

Haematological Changes in Peripheral Blood of HIV – Infected Persons with Correlation to CD4 Cell Count

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Summary:

Objective: Aims at recognizing the haematological abnormalities in peripheral blood associated with HIV infection and to correlate the haematological abnormalities with CD4 cell count to highlight these manifestations with disease progression.

Methodology: Observational cross sectional study.

Setting: Department of Haematology, Armed Forces Institute of Pathology (AFIP), Dhaka cantonment.

Patients: Two hundred four (204) HIV – infected patients receiving antiretroviral therapy aged from three years to 65 years. There were 132 male and 72 female patients.

Results: Anaemia was found in 103 (50.5%) cases. Leucopenia and thrombocytopenia were observed in ten (4.9%) and seven (3.4%) cases respectively. Lymphopenia

was found in 12 (5.9%) cases. In 50 (24.5%) cases Erythrocyte Sedimentation Rate (ESR) was > 20 mm at the end of 1st hour. Flow cytometric analysis for CD4 cell count showed < 200 cells/cmm in 65 (31.8%) cases, in between 200 cells/cmm and 499 cells/cmm in 117 (57.4%) cases and > 500 cells/cmm in 22 (10.8%) cases.

Conclusion: Haematological abnormalities are common in HIV – infected patients and responsible for significant morbidity and mortality in these patients. These abnormalities are more frequent with disease progression. The present study revealed a significant increase in the number of anaemia, leucopenia, lymphopenia and thrombocytopenia with decreasing CD4 cell count.

Keywords: CD4 cell count, Haematological abnormalities, HIV, Peripheral blood.

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Introduction:

Acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 and human immunodeficiency virus (HIV) was identified in 1983¹. Globally the phenomenon of HIV/AIDS is best viewed as a pandemic affecting nearly all the countries of the world². The first case of HIV/AIDS in Bangladesh was detected in 1989. Since then 1495 cases of HIV/AIDS have been reported (as of December 2008). However, UNAIDS estimates that the number of people living with HIV in the country may be as high as 12000, which is within

the range of the low estimate by UNICEF's State of the World's Children Report 2009³.

Peripheral blood changes commonly seen in human immunodeficiency virus – infected individuals and disease associated with HIV may reflect disease elsewhere in the body, may result from treatment for that disease, may reflect an attempt to attack the HIV itself, or may seem to be isolated haematological disorders⁴.

The CD4+ lymphocyte is the primary target of HIV infection and leads to progressive impairment of cellular function, characterized by a gradual decline in peripheral blood CD4+ lymphocyte levels⁵.

This study aims at recognizing the haematological abnormalities associated with HIV infection, to correlate the haematological abnormalities with CD4 cell count and to highlight these manifestations with disease progression.

Materials and Methods:

This observation cross - sectional study was carried out at Armed Forces Institute of Pathology (AFIP) in the department of haematology during a period of eight months from June 2012 to January 2013. A total of 204 HIV – infected patients on antiretroviral therapy (AZT)

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irrespective of age and sex from a Non-government Organization (NGO) were included in this study. All the patients were brought to AFIP by a representative of that NGO for blood sampling. Ethical issues were properly addressed and also cleared by the ethical committee of Directorate General of Medical Services (DGMS) of Bangladesh Armed Forces. About two ml venous blood in EDTA bottle was taken for complete haemogram and CD4 cell count. Complete haemogram was performed by automated haematology analyzer Sysmex XT 1800i. Before running the specimen, the analyzer was calibrated by low, normal and high control supplied by the manufacturer. Erythrocyte Sedimentation Rate (ESR) was done by Westergren method. CD4 lymphocyte count was done by Partec Flow Cytometer (cyFlow), an automated multicolour system that performs both analysis and sorting using dual lasers 488 nm air cooled argon-ion blue and 532 nm green diode solid state laser. Cells are treated with monoclonal antibody Men-41 which recognizes the human CD4 antigen. As a cell passes through the flow chamber, it is intersected by a laser beam. Forward light scatter is proportional to the cell size and side scatter is related to cell granularity which allows separation of WBCs based on size and granularity. Analysis of CD4 – PE fluorescence signal helps in delineating subpopulation. Data was analyzed by cell quest software.

Statistical tests included mean, standard deviation, ANOVA (analysis of variance), chi-square test (χ^2). The data was entered in Microsoft Office 2010 Excel worksheet and statistical analysis was done using Statistical Package for Social Sciences Software (SPSS) version 21. Descriptive statistics were applied: p – value less than 0.05 was considered statistically significant.

Results:

During the study period, 204 HIV – infected patients were referred to the haematology department, AFIP and included in this study. The age ranged from three years to 65 years. Mean age was 35.3 ± 9.5 years. The majority of 91 (40.6%) cases were in the age group of 31 – 40 years followed by 55 (27.0%) cases in 21 to 30 years age group. There were 132 (64.7%) males and 72 (35.3%) females in this study with male to female ration 1.8: 1. Table – I shows the demographic data of the patients.

Table-I

Demographic data of the patients as per age and sex (n = 204)

Age (in years)	Sex
Range: 3 – 65	Male: 132 (64.7%)
Mean: 35.3	Female: 72 (35.3%)
	M : F= 1.8 : 1

M = Male; F = Female.

In this study haematological parameters that have been included were haemoglobin (Hb) level, RBC count, haematocrit (Hct), absolute values (MCV, MCH, MCHC), RDW, ESR, TLC, absolute neutrophil, lymphocyte, monocyte and eosinophil count, platelet count and CD4 count. Out of 204 patients, 17 (8.3%) cases had haemoglobin level equal to or less than 10.0 g/dl, 60 (29.4%) cases had haemoglobin level in between 10.1 g/dl and 12.0 g/dl and 127 (62.3%) cases had more than 12.0 g/dl. In case of haematocrit, 19 (9.3%) cases had Hct equal to or less than 0.30 L/L, 85 (41.7%) cases had in between 0.31 L/L and 0.36 L/L and 100 (49.0%) cases had more than > 0.36 L/L. Out of 204 cases, 154 (75.5%) cases had Erythrocyte Sedimentation rate (ESR) less than 20 mm in the 1st hour and 50 (24.5%) cases had more than 20 mm in the 1st hour. RBC count ranged from $2.9 \times 10^{12}/L$ to $5.2 \times 10^{12}/L$ in case of female and in case of male it was from $3.2 \times 10^{12}/L$ to $4.7 \times 10^{12}/L$. In 24 (11.8%) cases RBC count was equal to or less than $3.0 \times 10^{12}/L$, 79 (38.7%) cases had in between $3.1 \times 10^{12}/L$ and $4.0 \times 10^{12}/L$ and 101 (49.5%) cases had more than $4.0 \times 10^{12}/L$.

Mean Corpuscular Volume (MCV) ranged from 62.6 fl to 124.5 fl. Nineteen cases (9.3%) had MCV equal to or less than 76 fl, 104 (51.0%) cases had in between 76 fl and 96 fl and 81 (39.7%) cases had more than 96 fl. Mean Corpuscular Haemoglobin (MCH) ranged from 18.2 picograms to 43.7 picograms. Seventy eight (38.2%) cases had MCH within normal range (29 ± 2.5 pg), 45 (22.1) cases had MCH equal to or less than 27.0 pg and 83 (40.7%) cases had more than 32 pg. Mean Corpuscular Haemoglobin Concentration (MCHC) ranged from 29.1 g/dl to 36.9 g/dl. Out of 204 cases, 20 (9.8%) cases had MCHC equal to or less than 31.5 g/dl, 97 (47.5%) cases had MCHC in between 31.5 g/dl and 34.5 g/dl and 87 (42.6%) cases had more than 34.5 g/dl. Red Cell Distribution Width – Co-efficient of Variation (RDW - CV) ranged from 10.3% to 35.2%. In 10 (4.9%) cases, RDW – CV was equal to or less

than 11.6%, 124 (60.8%) cases had in between 11.6% and 14%, 70 (34.3%) cases had more than 14%.

Total Leucocyte Count (TLC) in this study ranged from $2.1 \times 10^9/L$ to $15.4 \times 10^9/L$. Ten (4.9%) cases had leucopenia ($< 4.0 \times 10^9/L$), 19 (9.3%) had leucocytosis and 175 (85.8%) cases had leucocyte count within normal range. Absolute neutrophil count ranged from $9.0 \times 10^9/L$ to $13.9 \times 10^9/L$. Neutropenia ($< 2.0 \times 10^9/L$) was found in 20 (9.8%), 18 (8.8) cases had neutrophilia ($> 7.0 \times 10^9/L$) and 166 (81.4%) cases had absolute neutrophil count in between $2.0 \times 10^9/L$ and $7.0 \times 10^9/L$. Absolute lymphocyte count ranged from $0.6 \times 10^9/L$ to $6.5 \times 10^9/L$. The majority of 133 (65.2%) cases had absolute lymphocyte count within the normal range (from $1.0 \times 10^9/L$ to $3.0 \times 10^9/L$), 12 (5.9%) cases had lymphopenia ($< 1.0 \times 10^9/L$) and 59 (28.9%) cases had lymphocytosis ($> 3.0 \times 10^9/L$). Absolute monocyte count ranged from $0.1 \times 10^9/L$ to $2.0 \times 10^9/L$. Only one (0.5%) case had monocytopenia ($< 0.2 \times 10^9/L$), seven (3.4%) cases had monocytosis ($> 1.0 \times 10^9/L$) and rest of the 196 (96.1%) cases had absolute monocyte count within the normal range ($0.2 \times 10^9/L$) to $1.0 \times 10^9/L$. In this study, 68

(33.3%) cases had eosinophilia ($> 0.5 \times 10^9/L$), absolute eosinophil count ranged from $0.03 \times 10^9/L$ to $0.5 \times 10^9/L$. Eosinopenia was not found in this study. Platelet count ranged from $60.0 \times 10^9/L$ to $573 \times 10^9/L$. Only seven (3.4%) cases had thrombocytopenia ($< 150 \times 10^9/L$), 189 (92.7%) cases had platelet count in between $150 \times 10^9/L$ and $400 \times 10^9/L$, eight (3.9%) cases had thrombocytosis ($> 400 \times 10^9/L$). CD4 lymphocyte count was in between 52 cells/cmm and 908 cells/cmm in this study. Out of 204 cases 65 (31.9%) had CD4 count less than 200 cells/cmm, 117 (57.3%) cases had CD4 count in between 200 cells/cmm and 499 cells/cmm and 22 (10.8%) cases had more than 500 cells/cmm. Table – II shows the pattern of haematological parameters in HIV – infected persons in this study.

Common haematological abnormalities found in this study were anaemia, raised ESR, leucopenia, leucocytosis, neutropenia, neutrophilia, lymphopenia, lymphocytosis, monocytopenia, monocytosis, eosinophilia, thrombocytopenia, thrombocytosis and low CD4 lymphocyte count. Table – III shows the frequency and percent of these findings.

Table-II

Pattern of haematological parameters in HIV- infected persons (n=204)			
Parameters	Range	Mean \pm 2SD	P - value
ESR (mm in 1 st hour)	6 – 17 (M)	19 ± 28	$P < 0.001$
	5 – 50 (F)	20 ± 28	$P < 0.0001$
Hb (g/dl)	9.0 – 17.2 (M)	12.5 ± 3.6	$P > 0.0001$
	7.8 – 15.2 (F)	11.6 ± 3.0	$P > 0.0001$
RBC count ($\times 10^{12}/L$)	3.2 – 4.7 (M)	4.0 ± 1.6	$P > 0.0001$
	2.9 – 5.2 (F)	3.8 ± 1.6	$P > 0.001$
Hct (L/L)	0.27 – 0.47 (M)	0.37 ± 0.10	$P > 0.0001$
	0.27 – 0.45 (F)	0.35 ± 0.08	$P > 0.001$
MCV (fl)	62.6 – 124.5	93.1 ± 28.4	$P < 0.001$
MCH (pg)	18.2 – 43.7	37.8 ± 11.2	$P < 0.0001$
MCHC (g/dl)	29.1 – 36.9	34.1 ± 4.0	$P < 0.001$
RDW – CV (%)	10.3 – 35.2	14.1 ± 5.4	$P < 0.001$
TLC ($\times 10^9/L$)	2.1 – 15.4	7.6 ± 5.0	$P < 0.0003$
ANC ($\times 10^9/L$)	0.9 – 13.9	4.1 ± 4.0	$P < 0.0001$
ALC ($\times 10^9/L$)	0.6 – 6.5	2.4 ± 2.0	$P < 0.0001$
AMC ($\times 10^9/L$)	0.1 – 2.0	0.6 ± 0.4	$P < 0.0001$
AEC ($\times 10^9/L$)	0.03 – 5.0	0.5 ± 0.8	$P < 0.0001$
PLC ($\times 10^9/L$)	60 – 573	265 ± 152	$P < 0.0001$
CD4(/cmm)	52 - 908	278 ± 214	$P > 0.0001$

M = Male; F = Female; RDW – CV = Red Cell Distribution Width; TLC = Total Leucocyte count; ANC = Absolute Neutrophil count; ALC = Absolute Lymphocyte count; AMC = Absolute Monocyte count; AEC = Absolute Eosinophil count; PLT = Platelet. Z test was done to analyze the data.

Table-III*Common haematological abnormalities in HIV- infected persons (n=204)*

Findings	Frequency	Percentage (%)
Anaemia	103	50.5
ESR (> 20 mm in 1 st hour)	50	24.5
Leucopenia	10	4.9
Leucocytosis	19	9.3
Neutropenia	20	9.8
Neutrophilia	18	8.8
Lymphopenia	12	5.9
Lymphocytosis	59	28.9
Monocytopenia	01	0.5
Monocytosis	07	3.4
Eosinophilia	68	33.3
Thrombocytopenia	07	3.4
Thrombocytosis	0865	3.931.9
CD4 count (< 200/cmm)		
CD4 count (200/cmm to 499/cmm)	117	57.4
CD4 count (>500/cmm)	22	10.8

Table-IV*Comparison of number of anaemia cases in present study with others*

Authors	No of anaemia cases	Total cases	Percentage (%)
Parinitha et al	210	250	84.0
Karcher et al Tripathi et al	17561	19774	89.082.4
Sitalakshmi et al	27	42	64.2
Kalousti et al	34	40	85.0
Present study	103	204	50.5

Table-V*Comparison of morphological patterns of blood picture in present study with other studies*

Patterns of blood picture	Parinitha et al		Khandekar et al		Tripathi et al		Present study	
	No	%	No	%	No	%	No	%
Normocytic normochromic blood picture	101	48.1		13	17.6	101	49.5	
Normocytic normochromic anaemia	29	13.7	68	48.7	54	79.9	28	13.7
Microcytic hypochromic anaemia	18	8.6	15	10.7	04	5.4	10	4.9
Macrocytic anaemia	15	7.2	32	29.9	03	4.1	30	14.
Anaemia of Chronic Disorder	-	-	-	-	-	-	35	17.2
Dimorphic anaemia	47	22.4	25	17.9		-	-	-
Total	210	100	140	100	74	100	204	100

Table-VI*Comparison of haematological parameters in patients with different CD4 counts*

Parameters	CD4 > 500 cells/cmm (n= 22)	CD4 200 – 400 cells/cmm (n= 117)	CD4 < 200 cells/cmm (n= 65)	Statistical test	p – value
Anaemia (No of cases)	09 (41.0%)	39 (33.3%)	55 (84.6%)	$\chi^2= 45.28$	$P < 0.0001$
Total leucocyte count (mean±SD)	8.1 ± 2.8	7.8 ± 2.4	7.0 ± 2.5	F= 5.0	$P < 0.01$
Leucopenia (No of cases)	01 (4.5%)	02 (1.7%)	07 (10.8%)	$4\chi^2= 8.68$	$P < 0.01$
Absolute lymphocyte count (mean±SD)	3.0 ± 1.3	2.7 ± 0.9	1.8 ± 0.9	F= 0.04	$P > 0.05$
Lymphopenia (No of cases)	00 (00%)	00 (00%)	12 (18.5%)	$\chi^2= 94.8$	$P < 0.001$
Platelet count (mean±SD)	265 ± 78	267 ± 68	254 ± 95	F= 2.54	$P > 0.05$
Thrombocytopenia (No of cases)	01(4.5%)	01 (0.9%)	05 (7.7%)	$\chi^2= 5.99$	$P= 0.05$
ESR (mean±SD)	22 ± 13	17 ± 12	22 ± 16	F= 1.79	$P > 0.05$

χ^2 = chi square test, F = analysis of variance (ANOVA) test.

Discussion:

Haematological abnormalities frequently encountered in HIV-infected individuals are anaemia, granulocyte disorders, thrombocytopenia, lymphomas, coagulopathies and vascular malignancies like Kaposi sarcoma. Although in the majority of cases, haematologic abnormalities are detected in middle or advanced stages of HIV infection, some of these like anaemia and thrombocytopenia have been reported to occur in early stages of HIV infection⁶.

The origin of haematological disorders in HIV infection remain incompletely understood, but has been attributed to dysfunctional haematopoiesis in bone marrow caused by several factors. These include severe nutritional stress in advanced stages of HIV infection, suppression of marrow by invading opportunistic infections or neoplasm, chronic disease associated changes and toxic effects of antiretroviral compounds (or other medications used to combat the complications of HIV disease). The possibility of HIV directly infecting the haematopoietic precursor cells and inhibiting their differentiation and development to mature cells, has been an attractive hypothesis for the origin of HIV associated dysfunctional haematopoiesis, but to date it remains, to a great extent, an incompletely understood phenomenon⁷.

In the present study, haemoglobin level ranged from 7.8 g/dl to 17.2 g/dl with the mean being 12.5 g/dl. The majority (50.5%) of cases in this study had anaemia

with haemoglobin level less than the lower limit of their respective age and sex. Parinitha SS et al reported haemoglobin ranged from 3.3 g/dl to 19.3 g/dl with the mean being 10.2⁸. Kaloutsi et al reported haemoglobin in the range of 3.8 g/dl to 17.3 g/dl and a mean of 10.8⁹. However Tracy et al¹⁰ reported mean closer to the present study of 11.4 g/dl. Mean haematocrit in this study was 0.37 L/L. Tripathiet al¹¹ reported a mean haematocrit of 0.28 L/L. A better haemoglobin and haematocrit level in this study may be due to inclusion of cases with early HIV infection and good treatment response. Mean RDW – CV was 14.1% in the present study. A closer observation was made by Schneider et al¹². Mean RBC count was $4.1 \times 10^{12}/L$ in this study with standard deviation of 0.81. A similar observation was made by Parinitha SS et al⁸. Tripathi et al reported a mean RBC count of $3.1 \times 10^{12}/L$ and a standard deviation of 0.36 among 55 AIDS patients¹¹. In this study, mean MCV, MCH and MCHC were 93.1 fl, 37.8 pg and 34.1 g/dl with standard deviation of 14.2 fl, 5.6 pg and 2.0 g/dl respectively. Parinitha SS et al reported findings close to this study⁸. Tripathi et al reported a mean MCV, MCH and MCHC of 81.8 fl, 27.6 pg and 32.5 g/dl¹¹. Erythrocyte Sedimentation Rate (ESR) ranged from 5 mm in 1st hour to 70 mm in 1st hour with mean and standard deviation were 19.5 and 14.1 respectively in this study. The majority of 154 (75.5%) cases had ESR less than 20 mm in 1st hour. Thirty 34 (16.7%) cases had ESR equal to or more than 40 mm in

1st hour. Raised ESR found in HIV – infected persons may be related to chronic nature of HIV infection⁸.

In the present study, anaemia was observed in 103 (50.5%) cases. Paranitha et al⁸ reported anaemia in 84.0% (210/250) Kaloutsi et al reported anaemia in 85% (34/40)⁹, Karcher et al reported anaemia in 89% (175/197) of cases¹³ and Tripathi et al in 82.4% (61/74) of cases¹¹. However Sitalakshmi et al¹⁴ reported anaemia in 64.2% (27/42) of cases which closer compared to the present study. This difference in anaemia in different study may be due to variation in large sample size and treatment response. Table – IV shows a comparison of number of anaemia cases in the present study with other studies.

Macrocytosis without anaemia was found in 81 (39.7%) cases. Treatment with reverse transcriptase inhibitors will cause macrocytosis because they interfere with DNA production, which may lead to megaloblastic changes. Most patients with HIV who are being treated with reverse transcriptase inhibitors will display macrocytosis without anaemia. This indicates medications compliance by the patient, and no treatment is necessary¹⁵. The most common type of anaemia was anaemia of chronic disorder (ACD) observed in 35/103 (34.0%) cases, followed by macrocytic anaemia in 30/103 (29.1%) cases. Table – V shows the comparison of morphological patterns of blood picture in the present studies with other studies.

Mean Total Leucocyte Count (TLC) was $4.1 \times 10^9/L$. Paranitha et al⁸ reported mean of TLC $5.8 \times 10^9/L$, Kaloutsi et al⁹ reported a mean of $5.2 \times 10^9/L$. The majority of 175 (85.8%) cases had normal total leucocyte count. Patwardhan et al¹⁶ reported in 75.6% (378/500) of cases almost similar observation. Leucopenia was seen in 10 (4.9%) and leucocytosis 19 (9.3%) cases. Neutropenia and neutrophilia were found in 20 (9.8%) and 18 (8.8%) cases respectively. In 12 (5.9%) cases, lymphopenia and 59 (28.9%) cases, lymphocytosis was observed in this study. Paranitha et al⁸ reported lymphopenia in 163 (65.2%) cases out of 250 cases, Tracy et al¹² in 70% (14/20) and Tripathi et al¹¹ in 25.6% (19/74) of cases. In the present study, monocytopenia was seen in one (0.5%) cases and monocytosis was found in seven (3.4%) cases. Eosinophilia was observed in 68 (33.3%) cases in this

study. Paranitha et al⁸ observed eosinophilia in 54 (21.6%) cases and Khandekar et al¹⁷ in 16 (11.4%) cases out of 140 cases. Thrombocytopenia was observed in seven (3.4%) cases in this study. Paranitha et al⁸ reported thrombocytopenia in 45 (18%) cases, Patwardhan et al¹⁶ in 65/500 (13%) cases and Castello C et al⁵ in 121/925 (13%) cases. However, Karcher et al¹³ reported thrombocytopenia in 88/196 (45%) cases, much higher compared to the present study.

CD4 lymphocyte count is essential for assessment of immune status in HIV – infected persons as the pathogenesis of AIDS is largely attributed to a decrease in absolute CD4 cell count. CD4 cell counts are the criterion for categorizing HIV-related clinical conditions by CDC classification system for HIV infection¹⁸. Patients in the present study were divided into three groups based on absolute CD4 lymphocyte count.

Haematological parameters were compared in these three groups. The number of cases with anaemia, leucopenia, lymphopenia and thrombocytopenia increased with reducing CD4 cell counts. Mean total leucocyte count, mean absolute lymphocyte count was lower with reducing CD4 cell count. These parameters showed significant difference (p value < 0.05) between three groups with differing CD4 cell count. This indicates higher occurrence of anaemia, leucopenia, lymphopenia and thrombocytopenia with progression of disease. These haematological findings almost correlate with Paranitha et al⁸. Table – VI shows the comparison of haematological parameters in patients with different CD4 cell counts.

Conclusion:

Haematological manifestations are common in HIV – infected patients. Anaemia is the most common manifestation and the most frequent form is anaemia of chronic disorder followed by macrocytic anaemia. A proportion of patients also show leucopenia and thrombocytopenia. Incidence of anaemia, leucopenia and thrombocytopenia correlates with disease progression. The present study also showed significant correlation of absolute lymphocyte count with CD4 cell count. Thus absolute lymphocyte count can be used as a predictor of CD4 count and also to assess the stage of the disease in centres where CD4 count evaluation is not available.

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