

Neutropenia and Human Immunodeficiency Virus-1 Infection: Analysis of 43 Cases

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ABSTRACT

Background: Neutropenia has been reported in patients with early asymptomatic HIV infection as well as in those with more advanced HIV-related immunodeficiency. As with other peripheral cytopenias in the setting of HIV infection, multiple aetiologies may be present either singly or in combination. The study aims to determine the prevalence of Neutropenia and the association with the level of deterioration of CD4+ T lymphocyte subset in antiretroviral naïve HIV-1 infected patients.

Method: Four hundred consecutive HIV-1 infected patients undergoing investigations for pre treatment and staging were recruited over a one year period, at the HIV subspecialty clinic of Ahmadu Bello University Teaching Hospital, Zaria. All the patients were confirmed HIV-1 infected, repeatedly reactive by ELISA. White cell count was determined by standard manual method and CD4+ T cell enumeration by Dynal® (Oslo Norway) manual method.

Results: Of the 400 patients studied, the prevalence of neutropenia was 17.5%; 4.5% and 13% amongst the asymptomatic and symptomatic group respectively. There is a significant positive correlation between absolute neutrophil count and CD4 + T lymphocyte count $p < 0.05$.

Conclusion: This study demonstrates that Neutropenia is relatively common in HIV infected patients and is associated with the severity of the immunological deterioration.

Key Words: HIV infection, Antiretroviral naïve, Neutropenia, CD4 cell count.

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INTRODUCTION

Neutropenia is commonly seen in patients with HIV infection with the incidence increasing as the disease progresses, although it may be present in asymptomatic individuals.¹ Impaired haematopoiesis is likely to be the major factor, due to direct infection of the precursor cells, or marrow stromal cells.¹ A number of indirect mechanisms of HIV mediated suppression of haematopoiesis has been suggested. Suppression and apoptosis induced by the viral glycoprotein gp 120,

suppression of myelopoiesis by T lymphocytes, cytokines produced by HIV infected cells, transforming growth factors, tumour necrosis factor, and viral gene products such as Tat and gag gene products.¹ A possible autoimmune mechanism has been suggested by the presence of antineutrophil immunoglobulins in as high as 67% of patients with AIDS.² A number of drugs (Zidovudine, interferons, trimethoprim/sulfamethoxazole, chemotherapeutic agents) as well as infectious and neoplastic complications of AIDS can produce neutropenia, although reversible iatrogenic or secondary aetiologies are often not found.³

Some reports have noted an improvement of HIV-related neutropenia following the initiation of antiretroviral therapy.³ Early observations have shown that AIDS-related neutropenia can respond dramatically to therapy with GM-CSF. This has formed the rationale for the use of recombinant GM-CSF or G-CSF in a variety of clinical settings in which neutropenia is common.⁴ When drugs are implicated as the cause of the neutropenia, management decisions are frequently complicated by the risks associated with discontinuing or reducing the dose of drugs for treating infections or neoplasms.⁴ Therapy can however, continue without a major increase in the incidence of bacterial infection, provided the neutrophil count does not fall to below $0.5 \times 10^9/L$.¹

MATERIALS AND METHODS

Patients referred to Ahmadu Bello University Teaching Hospital, Haematology HIV sub-specialty clinic (from May 2003 to October 2004) for care were studied while undergoing evaluation for commencement of HAART. An informed consent was obtained; this was approved by the hospital's ethical committee. Pregnant women and paediatric patients were excluded from the study. All the patients were reactive for HIV-1 antibodies using double ELISA technique. Total white cell count (WBC) was determined by manual cell count adopted from Dacie and Lewis.⁵ Absolute Neutrophil (ANC) was calculated as a percentage of the WBC. Neutropenia was defined as ANC of less than 1500 cells/mm^3 , mild neutropenia was defined as ANC of between 1500 to 1000 cells/mm^3 , moderate neutropenia as ANC of 1000

to 500 cells/mm³ and severe neutropenia as ANC of less than 500 cells/mm³.^{3, 6} CD4+T Cell Count (CCC) were determined by using monoclonal antibody labeled microspheres (Dynal manual method) developed in Oslo Norway. All analysis was conducted using computerized statistical software SPSS version 11.5.

RESULTS

A total of 400 patients comprising 187 (46.8%) males and 213 (53.2%) females, were recruited into the study. The patient's mean age was 34.8 ± 8.9 years with a mean weight of 58.1 ± 12.2kg. The mean ANC 3,200 cells/mm³ ± 1.84 with a range of 690 to 15,600 cells/mm³. The mean CCC was 282.5 cells/μL ± 219.0 with a range of 20 to 1440 cells/μL. Of the total number of patients recruited, 43 patients (17.5%) had 'HIV-related neutropenia' (HIV-RN). Of the total number of patients with HIV-RN, 25 (58.1%) and 18 (41.9%) were males and females respectively with a Male to female ratio of 1.4:1. The haematological parameters of these patients are shown in the table below. These patients were also assessed clinically and immunologically, and categorized into three clinical stages A, B, and C according to CDC criteria and is represented in the pie chart below. The ANC of all the patients recruited into the study was correlated to the CCC and is presented in the scatter diagram below.

Table Showing The Haematological Parameters Of Patient With Hiv-rn

PARAMETER	RANGE	MEAN	STD
AGE (YRS)	17 63	34.80	9.39
WEIGHT (KG)	39 82	59.35	10.43
PCV (L/L)	22 42	34.51	5.58
PLT CELLS/MM ³	88 321	185.40	64.51
ANC \bar{y} 10 ⁹ /L	1.10 5.80	1.24	0.21
CCC CELLS/ \bar{y} L	20 820	254.00	196.82

Degree Of Neutropenia

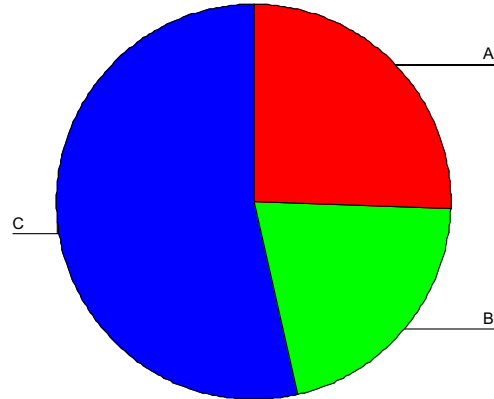
- Mild - 16.25%
- Moderate - 1.25%
- Severe Nil

ASSOCIATION OF NEUTROPENIA WITH OTHER CYTOPENIA

1. NEUTROPENIA AND ANAEMIA 18.6% (8 PATIENTS).
2. NEUTROPENIA AND THROMBOCYTOPENIA 7.0% (3 PATIENTS)

3. PANCYTOPENIA 0% (NIL)

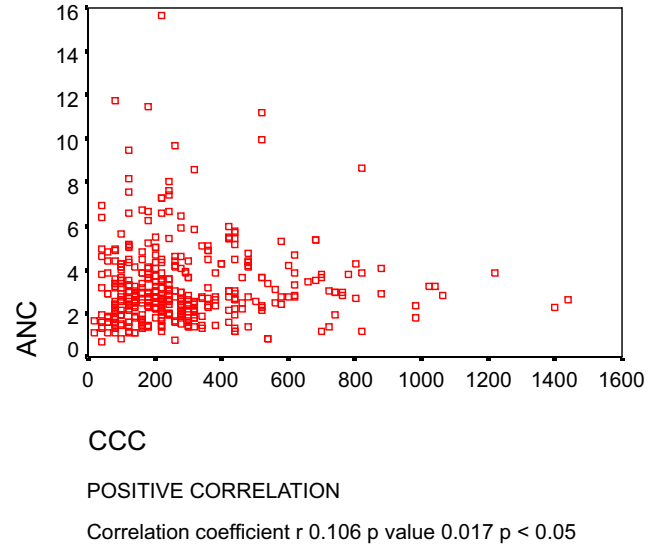
PIE CHART SHOWING THE DISTRIBUTION OF PATIENTS WITH HIV-RN BY CDC CLINICAL /IMMUNOLOGICAL CRITERIA



- STAGE A 11 patients (25.6%)**
- STAGE B 9 patients (20.9%)**
- STAGE C 23 patients (53.5%)**

Scatter Diagram Showing Correlation Of Hiv-rn To

The Cd4 + Cell Count In The Study Patients



Correlation is therefore significant at the level P < 0.05.

DISCUSSION

This study shows that HIV-RN is relatively common in our environment; a prevalence of 17.5% among all the HIV infected patients was obtained in our study. Similarly in Nigeria, Adetifa et al reported a prevalence of 16% in 2004 in 66 patients⁷ and 17.5% in 2006 in a study of 68 children⁸ with confirmed HIV infection in the department of paediatrics, Lagos university teaching hospital. Amongst the symptomatic group (Stages B and C), the prevalence was 13% which is lower than

17% reported by Keizer et al in United states⁹ and over 50% reported in other studies.⁴ Adetifa also reported more of the patients in clinical stages B (45%) and C (36.6%), though this relationship was statistically not significant.⁸ In the early, asymptomatic HIV infection (Stage A), an incidence of 4.5% was reported in our study which is lower than 10% reported in other studies.^{4,12} This supports the fact that the incidence of HIV-RN increases with worsening or deterioration of the immunological status, thus of the 17.5% of the patients analyzed, a larger proportion of about 83.4% were in the immunodeficient stage B and C while only 25.6% were in stage A where there is a significant preservation of the immune function. This is illustrated in the Pie chart above. Further correlation of the ANC with CCC shows a significant positive correlation $r = 0.108$ $p < 0.05$, this further buttress the direction relationship of Neutropenia with CD4 + T lymphocyte level and this is demonstrated in the scatter diagram above.

Further characterization of the degree of Neutropenia showed that of 17.5% of the patients with HIV-RN, 16.25% had mild Neutropenia, 1.25% had moderate Neutropenia but none had severe Neutropenia. Thus the risk of bacterial infection will be low in these patients since previous studies as shown that bacterial infection rises when the ANC falls below 1000 cells/mm³ and increases again when the ANC falls below 500 cells/mm³.¹⁰ Moore and colleagues also found that the risk of bacterial infection increases 2 to 3 fold for HIV-infected individuals with less than 1000 cell/mm³ and rose by 7 to 9 fold in those with ANC levels less than 500 cell/mm³.^{3,11} On multivariate analysis, severity and duration of Neutropenia were found to be significant predictors of the incidence of hospitalization for serious bacterial infection.¹²

We also investigated the association of Neutropenia coexisting with other cytopenias and found that of the 43 patients with Neutropenia, 8 (18.6%) had an associated anaemia while 3 (7%) had thrombocytopenia. Pancytopenia was not recorded. This means that neutropenias generally occurs as an isolated haematological abnormality although immunosuppression is the basis for all cytopenias in HIV-infected individuals.

CONCLUSION

Neutropenia is relatively common in HIV infected individuals and it occurs often as an isolated haematological abnormality in immunocompromised patients. Prompt initiation of HAART and other appropriate measures are necessary to avoid life threatening bacterial infections.

LIMITATION

The differences observed in this study as compared to others may be largely due to methods of cells enumeration. Most studies use automated techniques for cell counts and Flow cytometry as the standard technique used in determining CD4+ T lymphocyte subset. The inherent errors associated with manual method is large, coefficient of variation for leucocytes count for manual method is 16% and for automated analytical method is 1.5%. The presence of co-infections (Tuberculosis, Malaria, Enteric fevers, Hepatitis B, C, HTLV 1 and Syphilis) will also influence the CD4+ LC. These were not studied. Further studies are also necessary to identify aetiological factor/s of neutropenia, their effect on survival and whether HAART may have a positive impact on reducing their prevalence in HIV/AIDS patients.

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