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GRADUATE PROGRAM

STUDY OF THE IMMUNOLOGIC AND HEMATOLOGIC PROFILE OF CHILDREN ON HAART: A RETROSPECTIVE COHORT STUDY AT ZEWDITU MEMORIAL HOSPITAL

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List of Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ALC	Absolute lymphocyte count
ANC	Absolute Neutrophil Count
ART	Antiretroviral Therapy
AZT	Zidovudine
CD	Cluster of Differentiation
CI	Confidence Interval
d4t	Stavudine
DHS	Demographic Health Survey
HAART	Highly Active Antiretroviral Therapy
HAPCO	HIV/AIDS Prevention and Control Office
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
IQR	Inter Quartile Range
LC	Lymphocyte Count
LC	Lymphocyte count
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MPV	Mean platelet volume
OD	Odds Ratio
PCV	Packed cell volume
PLT	Platelet Count
RBC	Red blood cells
RDW	Red cell distribution width
TLC	Total Lymphocyte Count
TLC	Total lymphocyte count
UNAIDS	United Nations Joint Program on HIV/AIDS

WBC	White blood cells
WHO	World Health Organization
3TC	Lamivudine

Abstract

Background: In HIV infected individuals immunologic and hematologic abnormalities are common and they increase the risk of morbidity and mortality. However little is known about the profile of immunologic and hematologic abnormalities in Ethiopia in those children who are on Highly Active Antiretroviral Therapy. Evaluating the haematological and immunological parameters in HIV/ AIDS patients on HAART is important in order to monitor the body responses to the drugs. Therefore, assessment of haematological and immunological changes in HIV/ AIDS patients in HAART is of a paramount importance.

Objective: the main objective of this study was to assess immunologic and hematologic profile of HIV infected children on highly active antiretroviral therapy in Zewditu Memorial Hospital.

Methodology: A retrospective cohort study was conducted among HIV infected children who received HAART between September 2008 and March 2013 at ART clinic of Zewditu Memorial Hospital in Addis Ababa, Ethiopia. Data were collected using structured questionnaire that included variables related to socio-demographic characteristics, immunohematological profiles and clinical conditions of the study individuals**.** Data was analyzed using SPSS for Windows version 16.0 soft ware.

Result: The mean level of hemoglobin, thrombocyte count and CD4 count showed statistically significant increment from the baseline (p-value <0.05). After six months of HAART, the prevalence of anemia, thrombocytopenia and neutropenia among the study children was 21%, 8.3% and 13.3%, respectively.

Conclusion: Our study indicated that the mean hemoglobin, thrombocyte count and CD4 count increased significantly in children who received HAART, but anemia, neutropenia and thrombocytopenia were common before and after treatment among the study subjects. Hence, we recommend the need for regular monitoring and evaluation of immunological and hematological values to enhance targeted interventions for encountered abnormalities.

1. Introduction

According to the 2012 Joint United Nations Program on HIV/AIDS (UNAIDS) report on the global AIDS epidemic, 34.2 million people were living with Human Immunodeficiency Virus (HIV) worldwide with 2.5 million new infections and 1.7 million deaths [1]. About 3.4 million children younger than 15 years were living with HIV worldwide in 2011 with 330,000 new infections [1].

In Sub-Sahara Africa 23.5 million people were living with HIV, including 3.1 million children**.** In this Region, new HIV infection in children were 300,000. As of December 2011, 562, 000 children were receiving antiretroviral therapy [1].

In Ethiopia, the 2011 Demographic and Health Survey (DHS) estimated the national adult HIV prevalence to be 1.5% [2]. The estimated number of people living with HIV in Ethiopia was 798,960 (479,940 female and 310,020 male) [3].

It has been demonstrated that patients taking highly active antiretroviral treatment (HAART) produce various clinical effects and also have been shown to affect the profiles of laboratory results, particularly the Haematological and Immunologic profiles. Some of the Hematologic parameters are: hemoglobin (Hb), packed cell volume (PCV), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red blood cell count (RBC), red cell distribution width (RDW), white blood cell count (WBC), lymphocyte count (LC), total lymphocyte count (TLC), platelet count (PLT) and mean platelet volume (MPV), and the most common immunological profiles to be affected are the CD4 and CD8 level[4].

Hematologic abnormalities are common in patients with advanced human immunodeficiency virus (HIV) infection and can affect the outcomes of HAART, resulting in higher mortality [5]. In both antiretroviral-treated and untreated individuals, anemia is independently associated with an increased risk of disease progression and death [6,7].

Anemia, neutropenia and thrombocytopenia are defined based on the World Health Organization (WHO) classification [8] . Accordingly, anemia is defined as Hb concentration less than 12g/dl and further severity is classified as follows: Hb level of 10 – 11.9 g/dl as mild; 8 - 9.9 g/dl as

moderate and < 8 as severe anemia [8]. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500 /mm3. Platelet count between 150,000 and 450,000/mm3 is classified as normal, greater than 450,000/mm3 as thrombocytosis and less than 150,000/ mm3 as thrombocytopenia[8].

Although HAART is known to profoundly suppress viral replication, increase CD4 cell count and delays disease progression and death; patients on Highly Active Antiretroviral Therapy (HAART) commonly suffer from side effects of the drug [10, 11]. Each antiretroviral drug is associated with specific adverse effects. Among the antiretroviral drugs, Zidovudine (AZT) remains to be the most widely used drug resulting in myelosuppression [11]. Several studies in developed countries have shown that AZT alone and AZT based HAART regimen is associated with significant reduction of hemoglobin (Hb) level and neutrophil number [7, 11, 12].

Though free Antiretroviral Therapy (ART) has been provided since 2005 in Zewditu Memorial Hospital, the outcome in immunological and hematological profiles has not been studied. The information above shows the importance of evaluating the haematological and immunological parameters in HIV/ AIDS patients under HAART in order to monitor the body responses to the drugs. These responses may be used as a monitoring tool for patients under HAART.

Little is known about the profile of immunologic and hematologic abnormalities in Ethiopia in those children who are on HAART. Therefore, this study was conducted to determine hematological and immunological laboratory profiles of children on HAART, in Zewditu Memorial Hospital

2. Literature review

2.1. HAART and hematological abnormalities

Patients on HAART produce various Immunologic and Hematologic laboratory profiles. Hematological complications have been documented to be the second most common cause of morbidity and mortality in HIV patients and are generally marked with cytopenias such as anemia, neutropoenia, lymphopoenia and thrombocytopenia [13].The incidence and severity of the cytopoenia generally correlate to the stage of the disease with anemia being the most commonly encountered hematologic abnormality and a significant predictor of progression to AIDS or death [14].

A report from South Korea indicated a low prevalence of cytopenia in HIV patients receiving HAART [5], and another study reported that the prevalence of cytopenia in HIV patients at initiation of ART in Africa and America were as follows: anemia, 12%; neutropenia, 14%; and thrombocytopenia, 7% [15].

2.2. HAART and anemia

Several studies in developed countries have shown that AZT alone and AZT based HAART regimen are associated with significant reduction of Hb level and neutrophil number [11, 12]. Though most of the studies on hematological abnormalities are on adults, one randomized comparative trial done to assess the safety and efficacy of AZT and d4T in symptomatic HIV infected children showed a prevalence of anemia to be 5% among the AZT group whereas 2% among the Stavudine (d4T) group [13]. Similarly the prevalence of neutropenia was higher in AZT group [16].

Since the earliest days of the epidemic, anemia has been recognized as an important clinical problem in HIV/AIDS [17]. It was a very common occurrence associated with the use of the first antiretroviral agent AZT , and frequently seen in advanced stages of the disease. In the late 1980s and early 1990s, blood transfusions used to treat anemia in the setting of HIV disease were found to be associated with a significant increase in mortality in patients with AIDS, and recombinant

human erythropoietin (epoetin alfa, Procrit) was approved as an alternative treatment option for anemia in HIV/AIDS patients treated with AZT [17].

Anemia is an important hematological marker since it has been reported to be a significant independent risk factor for mortality in HIV-1-infected patients [15]. The high rate of anemia in Africa and Haiti for example, could be related to the levels of poverty, malnutrition, and the overall poor economic state in these areas of the world [15].

The mean corpuscular volume (MCV) is used as a pointer to distinguishing between the different types of anemia, the normal range being 80-95 fL. Lower MCV (microcytic anemia) is associated with iron deficiency and elevated MCV (macrocytosis) typically with vitamin B12 or foliate deficiency although in the setting of HIV treatment often simply reflects use of AZT or d4T. Both AZT and d4T lead to macrocytosis, but only AZT causes anemia [9].

In another study, anemia was also more likely to occur in HIV infected women who had a CD4 count of <200 cells/mm3, higher plasma HIV RNA level, history of an AIDS-defining condition, and in those currently taking AZT or have had a history of taking AZT within the past six months [17]. The use of nucleoside analogs other than AZT was not statistically associated with anemia. The HIV epidemiology research study group had remarkably, similar findings, age(per 5- year increase), lower body mass index, history of pneumonia, oral candidiasis or fever, CD4 <200/mm3 and AZT use all increased the risk of anemia significantly[19]. Of note, however, the significance of some of these factors was lost when patients treated in the HAART era (1996-2000) were examined. Specifically, pneumonia, fever and AZT use all lost significance [9].

A recent cohort analysis, from Johns Hopkins University suggested that the use of AZT was not a significant risk factor for anemia in HAART treated patients [9]. In this analysis of 905 patients receiving care at Johns Hopkins since July 1996, only 21% of patients starting HAART had a Hb >14g/dl, but after one year of therapy, 42% of individuals had Hb >14g/dl, this benefit being regardless of AZT use. Anemia was significantly more likely to recover if HAART was given compared with untreated persons. However, data from prospective randomized studies suggested that anemia events remain more common with AZT-based HAART relative to d4T-based therapy [9]. In the selection of thymidine analog regmen therapy trial studies, Indinavir-based

HAART regimens were compared by nucleoside back bone. In the AZT-3TC treated patients (n=206 randomized) Hb < 12 g/dl occurred in 16% of patients compared with 9% in d4T treated patients (n=203 randomized, 101 with 3TC, 102 with didanosine) amongst individuals with Hb >12 g/dl at baseline (p=0.046). Mean Hb fell in the AZT group, but raised with d4T over 48 weeks of treatment. Severe anemia (i.e. Hb <8 g/dl) occurred in 1.5% of AZT but 0% of d4T treated patients. These studies did not specifically evaluate whether specific baseline demographic characteristics were associated with an increased risk of anemia [20].

Initial data from the early HAART era indicated that severe anemia was less frequent, and anemia was subsequently perceived by many (both physicians and patients) to be less of a clinical issue. Additional studies suggested that mild-to-moderate anemia continued to be common despite HAART. A more recent data, again collected during the HAART era, show that anemia continues to be associated with a worse prognosis, decreased survival time, increased risk of clinical progression and reduced quality of life [14].

2.3. HAART and neutropenia

Neutropenia is a common hematological abnormality in persons with untreated HIV-1 infection. Several mechanisms for neutropenia in HIV-1 infection have been proposed, including decreased production of granulocyte colony-stimulating factor, a soluble inhibitory substance that decreases neutrophil production, and autoimmunity [21]. The Women's Interagency HIV Study cohort found baseline neutropenia in 44% of this cohort and a longitudinal analysis found that worsening HIV-1 disease was associated with subsequent neutropenia [22]. Likewise, neutropenia in the Pearls cohort was independently associated with CD4+ lymphocyte and platelet counts, hemoglobin level, sex, ethnicity, and country, suggests that the stage of HIV-1 infection is an important contributor to pre-treatment neutropenia [23].

A Meta-analysis of Six Prospective, Randomized, Comparative Studies showed 26-46% neutropenia in AZT [12]. Another randomized comparative trial of d4T and AZT in children also found 20% neutropenia over one year among AZT recipients [16].

2.4. Platelet response during HAART

A study on Effect of Highly Active Antiretroviral Therapy on Thrombocytopenia shows that after three months of highly active antiretroviral therapy, there were significant increases in the platelet count, which were independent of the use of zidovudine and of the base-line platelet count [24]. These increases were sustained for at least six months. In 26 patients (70 percent), the viral load decreased to undetectable levels (<200 copies per milliliter, as determined by reverse- transcriptase–polymerase-chain-reaction assay). Linear regression analysis showed no association between the increase in the platelet count and the number of CD4 T cells (r=0.0049, P=0.97). This research indicated that highly active antiretroviral therapy results in a sustained increase in the platelet count in HIV-infected patients with thrombocytopenia and that this increase is independent of the increase in CD4 T cells [24].

2.5. Treatment with HAART and immunological status

In a study conducted in Kenya, in the 52 children with CD4 cell results available at baseline and after 6 months of HAART, the absolute CD4 cell count increased from a median of 326 cells/μL at baseline to 536 cells/μL at six months after HAART initiation ($P < 0.001$). Similarly, the median CD4% increased from 5.8% at baseline to 15.4% at six months after initiation of HAART ($P < 0.001$). Among children with follow-up to 15 months ($n = 31$), the median absolute CD4 count rose from 286 to 682 cells/μL ($P < 0.001$). For this group, the CD4% increased from 5.4% to 18.1% ($P < 0.001$). Overall, the CD4% increased by a median of 7.4% within six months of receiving HAART, and in the subset of 31 children with longer follow-up, the CD4% rose by a median of 11.3% (interquartile range [IQR]: 3.4–16.2) after 15 months of therapy [25].

Another study in West Africa showed that, overall, the median (IQR) CD4% increased significantly from 13% (7 – 16) at baseline to 23.3% (18.0 – 28.5; $p<0.001$), 27% (20 – 34; $p<0.001$), and 27.5% (16 – 36; $p<0.001$) at 6, 12 and 18 months respectively. Among those aged less than five years at initiation of ART, the median (Inter Quartile Range) CD4% increase from baseline to 6, 12 and 18 months of therapy was 12.3% (8 – 14; $P <0.001$), 14% (8 – 19; $P = 0.0004$) and 18% (13 – 22; $p = 0.0048$) respectively [26]. CD4+ T cell count were used to assess

rate of immunological recovery in children ≥ 5 years of age at the start of ART. The median (IQR) increase in absolute CD4+ T cell count from baseline to 6, 12 and 18 months of therapy was 210 cells/mm3 (67.5 – 380; P = 0.0009), 470 cells/mm3 (270 – 650; p = 0.0005) and 375 cells/mm3 (62.5 – 835; p = 0.0085) [26].

Similarly, a study in four major hospitals of Addis Ababa showed that at ART initiation, 450 (37.9%) of the children were found to be in severe age adjusted immunodeficiency state. The mean CD4 count for the whole cohort at initiation of ART was 300 cells/mm3 (SD= 271 cells/mm3). After HAART the mean CD4 count was 685 cells/mm3 (SD =560cells/mm3), 741 cells/mm3 (SD = 373 cells/mm3), 772 cells/mm3 (SD= 423 cells/mm3) and 580 cells/mm3 (SD= 421cells/mm3) at one year, two years, three years and five years after initiation of ART respectively [27].

In Ethiopian studies that evaluate the magnitude and severity of diseases that arise due to complication of HAART treatment such as anemia, thrombocytopenia, and leukopenia were not undertaken. Therefore, the aim of this study was to determine the hematological and immunological laboratory profiles of patients taking HAART, in Zewditu Memorial Hospital.

3. Objective

3.1 General Objective:

The objective of this study was to assess immunologic and hematologic profile of HIV infected children on highly active antiretroviral therapy in Zewditu Memorial Hospital.

3.2 Specific objectives:

- To determine the profile of anemia on children on HAART
- To determine the magnitude of thrombocytopenia on children on HAART
- To evaluate the lymphocytosis and Neutropenia on children on HAART
- To assess the status of CD4 count on children on HART

4. Methodology

4.1 Study area

The study was conducted in the capital city of Ethiopia, Addis Ababa. Ethiopia is located in the Eastern part of Africa. The land area is estimated to be about 1.1 million square kilometers. The country is among the three most populous countries in Africa with a total population of 79,221,000 persons, of whom 65,996,000 (83.3%) are rural and 39,691,000 (50.1%) are males [28].

Addis Ababa being the capital city of Ethiopia has a total population of 3,147,000 [28]. This study was conducted specifically at Zewditu Memorial Hospital HAART clinic in Addis Ababa City Administration.

Zewditu Memorial Hospital was selected for this study since it is the oldest HAART clinic in the country. It had the highest number of people enrolled for HAART among all other sites in the country and the HAART site has a computerized data management system which facilitates the research process.

4.2. Study Period

The data of HIV/AIDS patients attended at the ART unite of Zewditu Memorial Hospital between September 2008 to March 2013 were collected on August 2013.

4.3. Study design

A retrospective cohort study was conducted on 300 HIV infected children who were on HAART between September 2008 to March 2013 in Zewditu Memorial Hospital.

4.4. Source population

The source population were children under 15 years living with HIV/AIDS.

4.5. Study population

The study population were children under 15 years who were receiving HAART from Zewditu Memorial Hospital and who had WBC, CD4 + T cell, Hb and platelet values taken at the time of ART initiation and at least 6 months after initiation of the treatment.

4.6. Inclusion and exclusion criteria for the study

Inclusion criteria

Patients

- Who were under 15 years and HIV positive
- Have been on HAART treatment for six months or more

Exclusion criteria

Patients

- Above the age of 15 years
- On HAART treatment for less than 6 months

4.7. Study variables

a). Dependent variables:-

- Hematological values; Hemoglobin (Hb), White blood cell count (WBC), Total lymphocyte count (TLC), Absolute neutrophil count (ANC), Thrombocyte count.
- Immunological characteristics; CD4 values.

b).Independent variables:-

- Socio-demographic variables; age, sex
- Types of regimen
- Clinical characteristics; WHO stage
- Parental status; Orphan, at least one parent alive

4.8. Sample size determination

All children who were on HAART for six months or more at the ART unite of Zewditu Memorial Hospital.

Sample size of patients involved in the study calculated using a formula of single population proportion;

$$n = [(z\ \alpha/2)^2 * p\ (1-P)]\ /d^2$$ where;

- 'n' is the required sample size
- 'P' the proportion of HIV positive children on HAART taken as 24 %, from UNAIDS report on the global AIDS epidemic, 2011.
- 'Z' is the standard score corresponding to 95% confidence level
- 'd' is the margin of error 5%

Therefore the required sample size will be

$$n = \frac{[(1.96)^2 * (0.24 * 0.76)]}{(0.05)^2} = 280$$

Therefore the required sample size is calculated to be **280** HIV positive children on HAART

4.9. Sampling procedures

All HIV infected children who attended at the ART unite of Zewditu Memorial Hospital between September 2008 and March 2013 and who were on HAART treatment for six months or more were included in the study.

4.10. Data collection procedures

A standardized data abstraction form, which addresses all study variables, was developed to collect quantitative data. Pretesting was done before the actual data collection and modification was done accordingly. The quantitative data were collected by trained nurses. The data were checked for completeness every day by a supervisor and the Principal Investigator. Incomplete data were rechecked by the supervisor and by the Principal Investigator.

Three nurses were recruited as data collectors and one supervisor was recruited to assist the data collection process with main responsibility of checking the completeness of the data abstraction form. Incomplete data were rechecked by the supervisor. The principal investigator was responsible for the overall supervision. The data collectors took training on the data collection tools, methodology, probing, maintaining quality, and other issues. The training was facilitated by the Principal Investigator.

4.11. Data quality management

Pretesting was done before the actual data collection and modification was done accordingly. All the data were checked for completeness, accuracy, clarity and consistency by the principal investigator immediately after data were collected.

4.12. Data processing and Analysis

Quantitative data were coded and entered into computer and analyzed by SPSS 16 soft-wares after cleaning of the data. In the analysis process, frequency distribution of variables was worked out in order to describe them in relation with the study population. Values were presented as mean ± SD. Percentages were used to describe the proportions of the discrete variables. A P-value <0.05 was considered statistically significant**.**

4.13. Operational definitions

Acquired Immune Deficiency Syndrome (AIDS): It refers to the advanced stage of HIV illness, when the CD4 count falls under 200 [29].

Antiretroviral (ARV) drugs: Refers to drugs used against retroviruses, commonly anti-HIV drugs [29].

Anemia: Hb concentration less than 12g/dl [8].

CD4: A receptor on the surface of cells that HIV attaches to. The cells involved in cell-mediated immunity known as T-lymphocytes have the CD4 marker. Other cells, including some in the brain have the same marker and are the targets of HIV [29].

CD4 count: Represents the count of the cells with CD4 receptor in circulation [29].

Highly Active Antiretroviral Therapy (HAART): A treatment with a combination of at least three different ARVs [29].

Human Immunodeficiency Virus (HIV): The virus that causes AIDS. There are two different types HIV-1 and HIV-2. Worldwide, HIV-1 is the most common type [29].

Immune Failure: developing or returning to CD4 < 200 cells/μl.

Neutropenia: neutrophil count (ANC) of less than 1500 /mm3 [8].

Regimen: Medicine or medicines formulated for a specific illness or disease [5].

Thrombocytopenia: platelet count less than 150,000/ mm3 [8].

Thrombocytosis : platelet count greater than 450,000/mm3 [8].

4.14. Ethical Considerations

Ethical clearance was obtained from the ethics review committee of the School of Public Health, Addis Ababa University College of Health Sciences. The study was conducted in the Zewditu Memorial Hospital after permission was obtained from the relevant body administering the institution. Names and any other sensitive personal information of individual study subjects were not recorded during data collection and access to the data was limited. Moreover the data collectors were professionals working in the ART clinics of the selected hospital.

4.15. Dissemination of findings

The findings of the study will be distributed to the participating health facility and different stakeholders through the appropriate channel. And the findings will also be submitted to the School of Public Health as partial fulfillment of the Master of Public Health and will also be published in local or international journals.

5. Results

5.1. Basic demographic and clinical characteristics

Of the 300 patients included in the study, 166 (55.3%) were male (Table 1). The mean age at initiation of HAART was 7.68 ± 4.15 years. The majority 115 (38.3%) were between the ages of 60 – 119 months, 107 (35.7%) were between the 120 – 179 months, 53 (17.7%) were between 12 – 59 months, 25 (8.3%) were less than 12 months of age (Table 1).

With regard to child status 233 (77.7%) patients were on follow up, 25(8.3%) lost to follow up, 18(6%) transferred out and 24(8%) died (Table 1). With regard to the survival status of their parents 119 (39.7%) were both alive, 78 (26%) were mother alive, 47 (15.7) were father alive, 56 (18.7) were neither alive (Table 1). According to WHO clinical staging 16 (5.3%) of the study participants were in stage I, 135 (45%) were in stage II, 118 (39.3%) were in stage III, 31 (10.3%) were in stage IV (Table 1). The most commonly prescribed initial regimen was AZT-3TC- NVP in 132 (44%) of cases, followed by d4t -3TC- NVP 118 (39.3%), AZT-3TC-EFV 28(9.3%) and d4t- 3T- EFV 22(7.3%) (Table 1).

Table1. Baseline demographic, clinical characteristics and drugs taken by HIV Infected children on HAART at Zewditu Memorial Hospital ART unit from September 2008 to March 2013.

Demography	**n (%) (N=300)**
Sex	
Male	166(55.3)
Female	134(44.7)
Age in months	
<12	25(8.3)
12 – 59	53(17.7)
60 – 119	115(38.3)
120 – 179	107(35.7)
Child status	
Still on follow up	233(77.7)
Lost to follow up	25(8.3)
Transferred out	18(6)
Died	24(8)
Parent status	
Both alive	119(39.7)
Mother alive	78(26)
Father alive	47(15.7)
Neither alive	56(18.7)
WHO stage	
Stage I	16(5.3)
Stage II	135(45)
Stage III	118(39.3)
Stage IV	31(10.3)
Type of ART drug	
AZT-3TC-NVP	132(44)
d4t-3TC-NVP	118(39.3)
AZT-3TC-EFV	28(9.3)
d4t-3TC-EFV	22(7.3)

5.2. Hematological values of HIV infected children

Mean CD4 count at the baseline for 300 patients was 370 ± 353 cells/µl and six months after initiation of HAART, increased to 649 ± 493 cells/µl ($P<0.05$) (Table 2). Mean CD4 count for children <5 years increased from 713 ± 481 to 1178 ± 597 six months after treatment. Mean CD4 count for children aged 5 years and above increased from 246 ±191 to 490 ± 320 six months after treatment (Table 2).

The mean haemoglobin concentration increased from baseline 11.9gm/dl to 12.9 six months after treatment (Table 2). Mean hemoglobin level in those patients who have been taking AZT and d4T were 12.5 ± 1.5 and 13.1 ± 1.3 six months after treatment respectively (Table 2). Mean thrombocyte count was 267,000 ± 127,000 and 338,000 ± 144,000, mean total WBC count was 7160 ± 3390 and 7500 ± 3700, mean absolute lymphocyte count (ALC) was 3130 ± 1870 and 3450 ± 2300 before and after six months of initiation of HAART respectively (Table 2). Whereas the mean absolute neutrophil count (ANC) decreased from baseline 3260 to 3230 six months after treatment (Table 2). The increments of hemoglobin, thrombocyte count, absolute lymphocyte count and CD4 count were statistically significant (p-value <0.05) (Table 2).

Table 2. Paired t- test model showing mean hematological values of HIV Infected Children, before and after 6 month initiation of HAART at Zewditu Memorial Hospital ART unit from September 2008 to March 2013.

Variables	Before HAART Mean(SD) (N=300)	Six months after HAART Mean(SD) (N=300)	P-value
CD4	370(353)	649(493)	0.00
Age < 5 yrs	713(481)	1178(597)	
Age ≥ 5 yrs	246(191)	490(320)	
Hemoglobin(Hb)	11.9(1.7)	12.9(1.5)	0.00
AZT based	11.2(1.7)	12.5(1.5)	
D4T based	12.3(2.0)	13.1(1.3)	
Thrombocyte × 1000	267(127)	338(144)	0.00
WBC × 1000	7.16(3.39)	7.5(3.7)	0.212
ALC × 1000	3.13(1.87)	3.45(2.3)	0.018
ANC × 1000	3.26(2.1)	3.23(2.1)	0.89

5.3. Hematological abnormalities

Hematological abnormalities were present both before and after treatment with HAART (Table 3). Anemia (<12g/dl) was found in 147(49%) of the subjects before and in 63(21%) of the subjects six months after initiation of HAART. Mild anemia was seen in 110 (74.8%) and 47 (74.6%), moderate anemia in 30 (20.4%) and 15 (23.8%), severe anemia in 7 (4.8%) and 1 (1.6%) of the children before and after six months of initiation of HAART respectively (Table 3)

Neutropenia was seen in 28(9.3%) and 40(13.3%), thrombocytosis in 19(6.3%) and 62(20.7%), thrombocytopenia in 46(15.3%) and 25(8.3%) of the children before and after six months initiation of HAART respectively (Table 3).

Of the study children 111(37%) and 30(10.7%) had severe immune suppression (CD4 count below 200) before initiation of HAART and six months after HAART respectively (Table 3).

Table 3. Pattern and severity of haematological abnormalities of HIV infected children before and after 6 months initiation of HAART at Zewditu Memorial Hospital ART unit from September 2008 to March 2013.

Variable	Before HAART (N=300) n(%)	Six months after HAART (N=300) n(%)	P-value
Hb			
Hb ≥ 12g/dl	153(51)	237(79)	0.26
Hb < 12g/dl	147(49)	63(21)	
Anemia severity			
Mild (10 – 11.9g/dl)	110(74.8)	47(74.6)	*N.A
Moderate (8 - 9.9g/dl)	30(20.4)	15(23.8)	
Severe (< 8g/dl)	7(4.8)	1(1.6)	
Neutrophil Count			
≥ 1500	272(90.7)	260(86.7)	*N.A
< 1500	28(9.3)	40(13.3)	
Thrombocyte			
>450 × 1000	19(6.3)	62(20.6)	*N.A
150 – 450 × 1000	235(78.4)	213(71)	
<150 × 1000	46(15.3)	25(8.3)	
CD4			
≥ 200	189(63)	268(89.3)	0.00
≤ 200	111(37)	32(10.7)	

*N.A (not applicable) as chi-square requirements are not met.

5.4. Variables associated with development of anemia

After controlling confounding effect, children who were below age five years (OR=4.5), female (OR=1.15), orphan (OR=1.16), WHO stage 4 (OR=1.77) and CD4 count <200 after HAART (OR=2), were more likely to have anemia as compared to their counter parts (Table 4). However only age below five years showed statistically significant association (OR: 4.5; 95% CI: 2.2, 9.15)

Table 4. Coefficients and OR from logistic regression model predicting the probability of anemia in HIV infected children on HAART at Zewditu Memorial Hospital ART unit from September 2008 to March 2013.

Variables	β coefficient	Crude OR (95% CI)	Adjusted OR (95% CI)
Age			
< 5 years	1.5	4 (2.1, 7.8)	4.5 (2.2, 9.15)
≥ 5 years			
Sex			
Female	0.143	1.03(0.55, 1.9)	1.15(0.59, 2.23)
Male			
Parental status			
Orphan	0.148	0.8(0.34, 1.9)	1.16(0.47, 2.8)
At least one parent alive			
WHO stage			
Stage 4	0.569	2(0.7, 5.6)	1.77(0.53
Stage 1-3			
CD4 count after HAART			
CD4 < 200	0.7	1.4(0.54, 3.45)	2.0(0.75, 5.4)
CD4 ≥ 200			

6. Discussion

Antiretroviral therapies (ARVs) have dramatically reduced the rates of mortality and morbidity as well as improved the quality of life for people living with HIV/AIDS [24]. Despite ARVs being of extreme impact on the pathogenesis and health of most HIV/AIDS patients, issues of drug induced toxicities and their drug-induced haematological consequences (anemia, neutropenia, and thrombocytopenia) have remained of great concern [12]. Our study focused on evaluation of haematological and immunological changes among HIV/AIDS patients under ARV therapy.

Haematologic complications occur frequently in children with HIV infection [12]. The present study has shown that out of 300 patients 147 (49%) were at baseline anemic. In agreement with this, another study conducted in Cambodian children showed that 50% cases were with Hb < 11.5g/dl at the baseline [30]. Studies from sub-Saharan Africa have reported anemia prevalence ranging from 42% to 75% among HIV-infected children [31]. A study done in Ugandan children also showed that 57.6% were anemic [32]. In another retrospective study conducted at Felege-Hiwot Referral Hospital, Bahir-Dar, Ethiopia demonstrated prevalence of 65% anemia, compared to this, our finding is lower. This difference could be possible due to high prevalence (71.7%) of WHO clinical stage III and IV in Bahir- Dar patients (33). The most prevalent anemia in this study was mild anemia and this is also supported by a study conducted in Uganda which described that mild anemia occurred in 62% of study subjects [32].

In this study, thrombocytopenia was observed in 46 (15.4%) of patients before starting the treatment. Our findings are consistent to those of Firnhaber et al who reported that the prevalence of thrombocytopenia at baseline in India was 14% [15].

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The current study shows that at ART initiation, 111 (37%) of the children were found to be in severe immunodeficiency state (CD4 < 200). Similarly, an Ethiopian study in four major hospitals of Addis Ababa, Ethiopia showed that 37.9% of the children were in severe immunodeficiency state [27].

The present study compared hematological profile of HIV infected children at baseline and six months after initiation of HAART and showed that the mean hemoglobin value at the baseline for 300 patients was 11.9 ± 1.7 gm/dl and six months after initiation of HAART increased significantly to 12.9 ± 1.5 gm/dl ($P<0.05$), the prevalence of anemia at the baseline was 49.1% and after HAART decreased to 22.7 %. In consistent with this another study conducted in Zambia showed that the median hemoglobin at treatment initiation was 11.1g/dl and after six months of ART, the median hemoglobin increased to 12.3 g/dl [34]. Our study is in line with a study done in India, in which the prevalence of anemia at base line was 40% and after initiation of treatment, Zidovudine induced anemia was present in 30% of children [35].

Our study has shown that after initiation of HAART therapy, the mean Hb level increased by 1mg/dl from baseline. In further analysis, the mean hemoglobin level was 0.6 g/dl lower in patients who received AZT based than those who received d4T based HAART. This is in line with a meta-analysis of 6 randomized trials, in which the mean hemoglobin level was 0.8 g/dL lower in patients who received zidovudine than those who received stavudine after 48 weeks on ART [12]. The present study is also supported by another study conducted at Zewditu memorial hospital Addis Ababa, Ethiopia that indicated at the base line, the mean ± SD of Hb value of the total 1166 adults was12 ± 2.4 gm/dl and six months after HAART initiation increased to 13.2 ± 3.8 gm /dl [36].

In the current study, Platelet count was increased significantly after six months of initiation of treatment ($P< 0.05$). The mean platelet cells count at the baseline for 300 patients was 267,000 ± 127,00 cells/µ, and after six months of treatment with HAART, the mean platelet count was increased to 338,000 ± 320,000 cells/µl. Similarly, Caso J et al reported that after three months of highly active antiretroviral therapy, there were significant increases in the platelet count [24]. The prevalence of thrombocytopenia after treatment (8.4%) was similar with finding of the randomized comparative trial of AZT and d4T in children which showed 7% [7].

We showed in our study that the overall mean CD4 count increased with continued use of ARVs after six months of treatment, which is consistent with many previous findings [37, 38]**.** Our study showed that mean CD4 count at the baseline for 300 patients was 370 ± 353 cells/µl and

six months after initiation of HAART, increased to 649 ± 493 cells/µl (P<0.05). Similarly, a study conducted in Kenyan children showed that the median absolute CD4 count increased significantly from 326 to 536 after six month of HAART [25]. In agreement with this, a study in four major hospitals of Addis Ababa showed that the mean CD4 count at treatment initiation was 300 ± 271 cells/µl and after 12 month of ART, the mean CD4 count increased significantly to 685 ± 560 cells/µl [27].

Mean CD4 count for children < 5 years increased from 713 ± 481 cells/µl to 1178 ± 597 cells/µl after 6 months of treatment. Mean CD4 count for children aged five years and above increased from 246 ±191 to 490 ± 320 , after six months of treatment. This is in line with a study done in West Africa in which median CD4 count for children aged five years and above increased from 285 cells/µl to 495 six months after treatment [26].

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The current study showed that the mean white blood cell count at the baseline was 7160 ± 3390 cells/ul IQR and six months after initiation of HAART, increased to 7500 ± 3700. Our study also showed that the mean absolute lymphocyte count at the base line was 3130 ± 1870 cells/ul and six months after initiation of HAAT, increased to 3450 ± 2300. In agreement with this, a study in Kenya reported that at the baseline the median total lymphocyte count was 3849 and six months after HART the median total lymphocyte count increased to 4025 [25]. .

In the current study absolute neutrophile (ANC) count showed same decrement in the mean value. Neutropenia was seen in 28(9.3%) and 40(13.3%), of the children before and after initiation of HAART, respectively. Compared to randomized comparative trial of d4T and AZT in children which found neutropenia of 20% over one year among AZT recipients our finding is lower [16]. This difference could be possible due to the difference in age of the study population.

7. Strengths and limitations of the study

Strength

- Clinical record reviewed using pre-tested structured data collection format which minimize information bias.
- Data quality was assured by recruiting ART trained nurse data collectors and close supervision.

Limitations

- This study used secondary data in a single hospital. The result may not be representative of the national picture as it is done in one hospital with relatively well organized ART Clinic.
- The clinical records were very often incomplete lacking important socio-demographic and clinical variables.

8. Conclusion and Recommendation

Conclusion

Our study indicate that the mean hemoglobin, thrombocyte count and CD4 count increased significantly in children who received HAART but anemia, neutropenia, thrombocytopenia and thrombocytosis were common before and after treatment among the study subjects.

Recommendations

Hematological tests should be performed regularly to follow the effectiveness of the treatment

Physicians giving care for HIV infected children should routinely investigate and treat hematological abnormalities before and after treatment.

Additional studies are recommended to strengthen and explore the problem in depth

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Annex I. Data abstraction form

S.N	Variable	Categories	Remark
Part I: Socio-demographic Characteristics			
1	ART unique number		
2	Age		
3	Sex	1. Male 2.Female	
4	Child status	1.Still on follow up 2.Lost to follow up 3.Transferred out 4.Died after month initiation of ART	
5	Parental Status	1.Both alive 2.Father alive 3. Mother alive 4. Neither alive	
Part II: Base line at initiation of ART			
6	Date at initiation of ART		
7	CD4 count	cells/µl	
8	Hemoglobin	gm/dl	
9	WBC	cells/µl	
10	Total Lymphocyte count		
11	Neutrophil count	cells/µl	
12	Platelet	cells/µl	
13	WHO stage	1. I 2.II 3.III 4.IV	
14	Regimen	1) 4a 2) 4b 3)4c 4) 4d 5) 4e 6) 4f 7) Other	
Patient status at 6 months of ART treatment			
15	Date		
16	CD4 count	cells/µl	
17	Hemoglobin	gm/dl	
18	WBC	cells/µl	
19	Total lymphocyte count		
20	Neutrophil count	cells/µl	
21	Platelet	cells/µl	
22	Regimen	1) 4a 2) 4b 3)4c 4) 4d 5) 4e 6) 4f 7) Other	

Annex II: English Patient Information sheet

Participant information sheet

Description of the study

Title of the study: Study of immunologic and hematologic profile of children

on HAART: a retrospective record review

Objective of the study: To assess immunologic and hematologic profile of HIV infected children on highly active antiretroviral therapy in Zewditu memorial hospital.

Introduction

It has been demonstrated that patients taking highly active antiretroviral treatment (HAART) produce various clinical effects and also has been shown to affect the profiles of laboratory results, particularly the Haematological and Immunologic profiles.

Although HAART is known to profoundly suppress viral replication, it increases CD4 cell count and delays disease progression and death; patients on Highly Active Antiretroviral Therapy commonly suffer from side effects of the drug.

Rationale of the study and its benefits

Though free ART has been provided since 2005 in Zewditu Memorial Hospital, the outcome in immunological and hematological profiles has not been studied. It is important to evaluating the haematological and immunological parameters in HIV/ AIDS patients under HAART in order to monitor the body responses to the drugs. These responses may used as a monitoring tool for patients under HAART. Therefore, assessment of haematological and immunological changes in HIV/ AIDS patients under HAART therapy is of paramount importance.Information which is necessary for the study will be taken from pre ART and ART log books and other clinical and laboratory records. As the study will be conducted through review of medical records alone, the individual patients will not be subjected to any harm as far as the confidentiality is kept. To keep the confidentiality of the patients, personal identifiers will not be included in the data collection format. For any questions about this study contact principal investigator Abebe Habteselassie with (Tel: 0911502540 or E-mail: ab_habte@yahoo.com)

Annex III: English Consent Form

My name is _____, I am a ART clinic nurse working here in Zewditu Memorial Hospital ART clinic and now I am collecting data from our patients pre ART and ART logbook for the research being conducted to determine the effect of HAART on laboratory profiles, by Ato Abebe Habteselassie who is the Master of public Health student in Addis Ababa University. Your child is selected as one of study subject by chance. The investigator employed me (from this ART clinic) for this data collection to maintain your data strictly confidential. We believe that the findings of this study will have paramount in order to monitor the body responses to the drugs.

Information which is necessary for the study will be taken from pre ART or ART log book.

As the study will be conducted through review medical records alone, it will not harm your child as far as the confidentiality is kept. The information will be taken when you give permission, participation is totally voluntary.

Your willingness for pre ART or ART record information to be utilized in this study will help us achieve the stated benefits of the study. Name and other personal identifiers will not be recorded on data collection format and the information we got will be kept confidential and will also be used for this study purpose alone. You have full right not to let your information on pre ART or ART logbook to be consumed for this study. But the information that would be taken will be quite useful for the study. Your child will not face any problem if you do not allow the information to be taken from the records and your child will not also be denied of getting any medical services from the hospital. If you have any questions about this study you may ask me or the principal investigator Abebe Habteselassie (Tel: 0911 502540 or E- mail ab_habte@yahoo.com)

Are you willing to let your child information to be utilized for this study?

1. Yes 2. No

Signature of the interviewer which shows that the respondent has consented (verbally) to take part in the study _____

Annex IV: Amharic patient information sheet

ለጥናቱ ተሳታፊዎች መረጀ መስጫ ቅጽ

የጥናቱ መግላጫ

የጥናቱ ርዕስ፡- የፀረ ኤችአይቪ /ኤድስ መድሀኒት ሕክምና በሕፃናቶች የላቦራቶር ውጤት ላይ የሚያመጣው ለውጥ

የጥናቱ አላማ፡- የፀረኤችአይቪ /ኤድስ መድሀኒት ሕክምና በሕፃናቶች የላቦራቶር ውጤት ላይ የሚያመጣው ለውጥ በዘውዲቱ መታሰቢያ ሆስፒታል ውስጥ ማጥናት

መግቢያ፡- በተለያዩ የውጭ አገር ጥናቶች በታዩት መሠረት የፀረኤችአይቪ /ኤድስ መድሀኒቶችን የሚወስዱ ታከሚዎች የተለያዩ ተጓደኝ ችግሮች (Side effect) ያመጣሉ እንዲሁም የለቦራቶሪ ውጤቶች ላይ ለውጥ ያመጣሉ::

ምንም እንኳ ኤችአይቪ /ኤድስ መድሀኒቶች የቫይረስ መራባትን እና የነጭ የደም ሴሊን ቢጨምሩ የተለያዩ ተጓደኝ ችግሮች የስከትለሉ::

የጥናቱ አስፈላጊነት፡- በዘውዲቱ ሆስፒታል ውስጥ ከ1998 ዓ.ም ጀምሮ ነፃ የፀረ ኤች አይቪ ሕክምና ቢጀመርም በላቦራቶሪ ውጤቶች ላይ የሚያመጣውን ለውጥ የሚያሳይ ጥናት አልተሠራም:: መድሀኒቱ በሰውነታችን ላይ የሚያመጣው ለውጥ ለመቆጣጠር በተለያዩ ወቅት የተወሰዱ የላቦራቶሪ ውጤቶችን ማጥናት አስፈላጊ ነው ይህም የመረጃ ክፍተትን ለመሙላት አስተዋጽኦ ያረገል::

ስለዚህ ለጥናቱ አስፈላጊ የሆኑ መረጃዎቹ ከዘውዲቱ መታሳቢያ ሆስፒታል ከቅድመ ፀረ ኤች አይቪ /ኤዲስ ታካሚዎች መዝገብ ከፀረ ኤች አይቪ /ኤዲስ ታካሚዎች ከመዝገብ እንዲሁም ከምርመራ እና ከላቦራቶሪ መዝገቦች ላይ የሰባሰባሉ ጥናቱ የሚደረገው ምስጥራዊነቱን በጠበቀ መልኩ በታካሚዎች መረጃ ላይ ስለሆነ ግለሰቦቹን የሚጐዳ ምንም ነገር አይኖርም ምስጢራዊነቱን ለመጠበቅ እዚያም በኤች አይቪ /ኤድስ ክሊኒክ ውስጥ ሕክምና የሚሰጡ የጤና ባለሙያዎች መረጃውን ከመዝገብ እንዲሰበስቡ ይደረጋል:: በመረጃ ስብሰባ ወቅት ለሚመጡ ታካሚዎች ፈቃደኝነታቸውን በመጠየቅ መረጃ ይወሰደል::

በተጨማሪም የኤች አይቪ /ኤድስ ታካሚዎች ማንነት የሚገልፅ ምንም አይነት መረጃ መጠያቁ ላይ አይሞላም የተወሰደው መረጃ ምስጢራዊነቱ ተጠብቆ ሙሉ በሙሉ ጠቃሜታው ለምርምር ሥራ ብቻ ይውላል:: ጥናቱን በተመለከተ ጥያቄ ከለዎት አጥኝውን አቶ አበበ ሀብተስላሴ በስልክ ቁጥር **0911502540** ወይም በኤሜል አድራሻ ab_habte@yahoo.com መጠየቅ ይቻላል::

Annex V: Amharic consent form

ለጥናቱ ተሳታፊዎች የፍቃደኝነት መጠያቂያ ቅጽ

ስሜ ----------ይባላል፡፡ በዚህ በዘውዲቱ መታሰቢያ ሆስፒታል በኤች አይ ቪ /ኤድስ ክሊኒክ ውስጥ የምሠራ የጤና በለሙያ ስሆን አሁን የፀረ ኤች አይ ቪ /ኤድስ መድሀኒቶች ሕክምና በሕፃናቶች የላቦራቶሪ ውጤት ላይ የሚያመጣው ለውጥ በሚል ርዕስ በአዲስ አበባ ዩኒቨርሲቲ ድህረ ምረቃ ተማሪ የሆኑት አቶ አበበ ሀብተስላሴ ለሚሰሩት ጥናት መረጃ ከኤች አይቪ /ኤድስ ጋር በሚኖሩ ታካሚዎች መዝገብ ላይ እየሰበሰብኩ ነው፡፡ የእርሶ ልጅ የጥናቱ አካል በመሆን ተመርጦአል፡፡ አጥኝው እዚሁ ኤችአይቪ /ኤድስ መዝገብ ላይ የምሰራውን እኔን ለመረጃ ሰብሳቢነት ሲመርጠኝ የመረጃውን ምስጢራዊነት ለመጠበቅ ብሎ ነው፡፡ ማለትም ከክሊኒክ ውጭ ያሉት በመረጃ ስብሰባ ወቅት ስምዎንና ሌሎች መረጃዎችን እንደያዩ ሲባል ነው፡፡ የዚህ ጥናት ውጤት ለታካሚዎች የተለየ ጥንቃቄ እንዲደረግ አስተዋጽኦ የጐላ እንደሚሆን ይታመናል በመሆኑም ለጥናቱ አስፈላጊ የሆኑ መረጃዎች ከልጅዎ ከፀረ ኤች አይቪ /ኤድስ መዝገብ እንዲሁም ከምርመራና ላብራቶር ሕክምና መዝገብ ላይ ስለሆነ በልጅኦ ላይ ምንም አይነት ጉዳት አያመጣም፡፡ መረጃ እንዲወሰድ መፍቀድ ለተጠቀሰው የጥናቱ አለማ መሰካት የጐላ አስተዋጽኦ ይኖረዋል፡፡ ከሕክምና መዝገብ ላይ መረጃ ሲወሰድ የልጅዎን ማንነት የሚገልፅ ስም እና ሌላ ማንነትን የሚገልፅ ምንም አይነት ነገር ወደ መጠይቁ አይሞላም፡፡ የተወሰደውም መረጃ ምስጢራዊነቱ ተጠብቆ ሙሉ በሙሉ ለምርምር ሥራ ብቻ ይሆናል፡፡ የሕክምና መረጃውን ለምርምር ሥራ እንዳይውል የማድረግ መብት አልዎት ነገር ግን መረጃውን ለምርምር ሥራ ቢውል ጠቀሜታው የጐላ ነው፡፡ በጥናቱ ለመሰተፊ ፍቃደኛ ባይሆኑ በሕክምናው ላይ ምንም አይነት ጉዳት አይፈጥርም በሌላ በኩል መረጃውን በመስጠትዎ የሚያገኙት የተለየ ጥቅም አይኖርም፡፡ ጥናቱን በተመለከተ ጥያቄ ከለዎት እኔን ወይም አጥኝውን አቶ አበበ ሀብተስላሴ በስልክ 0911502540 ወይም በኤሜል አድራሻ ab_habte@yahoo.com **መጠየቅ ይቻላል፡፡ መጠየቅ ይቻላል፡፡**

መረጃውን ለምርምር ሥራ ቢውል ፍቃደኛ ነዎት?

1. **አዎ** 2. **አይደለም**

መረጃውን ለጥናቱ ሥራ እንዲውል ፈቅደዋል፡፡
የመረጃውን ሰብሳቢ ስምና ፊርማ ----------

Declaration

I, the under Signed, declare that this is my original work and has never been presented in this or any other university and that all the source materials used for the thesis have been duely acknowledged.

Name : Abebe Habteselassie

Signature . _____

Place : Addis Ababa University, Ethiopia

Date of submission: . _____

This thesis has been submitted for examination with my approval as a university advisor:

Name : Professor Ahmed Ali .

Signature . _____

Date::: _____