophylaxis, 4 (3.4%) were not, and of the 56 patients on stavudine, 54 (96.4%) were on co-trimoxazole, while 2 (3.6%) were not.

The mean age of the patients at recruitment was 4.1 ± 1.2 years, while there mean CD4 cell count, CD4 percentage and WHO clinical staging were 216.9 ± 104.2cells/ml, 11.7%, and stages 3 respectively, all signifying advanced immune suppression at recruitment, (table I). Table II shows WHO clinical staging and PCV values of recruited patients.A total of 56/173 (32.4%) of the patients were at WHO stage 4, 83/173 (48.0%) in stage 3, 34/173 (19.7%) in stage 2 disease, and none in asymptomatic stage 1. When compared to stage 2 patients, there is a statistical significant difference between their mean PCV and that of stage 4 disease (35.0% Vs 20.7%, $p = 0.002$).

There was also statistical significant difference between mean PCV of stage 2 and stage 3 disease (35.0% Vs 32.3%, $p = 0.034$). It was also noted that 18/56 (32.1%) of patients in stage 4, 12/83 (14.5%) in stage 3, 2/34 (5.9%) in stage 2 presented with PCV of less than 21% signifying severe anaemia. There is a positive correlation between the level of PCV and the degree of immune suppression ($r=0.48$, $p=0.06$).

Table 111 shows the changes in PCV level during one year treatment with different regimen of HAART. While there was a net increase in PCV of 6.8% from a baseline value of 28.3% to 35.1% after one year treatment for those on stavudine containing HAART without co-trimoxazole, patients on ZDV containing combination without co-trimoxazole prophylaxis had a slight decrease in PCV value from 30.5% to 29.6%, (0.9%). The sample size of the two groups were however too small for any meaningful statistical comparism (4 and 2 respectively).

When compared with stavudine containing HAART plus co-trimoxazole, and ZDV containing HAART with co-trimoxazole, that of ZDV group with co-trimoxazole showed a non significant decrease in PCV value from 30.2±5.5 to 29.0±2.3, (1.2% decrease), $p>0.05$, after one year treatment, while that of stavudine with co-trimoxazole instead showed a significant increase from 28.3±4.2 to 34.2±3.0, (5.9% increase), $p< 0.01$. In summary, while there was a net decrease in PCV value of 1.2% in ZDV group with co-trimoxazole, stavudine combination with co-trimoxazole showed an increase of 5.9%, $p< 0.05$ It is also obvious from the data that while patients on only ZDV containing HAART without co-trimoxazole prophylaxis showed a minimal decrease in their PCV (0.9%) after one year of treatment, those in the same regimen with additional co-trimoxazole prophylaxis instead showed a decrease in their PCV (1.2%), after the same duration of treatment. In the same vain, the increase in PCV for patients on stavudine containing HAART alone without co-trimoxazole was higher (6.8%), while those on stavudine containing regimen with co-trimoxazole had an increase of 5.9%.

Six patients died in the first year recruitment phase, two of which was from severe pneumonia, two from severe jaundice with positive antibody to hepatitis B surface antigen, one from HIV encephalopathy, and the remaining one from severe anaemia with septicemia. An additional two patients died during the second year from severe malaria and meningitis, making a total of 8 patients, with a mortality of 4.6%. At the end of the study, 150 patients (86.7%) were alive and on first line anti retroviral treatment, 3 (1.7%) were alive and on second line drugs, 10 (5.7%) were lost to follow up, while 2 (1.2%) discontinued ARD, as a result of adherence failure following several serious counseling sessions.

Table I : Characteristics of Recruited Patients

Variables	M	F	Total (%)
No of recruited patients on ARVDs	90	83	173
No on co-trimoxazole	88	79	167(96.5)
No not on co-trimoxazole	2	4	6(3.5)
Group 1	1	3	4 (1.2)
Group 11	61	52	113 (65.3)
Group111	1	1	2 (1.7)
Group 1V	30	24	54 (31.2)
Age (years)	*4.3+0.7	*3.9 + 2.0	*4.1+1.4
WHO clinical staging	3	3	3
weight (kg)	*13.1 ±1.8	*12.3 ± 5.2	*12.7 ± 3.5
CD_4 cell count (cells/ml)	*209.7 ±104.2	228.2 ± 109.7	216.7 ± 104.2
% CD_4 cell count	*11.4	*11.9	*11.7
PCV %	*30.0	*28.6	*29.3

*Values are means ± STD.

PCV – Packed Cell Volume.

WHO- World Health Organisation.

Table II: World Health Organization Clinical Staging and Packed Cell Volume of Recruited Infants at Recruitment.

WHO clinical staging	N (%)	Mean PCV (%)	Percentage with severe anaemia PCV < 21%	Mean Age (Years)
1.	0(0.0)	00.0	0/0 (0.0)	0.0
2.	34 (19.7)	35.0	2/34 (5.9)	3.2±1.6
3.	83 (48.0)	32.3	12/83 (14.5)	4.7±1.1
4.	56 (32.4)	20.7	18/56 (32.1)	4.3±0.6

Table III: Packed Cell Volume Changes during One Year Treatment on HAART.

Regimen	Total No	PCV at recruitment	PCV at 6months	PCV at one year	P-value
	173	29.3 ± 5.0	31.5 ± 4.7	32.0 ± 6.2	
1	4	30.5 ± 5.7	31.0 ± 3.4	29.6 ± 3.5	
11	101	30.2 ± 5.5	31.2 ± 4.1	29.0 ± 2.3	
111	2	28.3 ± 4.2	32.1 ± 6.0	35.1 ± 4.9	
1V	47	28.3 ± 4.2	31.6 ± 5.9	34.2 ± 3.0	

HAART – Highly Active Antiretroviral Therapy

Discussion

Anaemia is a common manifestation of HIV infection in children.[1-4,14] This is evident in this study where 129/173 (74.6%) of the patients seen presented with mild to moderate anaemia, (PCV of less than 30%), 32/173 (18.5%) with features of severe anaemia, (PCV of less than 21%), and 12/173 (6.9%) with no features of anaemia. The findings were similar with reports from Jos (73.7%) [16] and South Africa (72.0%).[5] The high prevalence of anaemia seen in HIV infected children in the present and other studies is to a large extent not only due to both direct and indirect effect of HIV infection on erythropioesis, but also as a result excessive destruction, erythropoietic factor deficiencies, and other co-existing disease conditions as highlighted in the introductory part of this article. The incidence of anaemia in HIV disease is dependent on the severity of HIV disease as well as the level of haemoglobin.[14]

In a survey by the Centre for Disease Control (CDC) in the United State of America (USA),[4] among 3,200 adolescents and adults with HIV infection and on treatment with the ARD, the prevalence of moderate anaemia with Hb of <10g/dL was found to be 31.6% in patients with CD4 cell count of <200cells/ml, and 4.5% in those with cells of >200cells/ml. The same study showed prevalence of mild to moderate anaemia of Hb of 10-14g/dL to be present in 31.3% of patients with AIDS and 26.6% in those without AIDS.[4] The present study noted severe anaemia of PCV of < 21% to be present in 32.1% of WHO stage 4 disease of severe immune suppression, and 5.9% in those in stage 2 of mild to moderate immune suppression.

This findings appears similar with CDC survey among adolescents and adults population,[4] but appeared much lower than the report from South African[5] were severe anaemia of PCV of <21% was found to be present in 92%, and 76% of patients with severe and moderate immune suppression. All these findings highlights not only the significant relationship between immunological status of HIV patients and their Hb level, but also the adverse effects of HIV infection on the haematopoietic systems.

In addition to the adduced reasons highlighted previously as the causes of high prevalence of anaemia in HIV infected individuals, which worsen as the disease progresses, the parvovirus B19 induce chronic anaemia in HIV infected may also be an additional factor.[19-21] HIV infected individual with severe immune suppression lacks the ability to mount antibody against the structural proteins of B19 parvovirus, a well known cause of severe anaemia in immune compromised individuals.[19-21]

Zidovdine, stavudine and lamivudine are the nucleotide reverse transcriptase inhibitors (NRTIs) component of HAART used in this study. They act by incorporating themselves into the DNA of HIV virus formed, thus stopping the building process and formation of the new virus.[6,10] Bone marrow suppression is a known and major side effect of ZDV, suppression being related to the marrow reserve, dosage of the drug, duration of treatment and stage of HIV disease. Stavudine is noted for its peripheral neuropathy from mitochondrial toxicity.[6,13] Marrow suppression or anaemia is not its major side effect.[6,13]

Trimethoprim and sulphametoxazole, are the two drug combinations in co-trimoxazole used as prophylaxis against most opportunistic infections in HIV infected individuals. Both drugs act at two levels in the biosynthesis of tetra-hydrofolic acid, a precursor in the synthesis of folic acid and purine. While sulphametoxazole inhibits the incorporation of para-amino benzoic acid (PABA) into folic acid, trimethoprim blocks the reduction of dihydrofolic acid to tetra-hydrofolic acid.[14,15] All this processes are needed in the synthesis of folic acid and purine. Failure of purine and folic acid synthesis results in megaloblastic changes in the bone marrow. At the end of one year treatment, children on HAART containing stavudine had a higher PCV than those on ZDV containing combination, even though the latter started off treatment with higher PCV. This was more pronounced in patients who received co-trimoxazole prophylaxis: thus depicting the probable bone marrow suppressive effect of ZDV,

as well as the anti-folate activities of co-trimoxazole which resulted in a slight drop in PCV value when ZDV plus co-trimoxazole combination.

Conclusion

A combination of HAART containing ZDV plus co-trimoxazole carries a greater risk of anaemia than that of stavudine containing HAART with co-trimoxazole. Such combinations may not be very advisable in anaemia patients. . Regular check in PCV of patients on HAART, especially those receiving ZDV containing HAART and co-trimoxazole prophylaxis is required for early detection of significant drop in PCV level.

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