Haematological features in Paediatric patients on second line Highly Active Antiretroviral Therapy in Zimbabwe.

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Abstract

Background: Human immunodeficiency virus/acquired immune deficiency syndromes (HIV/AIDS) is still a public health challenge globally, with over 3 million children living with HIV/AIDS. Its treatment in children has both positive and negative effects. Haematological abnormalities account for most causes of deaths associated with HIV infection and its treatment. Highly active antiretroviral therapy (HAART) is now recommended as the standard form of care for people living with HIV/AIDS. This has particularly improved the quality of life of children with the condition. However, HAART regimens are often associated with unfavourable drug reactions which may be life-threatening.

Objective: The major objective was to determine the effects of second line HAART combinations on haematological parameters in children living with HIV/AIDS.

Materials and Methods: A cross sectional clinical and laboratory based prospective study on the haematological manifestation of children on different combinations of HAART regimens was carried out at Harare Central Hospital from January to April 2017.

Results: A total of 97 EDTA blood samples from HIV paediatric patients on second line HAART treatment were analyzed for full blood count. Forty-four (45.4%) and 53 (54.6%) of them were females and males respectively. The four most frequent haematological abnormalities were neutropaenia (69.1%), leukopaenia (46.4%), anaemia (30.9%) and thrombocytosis (30.9%). The anaemia was of varying degrees of morphological classification and it was mainly caused by TDF-based combinations. The most common morphological classifications were normocytic normochromic anaemia (61.5%), microcytic hypochromic (26.9%) and macrocytic normochromic (7.7%). TDF/3TC/ATV/r (47.4%), ABC/3TC/LPV/r (18.6%), AZT/3TC/ATV/r (14.4%) and AZT/DDI/LPV/r (12.4%) were the most prescribed second line HAART combinations. Most haematological abnormalities were found to be commonly associated with TDF/3TC/LPV/r and AZT/3TC/ATV/r combinations.

Conclusions: It can be concluded that haematological abnormalities were also present in paediatric HIV positive patients on second line HAART. The abnormalities were similar to those found in children on first line HAART, although anaemia was nearly twice that found in first line HAART.

Key words: *HAART, haematological abnormalities, HIV, paediatric, second line*

Introduction

Human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) is still a public health challenge globally, with over 3 million children living with HIV infection or having developed AIDS. In 2017, World Health Organization has estimated that close to 40 million people are living with HIV/AIDS globally, with 26 million of them living in Africa. Zimbabwe is ranked 8th in global prevalence of HIV (*Fassinou et al., 2004; Oshikoya et al., 2012; Khan et al., 2014; WHO Report, 2017*). HIV/AIDS treatment in children has both positive and negative effects. These effects have to do with haematological manifestations. Haematological abnormalities account for most causes of deaths associated with HIV infection and treatment (*Gedefaw et al., 2013*).

The haematological abnormalities associated with HIV infection and treatment can impair the quality of life of people living with HIV/AIDS. The most common haematological abnormalities are cytopaenia which may manifest as anaemia, thrombocytopaenia and neutropaenia. These cytopaenia may be caused by various factors such as deficient blood production due to HIV bone marrow damage, suppression or abnormal cytokine expression by the drugs such as zidovudine (AZT) and other nucleoside analogues used for treatment (*Coyl, 1997; Addis et al., 2014; Kibaru et al., 2015*). Changes in some haematological parameters with HIV treatment may reflect improvements in the quality of life in these patients (*Mandisodza et al., 2007*).

In recent years, highly active antiretroviral therapy (HAART) has been recommended as the standard form of treatment for people living with HIV/AIDS. This has particularly improved the quality of life of children with HIV. However, HAART combinations are often associated with unfavourable drug reactions which may be life-threatening (Moyle et al., 2004; *Lawal et al., 2012*).

HAART is a combination of three or more antiretroviral agents, with different modes of action, taken simultaneously to suppress HIV replication to a level which prevents drug resistance. Because of their affordability and ability to suppress the HIV virus, the combinations have proved to be an effective form of treatment in resource limited settings were access to laboratory monitoring is limited. Therefore, HAART has substantially reduced morbidity and mortality amongst HIV infected populations (*Ministry of Health Team, 2013*). HAART regimens were first introduced in Zimbabwe in 2004 after the treatments were standardized globally. HAART combinations may contain different drug regimens such as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) (*Puthanakit et al., 2005; Gilks et al., 2006; Agarwal et al., 2010*).

HAART is classified into first line, second line and third line combinations. Second line HAART is the antiretroviral drug combination given to a patient after the first line has failed clinically, immunologically or virologically. However, it may be clinically indicated to give second line drugs as first line HAART therapy even though some second line HAART combinations have been associated with a number of side effects (*Malangu, 2010; Namukanja, 2011*).

The different classes of drugs which make up HAART have different modes of action. PIs inhibit protease enzyme by binding to the active sites thus preventing cleavage of precursor

proteins. NRTI are nucleoside analogues which inhibit HIV replication by competing for reverse transcriptase (RT) active sites and being incorporated into viral DNA. NRTI are active against HIV-1 and HIV-2 subtypes. NNRTI binds to the hydrophobic pockets on RT and inhibit HIV 1, thereby rapidly decreasing viral load and drug resistance. All these actions reduce the replication of the virus, thereby slowing down its multiplication (*Khan et al., 2014*). In Zimbabwe, some of the most commonly used antiretroviral drugs are: **ATV**= atazanavir; **AZT**=zidovudine; **RTV**=ritonavir; **3TC**= lamivudine; **TDF**= tenofovir; **r** = ritonavir and **EFV**=efavirenz and the commonly used HAART regimens are TDF/3TC/ATV/r, ABC/3TC/LPV/r, AZT/3TC/ATV/r, AZT/DDI/LPV/r and ABC/3TC/NVP (*Nicodimus et al., 2017*).

Cytopaenia are very common haematological manifestations of HIV infection. It has been suggested that some of the abnormal features are associated with multiple drug treatments, in addition to bone marrow damage and suppression (*Fassinou et al., 2004; Oshikoya et al., 2012; Khan et al., 2014*).

A previous study on the haematology of HIV infected children on first line HAART concluded that zidovudine based HAART combinations may cause cytopaenia, with the exception of thrombocytopaenia which was found to decrease with treatment (*Nicodimus et al., 2017*). Since there were significant abnormal haematological changes with first line HAART regimens, it was also found necessary to determine the effects of second line HAART combinations in children living with HIV/AIDS. It was also found necessary to determine the frequencies of these haematological abnormalities in order to identify the safest drug combinations to use. This information will assist healthcare givers to monitor and make appropriate decisions in the management of the paediatric HIV/AIDS pandemic.

Materials and Methods

A cross sectional clinical and laboratory based prospective study on the haematological manifestation of children on different combinations of HAART regimens was carried out at Harare Central Hospital (HCH) from January 2017 to April 2017.

The inclusion criteria were: children attending the HCH paediatric Opportunistic Infections (OI) Clinic, aged between 3-8 years who had been on HAART for at least 4 consecutive months and who had not been previously diagnosed with haematological disorders.

The exclusion criteria were: children who were on first or third line HAART whose ages were unknown and with infections such hepatitis, tuberculosis and malaria which would cause abnormal haematology; children who were on drugs, such as antibacterial, anti-inflammatory and anticonvulsants that might cause abnormal haematology and children who were ill and would require hospitalization at the time of enrolment.

Full blood count (FBC) was done using the Mindray BC-5800 Haematology Analyzer (China). Routine ethylene diamine tetra acetic acid (EDTA) blood samples from HIV infected children aged between 3 and 18 years were used. Permission to analyze the blood samples was obtained from the chief medical laboratory scientist of HCH Public Health Laboratory.

The data collected was used for research purposes only. For security and confidentiality, the data was kept in computers with secured passwords and samples were de-identified and allocated unique laboratory numbers. Patient information was accessed by the researcher and supervisors only.

The required minimum sample size of 85 was determined using the *Dobson's formula.* Patient demographic data and laboratory results were captured and statistically analyzed using the Microsoft Excel and the SOFASTATS Statistical Package respectively.

Permission to carry out the research was granted by the Harare Central Harare Central Hospital Ethics Committee and the Joint Parirenyatwa Hospital and College of Health Sciences (JREC). Access to patients for demographic data was granted by the sister-in-charge of HCH paediatric opportunistic infections (OI) clinic, with approval from the hospital clinical director.

Results

A total of 97 EDTA blood samples from HIV paediatric patients on second line HAART treatment were analyzed for full blood count. Forty-four (45.4%) and 53 (54.6%) of them were females and males respectively. There was no statistical significant association between haematological abnormalities and gender ($p>0.05$). Paediatric age groups were also not associated with haematological abnormalities ($p>0.05$).

The medians for all the haematological parameters were within the normal reference range. The four most frequent abnormalities were neutropaenia (69.1%), leukopaenia (46.4%), anaemia (30.9%) and thrombocytosis (30.9%) (*Table I* and *Figure1*). The anaemia was of varying morphological classifications and it was mainly caused by TDF-based combinations (*Table IV*). The three most common morphological classifications were normocytic normochromic anaemia (61.5%), microcytic hypochromic (26.9%) and macrocytic normochromic (7.7%).

TDF/3TC/ATV/r (47.4%), ABC/3TC/LPV/r (18.6%), AZT/3TC/ATV/r (14.4%) and AZT/DDI/LPV/r (12.4%) were the most prescribed second line HAART combinations and only 1(1%) patient was on ABC/3TC/NVP combinations (*Table II*).

Although there was no statistically significant association between haematological abnormalities and drug regimens, haematological abnormalities were found to be commonly associated with TDF/3TC/LPV/r and AZT/3TC/ATV/r combinations. Neutropaenia, leukopaenia and anaemia were also significantly associated with these two combinations. Patients on AZT/3TC/ATV/r were most likely to develop monocytopaenia and those on TDF/3TC/LPV/r were most likely to develop pancytopaenia (*Table III*).

Table I: Median Haematological Values in HIV paediatric Patients on Second Line HAART (*n=97*).

Haematological Parameters	Median	SD	Normal Range(*Mandisodza et al., 2007; Behrman et al., 2000*)
WBC (10^3/uL)	6.3	2.9	5.1-14.4
Neutrophil [$10^3/uL$]	2.54	2.73	2.5 - 4.5
Neutrophil [%]	41.68	16.27	40 – 76
Lymphocytes [$10^3/uL$]	2.55	1.36	1.5 - 3.0
Lymphocytes [%]	46.89	14.84	25 33
Monocytes [$10^3/uL$]	0.58	0.23	0.3 - 0.5
Monocytes [%}	7.54	2.31	3.0 - 7.0
Eosinophils [$10^3/uL$]	0.16	0.23	0.05 - 0.250
Eosinophils [%]	2.92	3.72	1.0 - 3.0
Basophils [$10^3/uL$]	0.03	0.02	0.0 - 0.050
Basophils [%]	0.50	0.42	0 - 0.75
RBC [10^6 /uL]	4.19	0.69	4.0 - 5.6
Hb (g/dl)	12.0	1.7	11.4-15.4
HCT [%]	37.34	5.28	25.0 - 48.0
MCV [fL]	91	11.4	76-95
MCH [pg]	29	4.5	25-33
MCHC [g/dl]	32.16	1.68	31 37
PLT [$10^3/uL$]	348.19	134.90	150 – 400

Table II: Distribution of prescribed Second Line HAART Combinations among the study Participants (*n=7*)

Second Line HAART Combinations	N (%)
AZT/3TC/LPV/r	3 (3.1)
TDF/3TC/LPV/r	3 (3.1)
AZT/3TC/ATV/r	14 (14.4)
TDF/3TC/ATV/r	46 (47.4)
ABC/3TC/LPV/r	18 (18.6)
AZT/DDI/LPV/r	12 (12,4)
ABC/3TC/NVP	1 (1)
Total	97 (100)

Table III: Distribution of abnormalities by drug combinations (*n=97*)

Abnormality	Drug Combination													
	2a		2b		2d		2e		5b		5c		5f	
	n	R Value	N	R Value	n	R Value	n	R Value	n	R Value	n	R Value	N	R Value
Anaemia	0	-0.12	1	0.009	4	-0.021	19	0.213	1	-0.262	5	0.087	0	-0.068
Leukopaenia	0	-0.166	2	0.073	10	0.206	23	0.069	6	-0.125	4	0.098	0	0.095
Leukocytosis	0	-0.032	0	-0.032	0	-0.073	2	0.069	0	-0.085	1	0.114	0	-0.018
Thrombocytosis	1	0.009	0	-0.12	6	0.106	13	-0.055	6	0.025	3	-0.048	1	0.153
Thrombocytopaenia	0	-0.05	1	0.18	2	0.112	4	0.054	0	-0.133	0	-0.105	0	-0.028
Neutropaenia	2	-0.009	3	0.12	11	0.084	31	-0.035	11	-0.082	9	0.048	0	-0.153
Neutrophilia	0	-0.054	0	-0.054	0	-0.123	5	0.091	3	0.146	0	-0.113	0	-0.031
Monocytopaenia	0	-0.111	1	0.022	10	0.399	11	-0.083	3	-0.119	2	-0.094	0	-0.063
Monocytosis	3	-0.054	0	-0.054	1	-0.123	10	0.091	6	0.146	7	-0.113	1	-0.031
Lymphopaenia	0	-0.079	0	-0.079	4	0.134	10	0.134	2	-0.069	0	-0.167	0	-0.045
Lymphocytosis	2	0.174	1	0.036	2	-0.1	6	-0.257	7	0.156	5	0.147	1	0.178
Eosinophilia	0	-0.082	0	-0.082	2	-0.035	8	-0.003	4	0.059	3	0.074	0	-0.047
Bicytopaenia	0	-0.085	1	0.068	2	-0.045	9	0.025	2	-0.091	4	0.143	0	-0.049
Pancytopaenia	0	-0.049	1	0.262	2	0.21	1	-0.093	0	-0.099	0	-0.078	0	-0.021

Key: **2a**-AZT/3TC/LPV/r; **2b**-TDF/3TC/LPV/r; **2d**-AZT/3TC/ATV/r; **2e**-TDF/3TC/LPV/r; **5b**-ABC/3TC/LPV/r; **5c**-AZT/DDI/LPV/r *and* **5f**-ABC/3TC/NVP

Table IV: Morphological classification of anaemia by drug combinations (*n=26*)

Morphology Classification	Drug Combination							N	%
	2a	2b	2d	2e	5b	5c	5f		
Normocytic Normochromic	0	1	2	11	1	1	0	16	61.5
Macrocytic Normochromic	0	0	0	1	0	1	0	2	7.7
Normocytic Hypochromic	0	0	0	0	0	1	0	1	3.8
Microcytic Hypochromic	0	0	1	5	0	1	0	7	26.9
Total	0	1	3	17	1	4	0	26	100

Key: **2a**-AZT/3TC/LPV/r; **2b**-TDF/3TC/ATV/r; **2d**-AZT/3TC/ATV/r; **2e**-TDF/3TC/LPV/r; **5b**- ABC/3TC/LPV/r; **5c**-AZT/DDI/LPV/r *and* **5f**-ABC/3TC/NVP

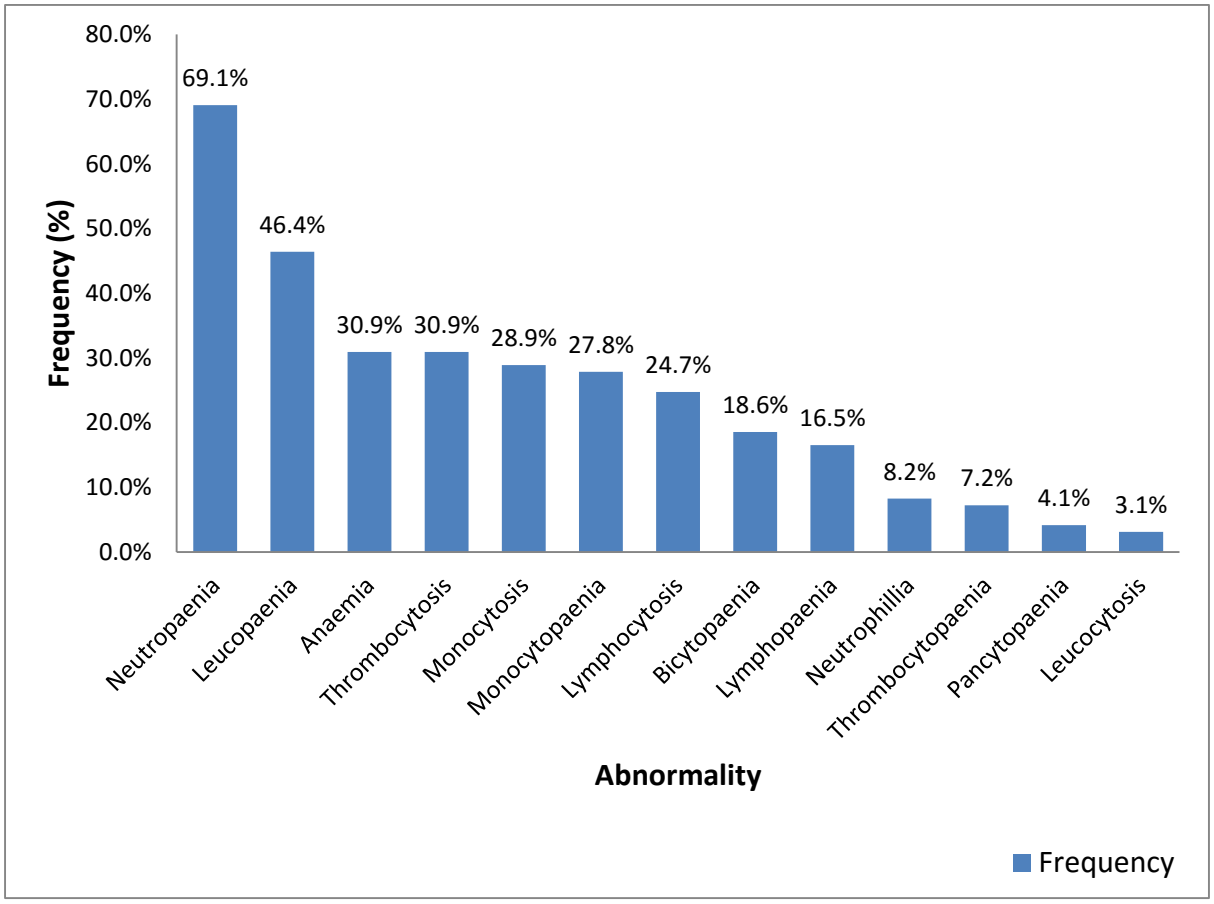

Fig 1: Frequency of haematological abnormalities in HIV paediatric patients on second line HAART combinations.

Discussions and Conclusions

The number of samples in the study was more than the calculated sample size. Therefore, the study was not affected by the sample size.

There was no significant association between haematological abnormalities and gender and age group of the participants. An earlier study on HIV paediatric patients on first line HAART treatment showed similar findings (*Nicodimus et al., 2017*).

Neutropaenia could be the major contributor of leukopaenia in these patients because neutrophils are the most abundant of white blood cell population (*Hoffbrand & Moss, 2016*). A significant decrease in neutrophil count may cause leukopaenia. Neutropaenia has been widely reported to be associated with some ART drugs, particularly combinations that included zidovudine. Prophylactic cotrimoxazole, which is often used in these patients to prevent opportunistic infections, is thought to be the cause of neutropaenia through an unknown mechanism (*Coutsoudis, 2010; Hoffbrand & Moss, 2011*). Neutrophils are responsible for bacterial killing and are increased in response to bacterial infection. Therefore, some prophylactic antibiotics may inhibit neutrophil production by the bone marrow resulting in progressive neutropaenia. Studies on bone marrow transplantation have shown a rapid recovery of neutrophils in patients on prophylactic ciprofloxacin than those on cotrimoxazole prophylaxis (*Imrie et al., 1995*).

Anemia was the second most common haematological abnormality in these patients. It has been found to be the most common cause of high morbidity and mortality in people living with HIV/AIDS, affecting 60-80% of the patients (*Meidani et al., 2012*). It cannot be concluded whether the cause of anaemia in this study was due to drugs or it was residual. However, since the study showed the prevalence of anaemia to be nearly half that of those living with HIV/AIDS without treatment, it can be concluded that HAART has helped reduce anaemia in HIV paediatric patients. The variations in the morphological classifications were consistent with other studies which showed high prevalence of normocytic normochromic anaemia followed by microcytic hypochromic anaemia (*Meidani et al., 2012; Nicodimus et al., 2017*). These morphological variations could have been largely caused by several factors involved in the disease process. These factors include viral or drug induced bone marrow suppression (normocytic normochromic), decreased red cell survival or haemorrhage (normocytic or macrocytic/normochromic), nutritional deficiency (microcytic/macrocytic normochromic/hypochromic) and chronic disease (microcytic normochromic/hypochromic) (*Hall & Malia, 1986*).

Thrombocytosis was significant. Studies have shown HAART to be associated with increased platelet production, markedly reducing HIV related thrombocytopaenia. Studies have confirmed reduced thrombocytopaenia and presence of thrombocytosis in HAART initiated HIV patients (*Scaradavou, 2002; Nicodimus et al., 2017*). However, it is feared that thrombocytosis may cause spontaneous in vivo platelet clumping or aggregation, creating reaction surfaces for coagulation leading to DIC or thrombosis.

Although the recommended drug combinations for HIV infected paediatric patients in Zimbabwe were ABC/3TC/NVP and ABC/3TC/EFV, TDF/3TC/ATV/r was the most prescribed second line HAART combination. This is the recommended combination if AZT (zidovudine) has been used in the first line dose. It has also been found to be relatively cheap

and has fewer side effects compared to other combinations. In Zimbabwe, AZT is the preferred combination for first line HAART (*EDLIZ Review Team, 2015; Nicodimus et al., 2017).* Haematological abnormalities in this study were commonly associated with TDF/3TC/LPV/r and AZT/3TC/ATV/r combinations. TDF/3TC/LPV/r is well known to cause side effects including haematological ones, although it was not a widely used combination. Many studies have implicated zidovudine in causing haematological abnormalities because of its tendency to suppress the bone marrow (*Nicodimus et al., 2017*). Tenofovir, as a substitute for zidovudine in the second line HAART combinations, may also be thought to have the same effects on the haematology of HIV paediatric patients.

It can be concluded that haematological abnormalities were significant in HIV infected paediatric patients on second line HAART. The most widely used combination was TDF/3TC/ATV/r. The abnormalities were similar to those found in HIV infected paediatric patients on first line HAART, although prevalence of anaemia was nearly twice that found in first line HAART. Although haematological abnormalities were mainly associated with TDF/3TC/LPV/r and AZT/3TC/ATV/r combinations, the TDF- based combinations were generally responsible for anaemia of varying morphological classifications in these patients.

It is recommended that close monitoring should also be done on HIV infected paediatric patients on second line HAART combinations to reduce abnormal haematological outcomes. Close monitoring of cotrimoxazole prophylaxis should also be done in order to reduce drug induced neutropaenia.

The study was limited by lack of information on the haematology of the patients before HAART initiation in order to exclude residual haematological abnormalities associated with HIV infection.

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