INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 12, No. 2, p. 35-42, 2018

RESEARCH PAPER OPEN ACCESS

Frequency of anemia in aids patients receiving zidovudine based highly active anti-retroviral therapy

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Key words: Anemia, Zidovudine, Anti-Retroviral therapy, AIDS.

http://dx.doi.org/10.12692/ijb/12.2.35-42 Article published on February 10, 2018

Abstract

Worldwide, there are an estimated 33 million persons infected with HIV. Before starting AIDS patient on Highly Active Anti-Retroviral Therapy (HAART), one or more of the following criteria should be met: CD4 count < 500cells/mcl, rapidly dropping CD4 count, hepatitis B or C co-infection, the risk of cardiac disease, HIV nephropathy, increased risk for non-HIV related cancers. Five categories of drugs are used usually in combination; the Nucleoside reverse transcriptase Inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors (PIs), Chemokine receptor antagonists (CCR5 antagonists) and integrase inhibitors (II). The objective of the study was to determine the frequency of anaemia in AIDS patients receiving Zidovudine based Anti-Retroviral Therapy. Total 209 patients were enrolled, 16.2% using Zidovudine based therapy for six months. Our study showed that among 209 patients mean age was 32 years with SD ± 3.51. Seventy-two percent patients were male while 28% patients were female. Mean HB level was 13 g/dl with SD ± 2.53. More over 20% patients were anaemic and 80% patients were not anaemic. Thus, this study concluded that the incidence of anaemia in AIDS patients receiving Zidovudine based Anti-Retroviral Therapy was found to be 20%.

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Introduction

HIV belongs to Retroviridae family, *Lentivirus* genus. Up till now, two distant species have been extensively studied (HIV-1 and HIV2). Among the various hematologic diseases associated with HIV infection, anaemia is the most common, affecting more than 60% of patients in the chronic stage. Most of the clinical manifestations related to anaemia include dyspnea, fewer exercise tolerance and lethargy. These symptoms are directly related to haemoglobin reduction. FDA gave the approval for Alere Determine HIV-1/2 Ag/Ab Combo test (organics, Ltd) in August 2013. It was the first rapid HIV test for the detection of antibodies and HIV-1 p24 antigen of HIV-1 and HIV-2 simultaneously, from the human blood plasma, serum or whole blood samples. Detection of HIV-antigen allows earlier discovery of HIV-1 infection rather than by testing HIV antibodies only (Forna *et al.,* 2009, Shet *et al* 2010). HIV treatment depends upon the stage of disease and any accompanying infection. Generally, the aim of the treatment is to prevent deterioration of immune system to the point where a person is more prone to opportunistic infections. Highly active antiretroviral therapy (HAART) is the prime course for the prevention of immune weakening. Efficient HAART in the long-term may result in reclamation of CD4 T-cell count and development of immune response. Peripheral T-cell number initially rise when the therapy begins, but this symbolizes the redeployment of triggered T cells from the lymph nodes where the virus replicates rather than a real increase of total CD4 T cells number. Treatment methods for HIV infections are specific to age.

Some antimicrobial and antineoplastic drugs used for HIV treatment also cause anaemia. One of the examples includes the usage of dapsone for the prevention of *Pneumocystis carinii* pneumonia (PCP) can also result in hemolytic anaemia or myelosuppression (Medina *et al.,* 1990). Anemia also occurs if HIV-related non-Hodgkin's lymphoma is treated with myelosuppressive chemotherapeutic agents. Anemia is aprognosticator of disease and death amongst people suffering from AIDS receiving HAART.

Proper management of HIV involves proper adhesion to highly active antiretroviral treatment (HAART) regimens (Katz *et al.,* 2015) but the complications of these plans sometimes restricts significant recovery. Nevertheless, most individuals suffering from HIV have longer life span because of these drugs. A few of the adverse effects of such drugs can be resolved by substituting for similar drugs. Clinical adverse effects of HAART are stated in about 50% of the patients (Agarwal *et al.,* 2010). To control the adverse effects, minor breaks are attempted in the treatment. Almost 25% of the patients alter or stop HAART regimen in between the first year of treatment. This results in the progression of disease resistance. Consequently, through management and avoidance of adverse effects are necessary for significant regimen outcomes in affected HIV patients. One of the most common adverse effect associated with HAART regimen termination is gastrointestinal. General manifestations include nausea, vomiting, diarrhoea and anorexia (Bekolo *et al.,*2010). Other disorders in the HAART discontinuation include Lipodystrophy syndrome, cardiovascular risk, hyperlactatemia, bone metabolism, sleep disturbances, peripheral neuropathy, urolithiasis, acute nephritic syndrome, nephrotoxicity andnephrolithiasis. Usually, nucleoside reverse-transcriptase inhibitors (NRTIs), such as abacavir, didanosine, tenofovir, and zidovudine, and most of the protease inhibitors (PIs) are associated with these complications.

Hematologic disruptions in HIV patients indicated a more dangerous problem. Hypersensitivity to nevirapine may lead to eosinophilia, individuals suffering from haemophilia under PI treatment may experience impulsive episodes of bleeding, and thus it may result in anaemia (Grant *et al.,* 2010; Cohen *et al.,* 2011, Choopanya *et al.,* 2013). Anemia is majorly present amongst the African-American women and such individuals having zidovudine usage, including other drugs such as gancuclovir and fluconazole for the treatment of opportunistic infections (Leibowitz *et al.,* 2011). It is also related to the increase of disease and mortality in people with HIV having HAART regimen.

Fatigue in most of the cases is neglected even though it is one of the major symptoms of anaemia. It was reported through a survey that most of the patients on HAART regimen having antiretroviral drugs experience troublesome fatigue. Yet, the physicians were likely to overview fatigue among the least important symptom of HIV infection (Marrazzo *et al.,* 2014). In most of the cases anaemia is treated by amending the fundamental cause but in those patients, that are obtaining zidovudine, epoetin or blood transfusion has promising results Choopanya *et al.,* 2013). In another study, Zidovudine (AZT) therapy was found to be the most common cause of anaemia in HIV patients. In a phase clinical trial, a significant reduction of haemoglobin was found in more than 34% of the HIV-infected individuals (receiving 12,000 mg/day)(Richman *et al.,* 1987). Almost 31% individuals having AZT-treatment needed erythrocytes transfusion during drug delivery (Walker *et al.,* 1998). Similar studies have shown that the rate of anaemia is less in individuals that are experiencing the initial stages of HIV disease and in those that receive less dosage of AZT drug (Volberding *et al.,* 1990, Collier *et al.,* 1990). Further studies have proved that individuals receiving a combination of antiretroviral therapy experience a restively low level of anaemia if the lowdosage of zidovudine is administered (Eron *et al.,* 1995). Regardless of these results, most of the individuals require blood transfusion even at alow dosage of zidovudine or substitution of an antiretroviral drug to reduce the toxicity.

Materials and Methods

This research work was conducted in the Department of Medicine, Lady Reading Hospital (LRH) Peshawar, Pakistan. The duration of this descriptive cross-sectional study was six months from 29thFebruary 2016 to 29thSeptember 2016. The sample size was calculated using the WHO sample size calculator and was estimated to be 209 using 16.2 % patients on Zidovudine based therapy developed anaemia, with 95% confidence interval and 5% margin error. The non-probability consecutive sampling technique was used to collect the sample.

Sample selection

Inclusion criteria

This study included all newly diagnosed AIDS patients taking Zidovudine as a part of their HAART regimen, AIDS patients taking Zidovudine singly or as a part of their regimen for at least one month and such patients of age between 18-60 years, including both the male and female genders.

Exclusion criteria

Patients with anaemia present prior to the commencement of HAART therapy were excluded from this study.

Data collection procedure

After getting the approval from the hospital ethical committee, patients meeting the inclusion criteria were recruited once the informed consent was taken and detailed sheets were given to the patients explaining the objective and procedures of this study. Patients were referred from OPDs, private clinics and admitted to the Medical Ward B of LRH. The basic information like name, age, gender, contact numbers etc. of the patients included in the study was recorded and documented in a proforma.

After detailed subjective examination and clinical examination, for those patients who were meeting the inclusion criteria, it was mandatory for all the newly diagnosed HIV positive patients to get their baseline Full blood count and CD4 counts done in Family Care Center (FCC) Hayatabad Medical Complex (HMC) Peshawar before starting the treatment. Patients who were continuously taking Zidovudine based HAART therapy for at least one month or more and meeting the inclusion criteria had their Hemoglobin level determined upon arrival in the study hospital and those developing anaemia due to Zidovudine were noted. Hemoglobin level was determined by haematologist using haematology automatic analyzer in pathology department LRH.

Data analysis

SPSS version 10 was used for data analysis. Mean and the standard deviation was calculated for numerical variables like age and Hemoglobin levels.

Frequencies and percentages were used for categorical variables like gender and anaemia. Anemia was stratified by age and gender to see effect modification. Post-stratificationChi-square test was applied keeping P-value<0.05 as significant.

All the results were presented in the form of tables, charts/graphs.

Results

Age

Age distribution (Fig. 1) among 209 patients was analyzed as 42(20%) patients were in age range 18-30 years, 79(38%) patients were in age range 31-40 years, 67(32%) patients were in age range 41-50 years, 21 (10%) patients were in age range 51-60 years. Mean age was 32 years with SD ± 3.51.

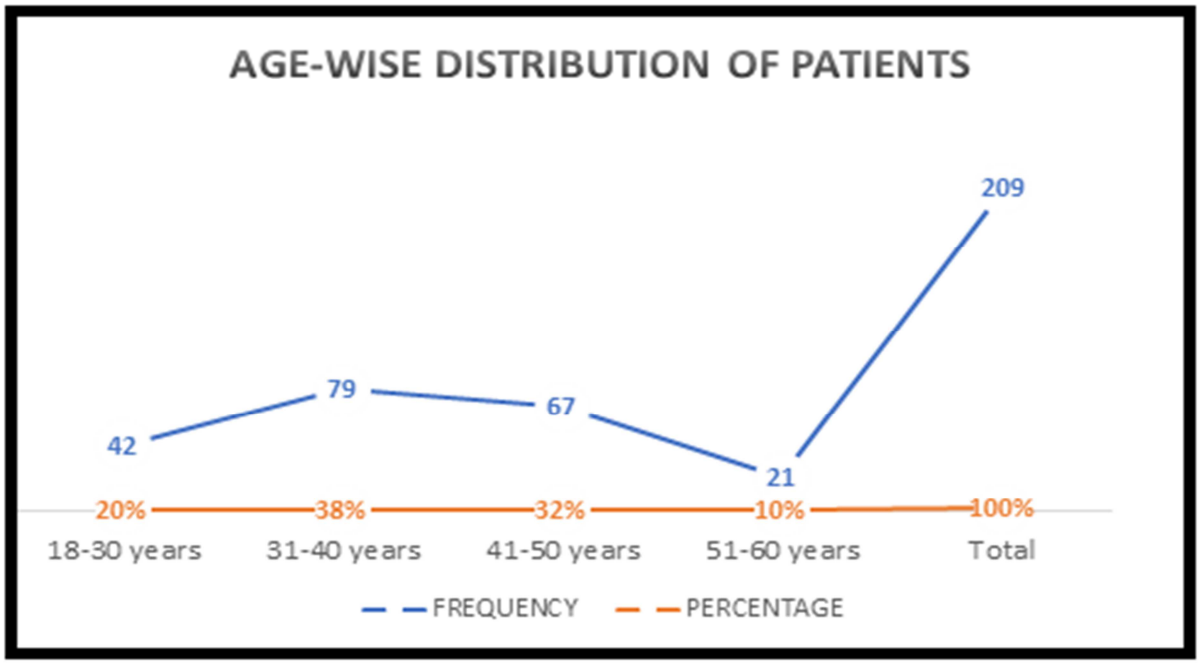

Fig. 1. Age-wise distribution of patients (n= 209).

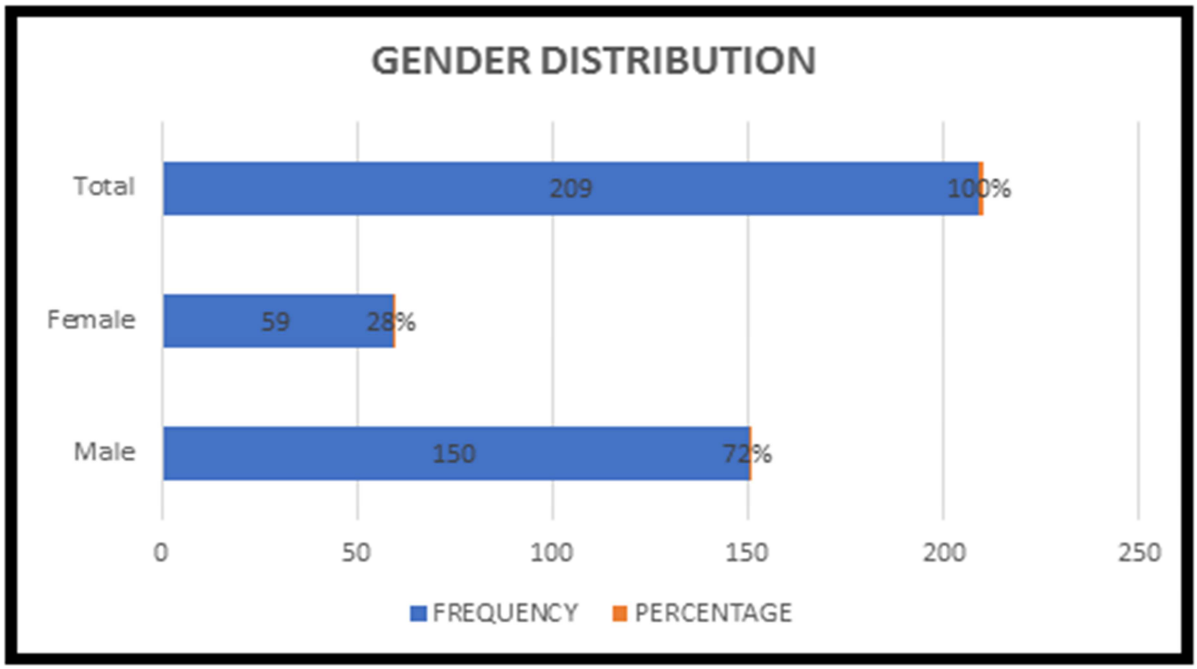

Fig. 2. Gender wise distribution of patients (n=209).

Gender

Gender distribution among 209 patients is shown in Fig 2. It was analyzed as 150(72%) patients were male while 59(28%) patients were female.

Mean Hb level

The mean Hb level of patients (n=209) was 13 g/dl with SD ± 2.53.

Frequency of anemia

Out of 209 patients, 42(20%) patients were anaemic while 167(80%) patients were not anaemic and it has been shown in Fig 3.

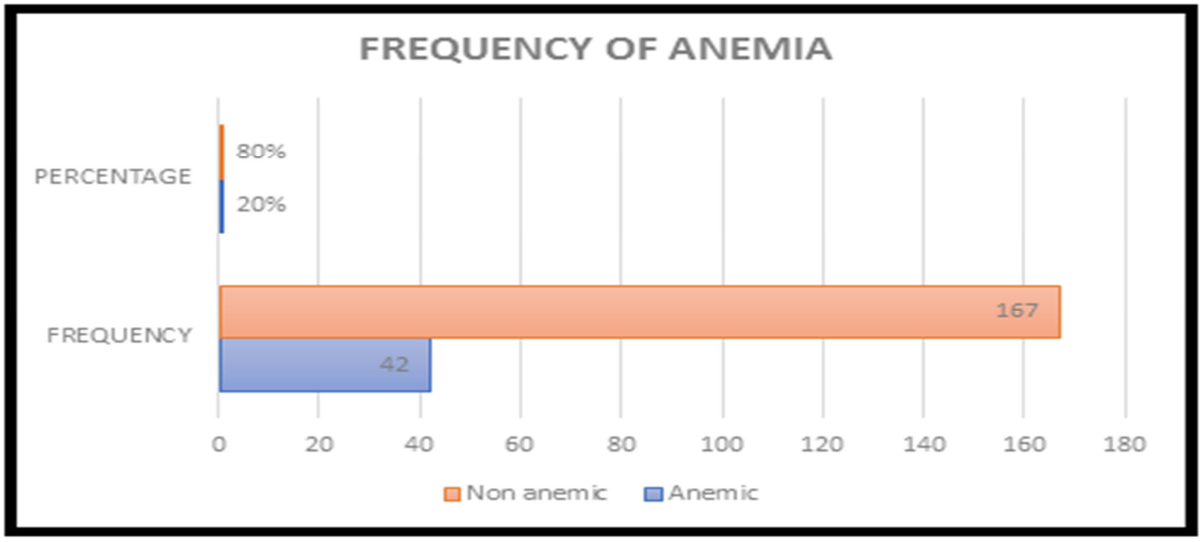

Fig. 3. Frequency of anaemia (n=209).

Stratification of anemia with respect to age and gender

Stratification of anaemia with respect to age and gender are shown in Fig. 4 and 5 respectively. Chi-Square test was applied in which the P value was 0.9950 and 0.9561 for age and gender respectively.

Discussion

Our study shows that among 209 patients mean age was 32 years with SD ± 3.51. Seventy-two percent patients were male while 28% patients were female. Mean HB level was 13 g/dl with SD ± 2.53. Moreover, 20% patients were anaemic and 80% patients were not anaemic. Zidovudine-inducedanaemia is by far the commonest serious complication of HAART therapy.

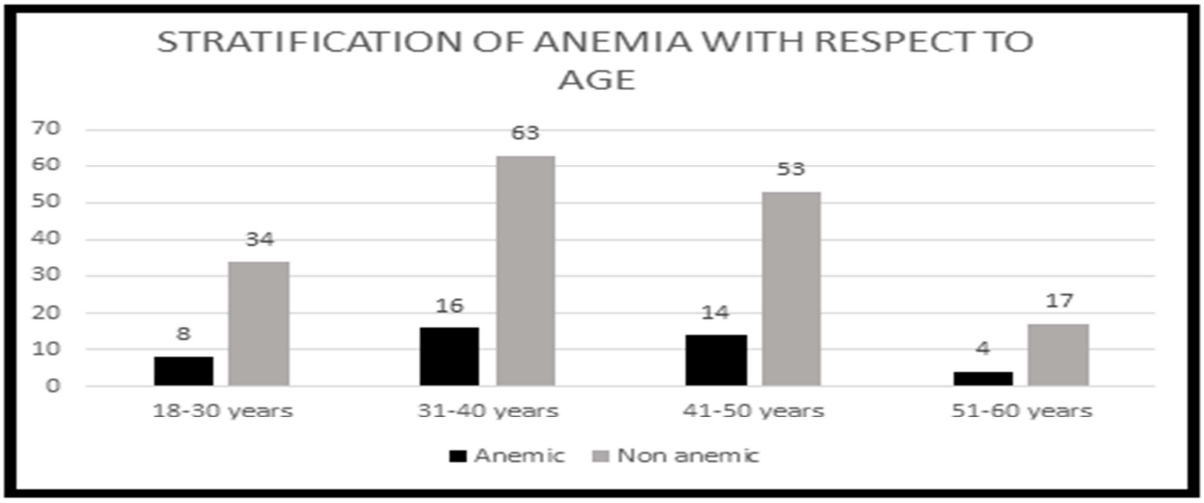

Fig. 4. Stratification of anaemia with respect to age (n=209).

The incidence was 37% over 2 years' time frame (Shet *et al.,* 2014). Another trial of the study (Forna *et al.,* 2009) was done in which Stavudine was replaced later by Zidovudine, and it showed that the incidence rate of anaemia shifted from 0.35/100 Persons-Month in case of Stavudine to 0.44/100 Persons-Month in case of Zidovudine. Another study (Isaakidis *et al.,* 2008) showed that 1 year after patients switched from Stavudine to Zidovudine, 21.9%, and developed anaemia.

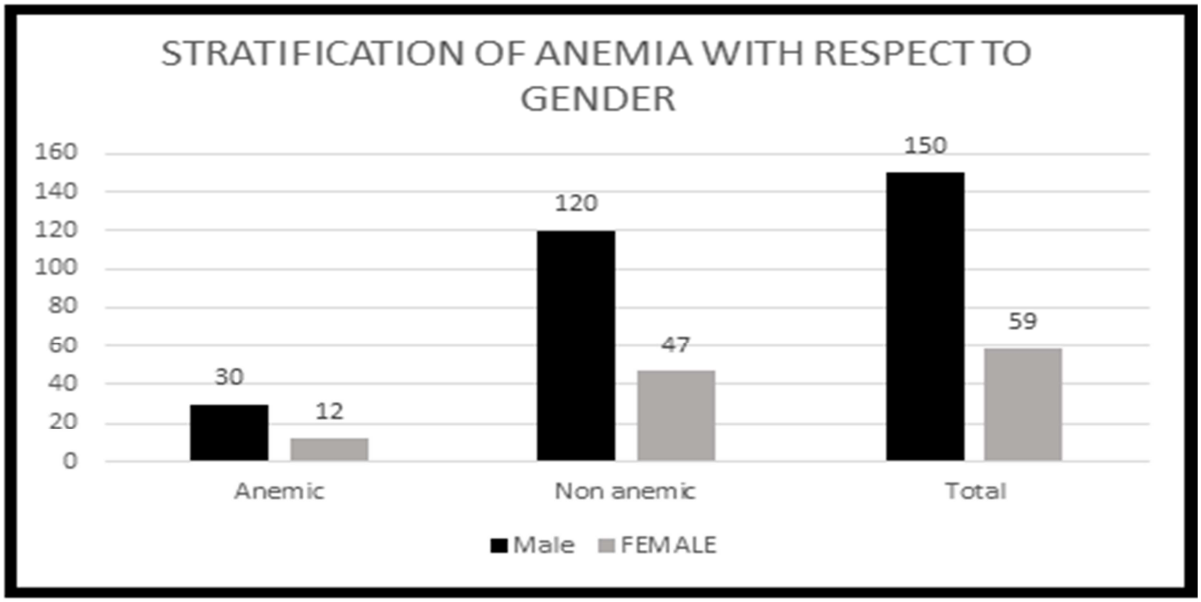

Fig. 5. Stratification of anaemia with respect to gender (n=209).

Similar results were found in another study conducted by Akhtar *et al,* (2008) conducted in PIMS Islamabad in which a total of 369 patients of HIV/AIDS were enrolled, 189 were found to be eligible for ARV (Anti-retroviral therapy) according to latest criteria. Initially there were 174 patients (65.60%) who were put on Zidovudine as part of first-line ARV regimen, 11 patients (5.82%) on Stavudine and 4 patients (2.11%) on second line ARVs from the beginning Out of 174 patients 100 patients were randomly selected to see anemia, pancytopenia, and macrocytosis after 6 months of initiation of therapy. Amongst 100 selected patients, fifteen patients developed anaemia (15 %), 76 (76%) patients had no anemia and 9 (9%) patients had no follow-up. Out of 15 patients who developed anaemia, haemoglobin was dropped by 1 gram in 3 patients, 2 grams in 3 patients and 3 grams or more in rest of the patients.

In another study conducted by Meidani *et al.* (2012) had shown as a total of 212 HIV positive cases were enrolled in which (males=179 (84.8%)) with a mean± SD age of 36.2 ±9.1 years (males=36.8± 8.5 years; females=32.9± 11.2 years).

The overall prevalence of anaemia was 71%, with the majority of patients having mild to moderate anaemia. Mild to moderate anaemia and severe anaemia occurred in 67% and 4% patients, respectively. Hemoglobin levels of the patients were between 4.7 and 16.5 g/dL. Mean ± SD of haemoglobin in anaemic and nonanemic patients were 11.2 ± 1.3 and 14.22 ± 1.1 g/dL, respectively. However, the difference was not statistically significant (P-value = 0.41). Microcytosis was more common in women than men (19% vs. 15%; P-value=0.418). In this study, 88 (72.7%) anemic patients were normocytic with decreased reticulocyte (men = 74.3%, women = 62%). Twenty (16.5%) and 13 (10.7%) have microcytic anaemia and macrocytic anaemia, respectively. The mean ± SD absolute CD4 count was 348 ± 267.8 cells/cubic mm (range 8–1594). Generally, 54 patients had used ZDV (600 mg daily). In ZDV users 43(79.6%) were anemic (P-value=0.38). Similar results were observed in another study conducted by Huffam *et al,* (2007), An observational database from Asia showed Anemia (Haemoglobin<or=10 g/dl) occurred in the first 6 months in 57 of 433 patients (13%) on zidovudine.

Baseline anaemia was the strongest predictive factor for subsequent anaemia.

Conclusion

This study concludes that the incidence of anaemia in AIDS patients receiving Zidovudine based Anti-Retroviral Therapy was found to be 20%.

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