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SERUM HEPCIDIN IS ASSOCIATED WITH IMMUNOLOGICAL STATUS RATHER THAN ANEMIA IN ADULTS LIVING WITH HIV RECEIVING ANTIRETROVIRAL THERAPY: A CROSS-SECTIONAL STUDY FROM INDIA

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ABSTRACT

Background: Anemia is a common complication of HIV infection and is associated with poor clinical outcomes. Hepcidin, the principal regulator of iron homeostasis, may contribute to HIV-associated anemia through inflammation-mediated iron sequestration. However, its relationship with anemia and immunological status in Indian people living with HIV (PLHIV) remains poorly understood. This study evaluated the prevalence and etiology of anemia and examined the association between serum hepcidin levels and immunological status.

Materials and Methods: A hospital-based cross-sectional study was conducted among **201 adults with HIV infection** receiving antiretroviral therapy at a tertiary care center in New Delhi, India. Clinical evaluation, hematological parameters, iron profile, serum ferritin, soluble transferrin receptor, erythropoietin, vitamin B12, folate, CD4 cell count, HIV viral load, and serum hepcidin levels were assessed. Associations between anemia, serum hepcidin, and immunological parameters were analyzed.

Results: Anemia was present in **64.7%** of participants. Anemia of chronic disease was the predominant subtype (**53.8%**), followed by iron deficiency anemia (**22.3%**) and vitamin B12 deficiency (**11.5%**). Lower CD4 cell count, detectable HIV viral load, altered iron indices, and elevated ferritin were significantly associated with anemia ($P<0.05$). Serum hepcidin was not associated with anemia subtype or severity but showed a significant inverse correlation with CD4 cell count and a positive correlation with soluble transferrin receptor.

Conclusions: Anemia remains highly prevalent among adults receiving ART. Although serum hepcidin was not useful for differentiating anemia subtypes, its association with CD4 cell count suggests a potential role as a biomarker of immune dysregulation in HIV infection.

Keywords: HIV, anemia, hepcidin, iron metabolism, CD4 count, antiretroviral therapy.

INTRODUCTION

Despite substantial advances in antiretroviral therapy (ART), anemia remains one of the most common hematological complications among people living with HIV (PLHIV), affecting 20–80% of patients depending on disease stage, ART status, and population studied.[1-3] Anemia is associated with impaired quality of life, accelerated disease progression, increased hospitalization, and higher mortality.[2-4]

The pathogenesis of HIV-associated anemia is multifactorial and includes chronic inflammation, nutritional deficiencies, opportunistic infections, bone marrow suppression, and adverse effects of ART.[5-7] Among these mechanisms, inflammation-induced disturbances in iron metabolism have received increasing attention. Hepcidin, a peptide hormone synthesized predominantly by hepatocytes, regulates systemic iron homeostasis by inhibiting intestinal iron absorption and iron release from macrophages through degradation of ferroportin.[8-10] Elevated hepcidin concentrations during chronic inflammation promote functional iron deficiency and contribute to the development of anemia of chronic disease.[9-11]

Although several international studies have investigated serum hepcidin in HIV infection, their findings have been inconsistent. Some studies have demonstrated an association between elevated serum hepcidin levels and advanced immunodeficiency, while others have reported limited diagnostic value in differentiating anemia subtypes.[11-14] Moreover, evidence from India regarding the relationship between serum hepcidin, anemia, and immune status among adults receiving long-term ART remains scarce.

Therefore, this study aimed to determine the prevalence and etiological spectrum of anemia among adults living with HIV receiving ART and to evaluate the association between serum hepcidin levels and immunological status, as assessed by CD4 lymphocyte count.

MATERIALS AND METHODS

Study design and participants

A hospital-based cross-sectional study was conducted at the Antiretroviral Therapy (ART) Centre, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India, between January 2021 and May 2022. Adult (≥18 years) people living with HIV (PLHIV) receiving ART for at least two years were consecutively enrolled. The study followed the STROBE reporting guidelines.[15]

Data collection

Demographic and clinical characteristics, ART duration, laboratory parameters, CD4 cell count, HIV viral load, and serum hepcidin levels were recorded using a standardized proforma. Anemia was defined according to the World Health Organization (WHO) criteria.[16] Patients were categorized into etiological subtypes based on hematological indices and iron studies.

Laboratory analysis

Complete blood count, peripheral smear, serum iron, ferritin, total iron-binding capacity (TIBC), soluble transferrin receptor (sTfR), erythropoietin, vitamin B12, folate, CD4 cell count, HIV viral load, and serum hepcidin were measured using standard laboratory methods. Serum hepcidin, sTfR, and erythropoietin were quantified using commercially available ELISA kits.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 16.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies and percentages. Group comparisons were performed using Student's t-test, Mann–Whitney U test, Chi-square test, or Fisher's exact test, as appropriate. Correlations were assessed using Pearson's or Spearman's correlation coefficients. A two-sided P value <0.05 was considered statistically significant.

Ethics

The study was approved by the Institutional Ethics Committee of ABVIMS and Dr. Ram Manohar Lohia Hospital, New Delhi, and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.[17]

RESULTS

A total of 201 adults living with HIV receiving ART were enrolled, of whom 130 (64.7%) had anemia. Most participants were male (69.7%), and the largest age group was 41–50 years. [Table 1]

Table 1: Baseline demographic and clinical characteristics of study participants

Variable	Value
Total participants	201
Male	69.7%
Female	30.3%
Most common age group	41–50 years (22.9%)

Anemia of chronic disease was the most common etiology (53.8%), followed by iron deficiency anemia (22.3%) and vitamin B12 deficiency anemia (11.5%). [Table 2] Normocytic normochromic anemia was the predominant morphological subtype.

Table 2: Etiological spectrum of anemia (n = 130)

Etiology	n	%
Anemia of chronic disease	70	53.8
Iron deficiency anemia	29	22.3
Vitamin B12 deficiency	15	11.5
IDA + Vitamin B12 deficiency	7	5.4

Folate deficiency	4	3.1
AOCD + IDA	3	2.3
Vitamin B12 + Folate deficiency	2	1.5

Anemia was significantly associated with shorter ART duration, lower CD4 cell count, higher HIV viral load, lower serum iron, lower TIBC, lower UIBC, elevated serum ferritin, higher erythropoietin levels, and abnormal peripheral smear findings (all P<0.05). [Table 3]

Table 3: Factors associated with anemia

Variable	*P* value
ART duration	<0.001
Serum iron	<0.001
TIBC	<0.001
UIBC	<0.001
Serum ferritin	0.003
Erythropoietin	<0.001
HIV viral load	<0.001
CD4 cell count	<0.001
Peripheral smear	<0.001

Patients with anemia of chronic disease had the highest serum ferritin concentrations and the lowest CD4 cell counts, whereas those with iron deficiency anemia had the lowest ferritin levels. Serum hepcidin was not significantly associated with anemia subtype, serum iron, ferritin, erythropoietin, or HIV viral load but showed a significant inverse correlation with CD4 cell count and a positive correlation with soluble transferrin receptor (*P*<0.05).

DISCUSSION

This study demonstrated that anemia remains highly prevalent among adults living with HIV receiving long-term ART, affecting nearly two-thirds of participants. Similar prevalence has been reported from other low- and middle-income countries, highlighting that anemia continues to be an important complication despite widespread ART availability.[1-4]

Anemia of chronic disease was the predominant etiology, followed by iron deficiency anemia and vitamin B12 deficiency. This finding supports previous studies showing that persistent inflammation and immune activation remain the major mechanisms of HIV-associated anemia.[5,6] The predominance of normocytic normochromic anemia further supports the inflammatory nature of anemia in this population.

Lower CD4 cell counts and higher HIV viral loads were significantly associated with anemia, indicating that worsening immunodeficiency contributes to impaired erythropoiesis. Similar associations have been reported previously, where anemia correlated with advanced HIV disease and poorer clinical outcomes.[2,4,11]

The principal finding of this study was that serum hepcidin was associated with immunological status rather than anemia itself. Although serum hepcidin did not differentiate anemia subtypes or correlate with conventional iron indices, it demonstrated a significant inverse relationship with CD4 cell count. These findings are consistent with previous studies suggesting that hepcidin reflects chronic immune activation rather than iron deficiency alone.[11-14]

The strengths of this study include comprehensive evaluation of iron metabolism, simultaneous assessment of serum hepcidin with conventional iron biomarkers, and inclusion of adults receiving long-term ART. However, the cross-sectional design limits causal inference, and the single-center setting may reduce the generalizability of the findings.

CONCLUSION

In conclusion, anemia remains a major hematological complication among adults living with HIV despite ART. Serum hepcidin appears to reflect immune dysregulation rather than anemia severity and may serve as a potential biomarker of immunological status. Prospective multicenter studies are needed to validate its clinical utility.

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