Full Length Research Paper

Prevalence of anaemia before and after the initiation of antiretroviral therapy at ART centre of Hawassa University Referral Hospital, Hawassa, South Ethiopia

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Ethiopia has experienced a rapid expansion in access to Antiretroviral Therapy (ART) for Human Immunodeficiency Virus (HIV) infected patients. HIV associated anaemia is always overseen and it could be a challenge for prognosis of patients who are taking ART. The prevalence of anaemia due to HIV at the early stage of infection is more prevalent than in the late stage. Knowing the impact of HIV on the haematopotosis of HIV infected patients is very essential for the management and care of people living with Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS). HIV related anaemia decreases the quality of life and survival rate of HIV patients. We conducted a cross-sectional analysis of hospital based retrospective study using a hospital secondary data. A total of 384 adult (≥15 years) patients with complete information of Cluster Difference (CD4) cell count, haemoglobin and hematocrit levels and red blood cell count were used from the registration book starting from 2005 to 2010. The measurement of Haemoglobin, CD4 + T cell, Hematocrit and Red Blood Cell (RBC) count was measured using standard methodology at baseline and after 6 months of antiretroviral therapy (ART). Paired t-test was used to assess mean differences for haemoglobin and CD4 + T cell count before and after ART initiation. The aim of this study was to determine prevalence of HIV associated anaemia before and after initiation of antiretroviral therapy (ART) in HIV infected adults. Of the 384 study subjects 90 (23.4%) were anemic before ART. However, the prevalence of anemia after ART 46 (12.0%) significantly decreased (p<0.05). The prevalence of anemia was higher in females than in males at base line (77.8 vs. 22.2%) (p=0.017), and after ART treatment (65.2 vs. 34.8%) (p=0.000).

Key words: Prevalence, highly active antiretroviral therapy (HAART), anaemia.

INTRODUCTION

The Human Immune-deficiency Virus (HIV) is a retrovirus that infects cells of the immune system, destroying or impairing their function. As the infections progresses, the immune system becomes weaker, and the person becomes more susceptible to infections. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS) (World Health Organization, 2006).

Ethiopia is one of the sub-Saharan countries which are highly affected by the HIV/AIDS pandemic. According to the ministry of Health (2007) report, about 977,394 people live with HIV/AIDS with the national adult HIV prevalence of 2.1% and total of 125,528 people are newly infected with HIV every year (Ministry of Health, 2007).

Anaemia is one of the most common blood abnormalities in people with HIV disease. Up to 90% of adults can develop anaemia during an HIV infection and especially, in individuals with advanced disease of lower CD4+ T-cell count (Sullivan, 1996; Shah and Murthy, 2005; Mildvan and Creagh, 2002; National Anemia Action council, 2001). People with anaemia after suffering a decreased quality of life potentially increase chance of mortality. The incidence of anaemia has been found to be strongly associated with the progression of HIV to AIDS (Sullivan, 1996; Mildvan and Creagh, 2002; National Anemia Action council, 2001).

The rate of anemia was reduced when patients started

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using combination of Highly Active Antiretroviral Therapy (HAART). In spite of these advances, mild to moderate anemia is still common. Anemia in general remains a persistent problem (Belperio and Rhew, 2004) and it is the most frequently recorded Adverse Drug Reactions (ADRs) to HAART (FMOH and HAPCO, 1998). Anemia is a frequent complication of infection with the human immunodeficiency virus type-1 (HIV-1) and may have multiple causes (Doukas, 1992).

In different study settings, the prevalence of anemia in persons with acquired immunodeficiency syndrome (AIDS) has been estimated at 63 to 95% (Groopman, 1990; Mir et al., 1989; Frontiera and Myers, 1987; Zone et al., 1987) making it more common than thrombocytopenia or leucopenia in patients with AIDS (Groopman, 1990; Calenda and Chermann, 1992). This high prevalence of anemia may be because of high incidence of anemia, long duration of anemia, or a combination of both. HIV infection may lead to anemia in many ways: changes in cytokine production with subsequent effects on hematopoietic production (Calenda and Chermann, 1992; Zauli et al., 1992; Spivak et al., 1989) decreased erythropoietin (Carnacho et al., 1992; Horsburgh, 1991) opportunistic infectious agents, such as mycobacterium avium complex (Naides et al., 1993) and parvovirus B-19 (Richman et al., 1987) administration of chemotherapeutic agents such as zidovudine (Faulds et al., 1990) ganciclovir (Keisu et al., 1990) and trimethoprim-sulfamethoxazole (Ellaurie et al., 1990) and myelophthisis caused by cancers such as lymphosarcoma.

Anemia has been associated with progression of HIV to AIDS and shorter survival times (Salrot et al., 1997; Agnes et al., 2010). Anemia is a frequent complication that occurs in 20 to 80% of HIV-infected persons and is associated with faster disease progression and mortality (Belperio and Rhew, 2004). Serious anemia used to be much more common over 80% of people with an AIDS diagnosis and some degree of anemia people without, had higher rates of anemia and the prevalence of anemia varies in different countries. At base line, the prevalence of anemia was reported 15% in Uganda (Johannessen et al., 2011) and 77.4% in Tanzania (Moor and Forney, 2002).

Some reports showed that anemia in HIV men patients is more prevalent (37.3%) than women (32.3%) (Mildvan and Creagh, 2002) and others showed that the prevalence of anemia in women is 29%. HAART is an effective treatment of the anemia of HIV infection (Mocroft et al., 1999). After HAART was introduced, the prevalence of severe anemia in HIV infection declined (Semba et al., 2001). HAART is associated with a large reduction in anemia among HIV infected women (Harris et al., 2008).

There are many medications that are used in treatment of HIV/ AIDS that can also cause anemia. Combination of therapy including as much as 3 to 5 drugs has become the standard of practice. Many of their mediations can cause side effects such as anemia. Anaemia is a common feature of HIV infection occurring in patients who initiate antiretroviral treatment (ART) in Europe and North America. HIV – associated – anemia is common and associated with poor prognosis (Ferri et al., 2001). Anemia developed in close to 90% of HIV infected patients before the initiation of HAART, and still found in up to 46% of patients in the HAART era (Francis et al., 2005).

There was no significant difference in anemia prevalence between patients receiving HAART and not receiving HAART. However, there was an increased prevalence of anemia in patients whose HAART regimen contained Azidothymidine (AZT). The high prevalence of anemia among patients with immunologic AIDS complicates the roll-out of antiretroviral regimens containing zidovudine, a drug which may exacerbate anemia. Following ART initiation, patients developed a new episode of anemia (worsening, or new episode following resolution), and 5.5% developed new severe anemia. The first grade 4(severe) anemia was identified a median of 12 weeks after initiation (WHO, 2007).

Anemia is associated with progression to death in HIV/AIDS patients after the initiation of ART. Most patients had anemia at enrollment or before the initiation of ART. The mean haemoglobin increased significantly in patients who received ART, but one third was still anemic (Molaghm, 1999). The treatment of people with HIV disease and collates with improved survival as well as improved quality of life and general sense of well being (Teklemariam, 2011).

There are reports on HAART effects on anaemia in HIV/AIDS patients in Ethiopia. The reports showed a reduction in the prevalence of anemia before and after the initiation of ART from 52.6 to 37.39% and from 62.8 to 16.1% (Izaks et al., 1999). Some reports showed that the levels of anemia varied based on geographical and other socio-demographical variations (Sullivan, 1996). However, there has been no similar published report from southern Ethiopia.

**MATERIALS AND METHODS**

**Study area**

The study was carried out in the University of Hawassa, College of Medicine and Health sciences at Teaching referral Hospital Hawassa City, South Ethiopia. The hospital as a teaching referral hospital has a referral status and is located in the Southern part of Ethiopia. Hawassa referral hospital provides HIV/AIDS interventions including free diagnosis, treatment and monitoring. The centre diagnoses new cases and monitors those on therapy. Also, structured HIV/AIDS data were available at this referral Hospital. Of these
data, 2007 to 2011 were used for this study.

Study population

A total of 384 HIV/AIDS patients data were recruited for this study. The patient’s secondary data consisted of 384 (130 males and 254 females) HIV/AIDS patients on HAART were selected for this study purpose. The age range of the patients was 15 to 61 years with a mean of 33.65 ± 8.92 years. In Hawassa referral hospital, the HAART regimen for HIV patients on HAART consists of zidovudine, stavudine and nevirapine.

Determination of haemoglobin concentration and definition of anaemia

The haemoglobin concentration of patients in Hawassa referral Hospital laboratory determined using an auto analyzer–Sysmex KX-21 (Sysmex Corporation, Kobe, Japan). Anaemia was defined according to the WHO criteria (Volberding, 2002). For males, anaemia was defined as haemoglobin concentration less than 13 g/dl, while for females; the value is less than 12 g/dl. We classified the anemia as mild (10 to 12 g/dl) for women and 10 to 13 g/dl for men) moderate (8 to 10 g/dl) and sever (<8 g/dl).

Statistical analysis

SPSS version 17 was used for statistical computation. Pearson’s Chi ($\chi^2$) square and Fishers exact tests, paired T-tests were done. The data were arranged in a 2 × 2 contingency table before manual analysis. For example, the HIV patients were grouped as HAART naïve and on HAART, and further grouped into those with and without anaemia.

Ethical considerations

The Ethical Committee of the University of Hawassa, College of Medicine and Health Sciences approved the protocol for this study. Letter of approval were given to the HIV/AIDS clinics and agreement were signed with researcher and college research office.

RESULTS AND DISCUSSION

A total of 384 patient results were reviewed. Majority of the patients were females 254 (66.1%) and 130 (33.9%) were males. About 78.3% of the study participants were between 20 to 39 years age. Overall, across time, 59.6% of patients had a pre-therapy and “baseline” CD4 T-cell count was <200 cells/mm$^3$, and the remaining 29.7 and 6.2% was 200 to 349 and 350 to 499 cells/mm$^3$ respectively. Among these participants, only 4.2% were TB patients before ART initiation. Overall, 100% of patients had pre-therapy stage documented by WHO: of those, 26 (6.8%) were Stage I, 100 (26%) were Stage II, 233(60.7%) were Stage III and 25(6.5%) were Stage IV. Table 1 gives an overview of patient characteristics and associations with anaemia. About 95.3% of the study subject has the weight range of 31 to 70 kg. However, there was no record on weight and body mass index value after ART initiation.

Among initial regimens which were available in 100% of patients, Stavudine (d4T) was the most common (43.8%) nucleoside reverse-transcriptase inhibitor component during the period of study. Overall, 39.6% of patients started ART regimens that contained AZT and 16.6% were started with Tenofovir Disoproxil Fumarate (TDF) combination therapy. Due to toxicity, intolerance, pregnancy and some other unknown reasons, 21.9% of the study participants were changed a first line drug and switched to other ART drugs.

The mean haemoglobin and HCT at enrollment was 12.7 g/dl (SD 2.2). Overall, 332 of the 384 study subjects (86.5%) were anemic before ART and 309 (80.5%) were anemic after ART initiation. About 103(26.8%) had mild anaemia, 67(17.4%) had moderate anaemia, and 162(42.2%) had severe anaemia before ART initiation. However, the prevalence of anaemia after ART was significantly decreased by 6% (p<0.05). The prevalence of anaemia was higher in females than in males before ART treatment (95.6 vs. 90.8% (p = 0.000), and lower after ART treatment (86.8 vs. 93.5%) (p= 0.000).

An initial ART regimen was stavudine/lamivudine/tenofovir in 99 patients (25.5%), stavudine/lamivudine/efavirenz in 70(18.2%), zidovudine/lamivudine/nevirapine in 93(24.2%), zidovudine/lamivudine/efavirenz in 52(13.5%), tenofovir/lamivudine/efavirenz in 47(12.2%), and tenofovir/lamivudine/nevirapine in 14(3.6). For all patients that had a baseline CD4+ T-cell measurement; the mean CD4+ T-cell count was 180 cells/µl (SD 138).

Anaemia is the most commonly encountered haematologic abnormality in HIV patients (Odunukwe et al., 2005). HAART which has been taken as the gold standard in the management of HIV patients was reported to improve haematocrit (Omoregie et al., 2008). However, Omorogie et al. (2009) observed that HAART did not improve haematocrit of HIV patients and Nadler et al. (2003) reported that HIV patients on HAART still develop mild to moderate anaemia.

In this study, an overall prevalence of anaemia of (86.5%) before and (80.5%) after ART initiation was higher than that reported by Omorogie et al. (2009), Nadler et al. (2003), Mildvan (2003 and Moyle (2002). This difference may be due to the definition of anaemia <13 g/dl for males while the females <12 g/dl and anaemia was defined as Hb ≤ 12.5 g/dl for both males and females (Mildvan, 2003; Moyle, 2002). It is important that a unified definition of anaemia, such as the WHO definition, be used. Also, Nadler et al. (2003) and Moyle
Table 1. Predictors of persistent anaemia before and after ART initiation among 384 HIV-infected adults who were anemic at ART* initiation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal n (%)</th>
<th>Mild anemia a n (%)</th>
<th>Moderate anemia b n (%)</th>
<th>Severe anemia c n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before ART</td>
<td>After ART</td>
<td>Before ART</td>
<td>After ART</td>
<td>Before ART</td>
</tr>
<tr>
<td>All (n=384)</td>
<td>52(13.5)</td>
<td>75(19.5)</td>
<td>103(26.8)</td>
<td>68(17.7)</td>
<td>67(17.4)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17(4.4)</td>
<td>50(13.2)</td>
<td>1(0.3)</td>
<td>3(0.8)</td>
<td>67(17.4)</td>
</tr>
<tr>
<td>Male</td>
<td>35(9.1)</td>
<td>25(6.5)</td>
<td>102(26.6)</td>
<td>64(16.7)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>16(4.2)</td>
<td>25(6.5)</td>
<td>21(5.5)</td>
<td>20(5.2)</td>
<td>34(8.9)</td>
</tr>
<tr>
<td>30-39</td>
<td>26(6.8)</td>
<td>27(7.0)</td>
<td>51(13.3)</td>
<td>59(15.4)</td>
<td>20(5.2)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>10(2.6)</td>
<td>23(6.0)</td>
<td>31(8.1)</td>
<td>24(6.3)</td>
<td>13(3.4)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>1(0.3)</td>
<td>0(0.0)</td>
<td>5(13.0)</td>
<td>5(13.0)</td>
<td>4(10.4)</td>
</tr>
<tr>
<td>No</td>
<td>51(13.2)</td>
<td>75(19.5)</td>
<td>98(25.5)</td>
<td>63(14.4)</td>
<td>63(14.4)</td>
</tr>
</tbody>
</table>

*Combination of different ART drugs aHaemoglobin 10 to 12 g/dl (10-13g/dl for men); bHaemoglobin 8 to10 g/dl; cHaemoglobin <8 g/dl; eOn tuberculosis treatment at enrollment

(2002) in their study reported that, not all patients on HAART had zidovudine (AZT) in their regimen as was the case in this study. This is important as AZT has been reported by several authors to cause anaemia by inhibition of haemoglobin synthesis and toxicity to bone marrow cells, particularly, erythroid lines (Omoregie et al., 2009; Paul et al., 2004).

An HIV patients before ART initiation had a significantly higher prevalence of anaemia (86.5%) than HIV patients after ART initiation. This finding is in line with the result of Omoregie et al. (2009) and Mildvan (2003) but not in agreement with that of Nadler et al. (2003) and Moyle (2002) in which no significant difference in the prevalence of anaemia was observed between HIV patients on HAART and their HAART naive counter parts. Again, the difference in anaemia definition may be responsible for the difference in the results. In addition, drugs may cause myelosuppression in HIV-infected patients such as antifungal agents, antiviral agents, antiretroviral, antipnumocystis carinii agents and antineoplastic agents (Curkendall et al., 2007).

It is important to note that the lower prevalence of anaemia among HIV patients receiving HAART, may indicate the effectiveness of the HAART therapy in reducing viral load and improving haemotocrit values and it has been reported that HAART increase haemoglobin concentration and decreases the prevalence of anaemia (Belperio and Rhew, 2004; Omoregie et al., 2008). A number of mechanisms have been suggested to explain the prevalence of anaemia among HIV patient on HAART. They include the presence of antibodies to HAART agents (Omoregie et al., 2009), the presence of AZT among the HAART regimen and CD4 counts (Moyle, 2002; Paul et al., 2004; Curkendall et al., 2007).

However, reports concerning the relationship between CD4 count and anaemia are conflicting. Anaemia is independent of CD4 count and viral load as reported by Moyle (2002) and Paul et al. (2004). Nadler et al. (2003), Moyle (2002) and Curkendall et al. (2007) reported that CD4 count is a predictor of anaemia. However, the value for CD4 count differs. Nadler et al. (2003) and Moyle (2002) reported that CD4 count <50 cells/μl is a significant predictor of anaemia. A CD4 count of <200 cells/μl was the value associated with anaemia as reported by Curkendall et al. (2007). Further studies are needed to resolve the effect of CD4 count on the prevalence of anaemia.

Female gender has been reported as a risk factor for anaemia among HIV patients (Moyle, 2002). In contrast to Omoregie et al. (2009) and (Mildvan, 2003), this study shows that there was
a significant difference in the prevalence of anaemia between male and females. The same picture was observed among HIV patients receiving HAART. However, among HAART naive HIV patients, males had significantly higher prevalence of anaemia than their female counterparts. The findings in this study differ from that of Nadler et al. (2003) and Moyle (2002) most probably due to the difference in the definition of anaemia. Also, it might be due to large attribution of menstrual blood loss and drains on iron stores that occur with pregnancy and delivery (Curkendall et al., 2007).

CONCLUSION

There was a decline in the prevalence of anaemia and increment of mean CD4+ T cell count among HIV infected patients after ART. However, a number of HIV/AIDS patients still had anaemia and their CD4+ T cell count is not improved. Thus, there should be a large scale and longitudinal study for further characterization of HIV related anaemia.

In conclusion, HAART naive HIV patients have significantly higher prevalence of anaemia than those receiving HAART. Gender difference in the prevalence of anaemia was observed only among HAART naive HIV patients with significant higher prevalence of anaemia observed among males. A unified definition of anaemia, such as the WHO definition, is advocated as this will give the true prevalence of anaemia and allow for policy and interventions to address it.

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