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FERRITIN AS A BIOMARKER OF INFLAMMATION AND IRON METABOLISM IN PEOPLE LIVING WITH HIV: CURRENT CLINICAL EVIDENCE

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ABSTRACT

Ferritin is a widely used biomarker of iron storage and has an important role in the assessment of iron metabolism. However, ferritin is also an acute-phase protein whose concentration may increase in response to inflammation, infection, and immune activation. These characteristics are particularly relevant in people living with human immunodeficiency virus, who may experience persistent immune activation and chronic inflammation even in the presence of effective antiretroviral therapy. This review examines the current evidence regarding the role of ferritin as a biomarker of inflammation and iron metabolism in people living with human immunodeficiency virus. This narrative review was conducted through literature searches in PubMed/MEDLINE and Scopus using keywords related to HIV, ferritin, inflammation, iron metabolism, hepcidin, anemia, and antiretroviral therapy. Relevant publications were screened based on their relevance to ferritin, inflammation, and iron homeostasis in people living with HIV. A total of 14 relevant articles were included in the narrative synthesis. Current evidence indicates that ferritin concentrations may reflect a complex interaction between iron stores, inflammation, immune activation, nutritional status, and treatment-related factors. Therefore, elevated ferritin should not be interpreted solely as evidence of increased iron stores, particularly in the presence of chronic inflammation. Understanding the biological context of ferritin measurement may improve its interpretation and support more appropriate assessment of iron status and inflammatory conditions in people living with human immunodeficiency virus.

Keywords: ferritin; human immunodeficiency virus; inflammation; iron metabolism; biomarkers

ABSTRAK

Ferritin merupakan biomarker yang banyak digunakan untuk menggambarkan cadangan besi dan memiliki peran penting dalam penilaian metabolisme besi. Namun, ferritin juga merupakan protein fase akut yang konsentrasinya dapat meningkat sebagai respons terhadap inflamasi, infeksi, dan aktivasi imun. Karakteristik tersebut sangat relevan pada orang dengan *human immunodeficiency virus* (HIV), yang dapat mengalami aktivasi imun persisten dan inflamasi kronis meskipun telah mendapatkan terapi antiretroviral yang efektif. Kajian ini bertujuan untuk menelaah bukti terkini mengenai peran ferritin sebagai biomarker inflamasi dan metabolisme besi pada orang dengan HIV. Kajian naratif ini dilakukan melalui penelusuran literatur pada PubMed/MEDLINE dan Scopus menggunakan kata kunci yang berkaitan dengan HIV, ferritin, inflamasi, metabolisme besi, hepcidin, anemia, dan terapi antiretroviral. Publikasi yang relevan diseleksi berdasarkan keterkaitannya dengan ferritin, inflamasi, dan homeostasis besi pada orang dengan HIV. Sebanyak 14 artikel yang relevan dimasukkan dalam sintesis naratif. Bukti terkini menunjukkan bahwa konsentrasi ferritin dapat mencerminkan interaksi kompleks antara cadangan besi, inflamasi, aktivasi imun, status gizi, dan faktor terkait terapi. Oleh karena itu, peningkatan ferritin tidak dapat diinterpretasikan semata-mata sebagai bukti peningkatan cadangan besi, terutama pada kondisi inflamasi kronis. Pemahaman terhadap konteks biologis pengukuran ferritin dapat meningkatkan interpretasinya dan mendukung penilaian status besi serta kondisi inflamasi yang lebih tepat pada orang dengan HIV.

Kata Kunci: ferritin; human immunodeficiency virus; inflamasi; metabolisme besi; biomarker

INTRODUCTION

Human immunodeficiency virus (HIV) infection is characterized by persistent immune dysregulation and inflammation that may continue despite effective antiretroviral therapy. Although antiretroviral therapy has substantially improved viral suppression and survival, people living with HIV (PLWH) may remain exposed to chronic immune activation and systemic inflammation. This persistent inflammatory state has been associated with an increased risk of several non-communicable comorbidities and may influence metabolic and hematological processes. Recent evidence indicates that inflammation may persist even among individuals with sustained virological suppression, suggesting that HIV-related immune dysfunction extends beyond uncontrolled viral replication. (Garrido-Rodríguez et al., 2022)

One metabolic pathway that may be affected by chronic inflammation in HIV infection is iron homeostasis. Iron is essential for oxygen transport, cellular metabolism, erythropoiesis, and immune function; however, its availability must be tightly regulated because excessive or insufficient iron can adversely affect cellular and systemic functions. Inflammatory signaling can alter iron distribution by increasing hepcidin production, which reduces iron export through ferroportin and promotes iron sequestration within macrophages and other storage sites. Consequently, individuals with HIV may exhibit alterations in circulating iron, transferrin, transferrin saturation, ferritin, and other indicators of iron metabolism. Evidence from HIV populations has demonstrated an association between altered hepcidin concentrations, ferritin, inflammatory markers, anemia, and indicators of disease status. (Minchella et al., 2015; Wisaksana et al., 2013)

Ferritin is primarily recognized as an intracellular protein responsible for storing iron in a bioavailable and relatively non-toxic form. Serum ferritin is therefore commonly used as a surrogate marker of body iron stores. However, ferritin also functions as an acute-phase reactant and may increase in response to inflammation, infection, and tissue injury independently of actual iron stores. This dual biological role makes ferritin particularly relevant in conditions characterized by chronic inflammation. In inflammatory states, increased ferritin may occur alongside reduced circulating iron availability as iron becomes sequestered within cells under the influence of inflammatory pathways. (Abioye et al., 2020, 2023)

The interpretation of ferritin in people living with HIV is consequently complex. A high serum ferritin concentration does not necessarily indicate iron overload, because inflammation and immune activation may contribute substantially to its elevation. Conversely, a normal or moderately elevated ferritin concentration may not reliably exclude iron deficiency when inflammation is present. This issue is clinically relevant because anemia and disturbed iron status are common among PLWH and may result from nutritional deficiencies, chronic inflammation, opportunistic infections, HIV-related mechanisms, or treatment-related factors. A systematic review of evidence on anemia and iron status in HIV also reported that high ferritin concentrations were associated with adverse clinical outcomes, although the contribution of iron status and inflammation could not always be clearly distinguished. (Abioye et al., 2020)

The current evidence therefore suggests that ferritin should not be interpreted as an isolated indicator of iron stores in PLWH. Its biological meaning may depend on the interaction between iron availability, inflammatory activity, immune status, nutritional factors, infection, and antiretroviral treatment. Studies in virologically suppressed individuals further indicate that alterations in iron metabolism may persist despite effective antiretroviral therapy, supporting the need to examine ferritin within a broader framework of iron and inflammatory biomarkers. (Garrido-Rodríguez et al., 2022)

Despite increasing interest in ferritin as both an indicator of iron status and an inflammatory biomarker, the evidence concerning its interpretation specifically in PLWH remains dispersed across studies addressing anemia, inflammation, immune activation, nutritional status, iron regulation, and treatment-related metabolic changes. The distinction between ferritin elevation caused by increased iron stores and elevation related to inflammation remains particularly important. Therefore, an

integrated assessment of the current evidence is needed to clarify the biological significance, clinical interpretation, and potential utility of ferritin in HIV infection.

This review aims to synthesize current evidence regarding ferritin as a biomarker of inflammation and iron metabolism in PLWH, with particular emphasis on the mechanisms underlying altered ferritin concentrations, its relationship with iron homeostasis and chronic inflammation, factors influencing its interpretation, and its potential clinical implications.

METODE PENELITIAN

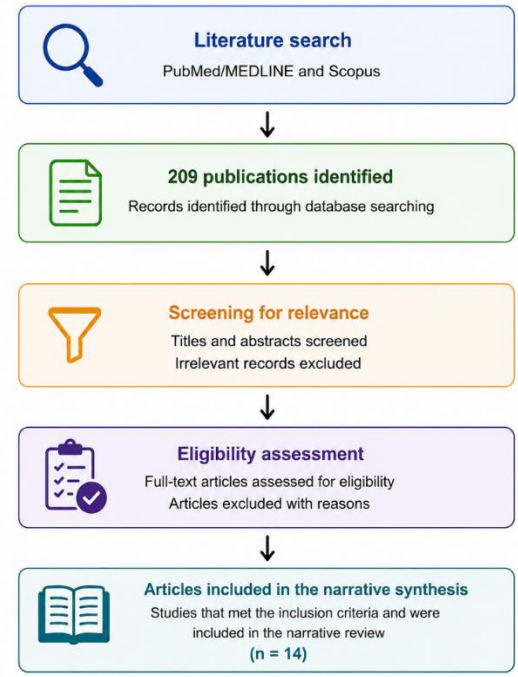
This article was developed as a narrative review to synthesize current evidence on ferritin as a biomarker of inflammation and iron metabolism in people living with HIV. Relevant scientific literature was identified through searches of PubMed/MEDLINE and Scopus using combinations of keywords including “HIV,” “human immunodeficiency virus,” “people living with HIV,” “ferritin,” “inflammation,” “iron metabolism,” “iron homeostasis,” “hepcidin,” “anemia,” and “antiretroviral therapy.”

Relevant original research articles and review articles were considered based on their contribution to the biological and clinical understanding of ferritin in HIV infection. Recent publications were prioritized, particularly studies published within the last five years, while earlier studies were retained when they provided important foundational evidence on ferritin, hepcidin, iron homeostasis, or HIV-associated inflammation.

The identified literature was critically reviewed and synthesized narratively according to the main themes of the article. The synthesis focused on ferritin and iron homeostasis, ferritin as an inflammatory biomarker, mechanisms underlying ferritin elevation in HIV, the relationship between ferritin, immune activation and HIV disease progression, nutritional and iron status, the influence of antiretroviral therapy, clinical interpretation and limitations of ferritin, and research gaps and future perspectives.

The literature identification and selection process is summarized in Figure 1. The flow diagram presents the process of identifying relevant publications from PubMed/MEDLINE and Scopus, screening the retrieved literature for relevance, and assessing potentially eligible articles for inclusion in the narrative synthesis. A total of 209 records were identified through the initial literature search. Following the screening and eligibility assessment, 14 articles met the inclusion criteria and were included in the final narrative synthesis.

Figure 1. Flow Diagram of Literature Identification and Selection



RESULTS AND DISCUSSION

Characteristics of the Reviewed Studies

The characteristics of the studies reviewed in this narrative review are summarized in Table 1. The included studies varied in terms of country, study design, population, research focus, and outcome measures. The evidence comprised observational, cohort, longitudinal, diagnostic, experimental, and review studies, reflecting the multidimensional relationship between ferritin, inflammation, iron metabolism, and HIV infection.

Table 1. Characteristics of Studies Included in the Narrative Review

Author, Year	Country	Study Design	Sample/ Population	Exposure/ Focus	Main Outcome	Key Finding/ Recommendation
Minchella et al., 2015	Gambia	Cohort study	PLWH	Hepcidin and iron regulation	Hepcidin, ferritin, anemia	Altered iron regulation was associated with inflammation and anemia
Wisaksana et al., 2013	Indonesia	Prospective cohort	PLWH with advanced disease	Hepcidin and iron status	Hepcidin, ferritin, CD4, hemoglobin	Higher hepcidin and ferritin were associated with advanced disease and poorer hematological status
Frosch et al., 2018	Kenya	Observational study	PLWH	Ferritin and soluble transferrin receptor	Iron deficiency and anemia	sTfR may provide complementary information when ferritin is influenced by inflammation
Abioye et al., 2020	Multiple countries	Systematic review	PLWH	Anemia and iron status	Anemia and clinical outcomes	Anemia and altered iron status are important clinical concerns in PLWH
Garrido-Rodríguez et al., 2022	Spain	Observational study	Virologically suppressed PLWH	Iron metabolism during ART	Ferritin and iron-related biomarkers	Alterations in iron metabolism may persist despite viral suppression
Szymczak et al., 2022	Poland	Pilot/observational study	PLWH	Iron metabolism and hepcidin	Iron parameters and hepcidin	Iron metabolism may remain altered even in clinically stable PLWH
Abioye et al., 2023	Tanzania	Longitudinal study	Adults initiating ART	Iron status during ART	Ferritin and inflammatory status	Iron status and inflammation may change during ART
Funderburg et al., 2024	USA	Longitudinal cohort	PLWH receiving ART	Persistent inflammation	Inflammatory biomarkers	Immune activation and inflammation may persist during viral suppression
Kamurai et al., 2024	Zimbabwe	Prospective study	PLWH with co-infections	Ferritin and inflammatory biomarkers	Ferritin, CRP, iron-related parameters	Concurrent infections may influence ferritin concentrations
Pavan Kumar et al., 2025	India	Prospective study	PLWH with latent TB	Ferritin, hepcidin and acute-phase proteins	Ferritin, hepcidin, CRP	Tuberculosis-related inflammation may affect ferritin and iron biomarkers

Author, Year	Country	Study Design	Sample/ Population	Exposure/ Focus	Main Outcome	Key Finding/ Recommendation
Saumoy et al., 2025	Spain	Prospective cohort	Virologically suppressed PLWH	Inflammation and clinical outcomes	Inflammatory biomarkers and non-AIDS events	Persistent inflammation may have clinical implications despite viral suppression
Lewis et al., 2007	Malawi	Diagnostic/observational study	HIV-positive adults with severe anemia	Iron deficiency assessment	Bone marrow iron and routine iron markers	Ferritin alone may be insufficient to distinguish iron deficiency from inflammation
Armitage et al., 2014	United Kingdom/West Africa	Comparative observational study	Individuals with HIV and other chronic infections	Hepcidin and iron regulation	Hepcidin and iron parameters	Hepcidin is influenced by infection and inflammatory status
Drakesmith et al., 2005	United Kingdom	Experimental study	Cellular HIV-1 model	Hepcidin–ferroportin pathway	Intracellular iron and HIV replication	Iron regulation may interact with HIV-1 replication mechanisms

Ferritin and Iron Homeostasis

Ferritin is a major intracellular iron-storage protein that maintains iron in a soluble and relatively non-toxic form. Serum ferritin is commonly used as an indirect indicator of body iron stores; however, its concentration is also influenced by inflammatory processes. Iron homeostasis is regulated by a broader network involving ferritin, transferrin, transferrin receptors, ferroportin, and hepcidin. The interaction among these components determines the availability of circulating iron for erythropoiesis and cellular metabolism. In virologically suppressed people living with HIV receiving effective antiretroviral therapy, altered concentrations of iron, transferrin saturation, soluble transferrin receptor, and ferritin have been reported, suggesting persistent disturbances in iron regulation despite successful viral suppression. (Garrido-Rodríguez et al., 2022)

Hepcidin is a central regulator of systemic iron homeostasis. It controls iron availability by binding to ferroportin, the principal cellular iron exporter, leading to ferroportin internalization and degradation. Increased hepcidin consequently reduces the release of iron into the circulation and promotes iron retention within macrophages and other storage compartments. Inflammatory signaling, particularly through interleukin-6, can stimulate hepatic hepcidin production and contribute to iron sequestration and reduced circulating iron availability. (Wisaksana et al., 2013)

This mechanism is particularly relevant to HIV infection. Evidence from an Indonesian prospective cohort demonstrated that patients with advanced HIV infection had higher serum hepcidin and ferritin concentrations. Serum hepcidin was inversely correlated with CD4 cell counts and hemoglobin and positively correlated with ferritin. These findings indicate that disturbances in iron regulation are associated with advanced HIV disease and may occur together with reduced iron availability and anemia. (Wisaksana et al., 2013)

The Indonesian cohort also demonstrated an important influence of tuberculosis on these findings. Patients who subsequently initiated tuberculosis treatment had higher hepcidin and ferritin concentrations at cohort enrollment, and the difference was particularly evident among those who started tuberculosis treatment within 31–60 days after enrollment. Thus, elevated ferritin and hepcidin in people living with HIV may reflect not only HIV-associated alterations in iron regulation but also underlying or developing inflammatory conditions such as tuberculosis. (Wisaksana et al., 2013)

Longitudinal evidence further demonstrates that iron status in HIV infection is dynamic and that ferritin interpretation is influenced by inflammation. In a study of 400 adults initiating antiretroviral therapy in Tanzania, the estimated prevalence of iron deficiency and elevated iron status differed substantially depending on whether ferritin was unadjusted or corrected for inflammation. During the first year of therapy, iron deficiency increased while elevated iron status decreased across

the inflammation-correction approaches. These findings emphasize that serum ferritin cannot always be interpreted independently of inflammatory status. (Abioye et al., 2023)

Thus, ferritin should be understood as one component of a dynamic iron-regulatory system rather than as an isolated indicator of iron status. An increased ferritin concentration in people living with HIV may reflect increased iron storage, inflammation-associated iron sequestration, concurrent infection, or a combination of these processes. Consequently, interpretation of ferritin requires consideration of other indicators of iron availability and inflammatory activity.

Ferritin as an Inflammatory Biomarker in HIV

Although ferritin is traditionally considered a marker of iron storage, its biological role extends beyond iron sequestration. Ferritin is an acute-phase reactant, and its circulating concentration may increase in response to infection and inflammation. Consequently, elevated serum ferritin may reflect inflammatory activity in addition to changes in iron stores. This dual biological role is particularly relevant in people living with HIV, in whom chronic inflammation and concurrent infections may influence both ferritin concentrations and iron availability.

Persistent immune activation and systemic inflammation may remain present in people living with HIV despite effective antiretroviral therapy and sustained virological suppression. Recent prospective evidence indicates that inflammatory biomarkers remain clinically relevant among virologically suppressed individuals and may be associated with subsequent non-AIDS-defining clinical events. These findings support the concept that HIV-associated inflammation may persist beyond uncontrolled viral replication and may contribute to long-term metabolic and clinical consequences. (Saumoy et al., 2025)

Recent evidence also demonstrates a close relationship between ferritin and inflammatory activity in people living with HIV with concurrent infections. In a prospective study of individuals receiving dolutegravir-based antiretroviral therapy, participants with co-infections had higher ferritin and C-reactive protein (CRP) concentrations and lower plasma iron before treatment. After six months of therapy, ferritin and CRP decreased and plasma iron increased; however, ferritin and CRP remained higher among participants with co-infections despite similar rates of virological suppression. These findings indicate that ferritin may reflect persistent inflammatory activity as well as alterations in iron availability. (Kamurai et al., 2024)

Further evidence from a prospective study of people living with HIV with latent tuberculosis infection showed that ferritin and hepcidin, together with several acute-phase proteins including CRP, were significantly higher in participants with latent tuberculosis than in those without latent tuberculosis. Following six months of isoniazid prophylaxis, several inflammatory and iron-related biomarkers decreased. These findings further demonstrate that concurrent infectious conditions can substantially influence ferritin concentrations in people living with HIV. (Pavan Kumar et al., 2025)

The interpretation of ferritin as an inflammatory biomarker should nevertheless be approached cautiously. Ferritin is not specific to HIV-associated inflammation and may be influenced by concurrent infections, liver disease, metabolic disorders, malignancy, and other inflammatory conditions. Therefore, ferritin should not be used as a standalone indicator of HIV-associated inflammation. Instead, its interpretation should be integrated with other clinical and laboratory indicators, particularly inflammatory markers such as CRP and complementary measures of iron status.

Mechanisms Underlying Ferritin Elevation in HIV

Several mechanisms may contribute to elevated ferritin concentrations in people living with HIV. One important mechanism involves inflammatory signaling and altered hepcidin activity. Hepcidin is a central regulator of systemic iron homeostasis and is closely associated with the inflammatory regulation of iron availability. In a cohort of antiretroviral-naive adults with HIV infection, higher hepcidin concentrations were associated with higher ferritin and inflammatory activity, as well as lower hemoglobin and other indicators of iron availability. These findings suggest that inflammation-associated changes in hepcidin may contribute to iron sequestration and altered ferritin concentrations during HIV infection. (Minchella et al., 2015)

A second mechanism involves direct effects of HIV-related proteins on cellular iron regulation. Experimental evidence has demonstrated that the HIV-1 Nef protein can interfere with the expression and localization of HFE, a protein involved in cellular iron homeostasis. In HIV-1-infected macrophages, alteration of HFE was accompanied by increased intracellular iron and ferritin accumulation, together with increased HIV-1 gene expression. These findings suggest that HIV may influence cellular iron metabolism through mechanisms extending beyond the systemic inflammatory response. However, because these observations were obtained primarily from experimental models, their direct clinical significance in people living with HIV remains uncertain. (Drakesmith et al., 2005)

A third mechanism involves the host response to infection and the concept of nutritional immunity. During infection, iron availability is tightly regulated to limit access to this essential nutrient by pathogens. Increased intracellular iron sequestration can therefore represent a protective host response. However, persistent disruption of iron distribution may impair iron availability for erythropoiesis and contribute to anemia. The relationship between HIV infection and iron regulation is not uniform, however. A pilot study among asymptomatic individuals with HIV-1 and relatively preserved CD4 cell counts found no major abnormalities in iron metabolism, inflammatory markers, or soluble transferrin receptor concentrations, indicating that alterations in iron homeostasis may depend on disease stage and clinical context. (Szymczak et al., 2022)

Coexisting infections may further amplify these mechanisms. Tuberculosis and other infectious conditions can increase inflammatory activity and alter iron distribution, thereby contributing to ferritin elevation in people living with HIV. Consequently, ferritin elevation should not automatically be attributed to HIV-associated inflammation alone. The presence of opportunistic or concurrent infections should be considered when evaluating changes in ferritin and other iron-related biomarkers.

Finally, persistent immune activation may provide an additional context in which these mechanisms operate. Recent longitudinal evidence indicates that inflammatory markers can remain altered during prolonged viral suppression, supporting the persistence of inflammatory processes despite effective antiretroviral therapy. Such persistent inflammation may contribute indirectly to continued alterations in iron metabolism and ferritin regulation. (Funderburg et al., 2024)

Overall, ferritin elevation in HIV infection is likely to result from multiple interacting mechanisms rather than a single pathway. These include inflammatory regulation of hepcidin, intracellular effects of HIV-related proteins, host nutritional immunity, concurrent infections, and persistent immune activation. The relative contribution of each mechanism may vary according to HIV disease stage, immune status, treatment, and comorbid conditions.

Relationship Between Ferritin, Immune Activation, and HIV Disease Progression

The relationship between ferritin and HIV disease progression is complex and appears to involve the interaction of inflammation, immune status, iron homeostasis, and comorbid conditions. Ferritin concentrations may increase as disease-associated inflammation becomes more pronounced, while altered iron distribution may contribute to anemia and impaired physiological function.

Evidence from cohort studies suggests that disturbances in iron-regulatory pathways are associated with markers of HIV disease severity. Higher hepcidin concentrations have been associated with lower CD4 cell counts, lower hemoglobin concentrations, and higher ferritin concentrations. In one cohort of individuals with newly diagnosed HIV infection, elevated hepcidin was also associated with greater all-cause mortality in a dose-dependent manner. (Minchella et al., 2015)

Ferritin itself has also been investigated as a potential prognostic marker. An earlier study among women with HIV found that increasing serum ferritin was associated with higher odds of mortality after adjustment for several potential confounders, although the confidence interval included the possibility of no association. More broadly, a systematic review found that elevated serum ferritin was associated with adverse clinical outcomes, including mortality, among people living with HIV. However, the biological basis of this association remains uncertain, as elevated ferritin may reflect increased iron stores, inflammation, infection, or a combination of these processes. (Abioye et al., 2020)

These findings suggest that ferritin may have prognostic relevance, but they do not establish ferritin as a direct measure of HIV progression. Ferritin elevation may instead represent a biological consequence of several processes occurring simultaneously. Therefore, its potential prognostic value is likely to be greatest when interpreted alongside CD4 cell count, viral load, inflammatory markers, nutritional indicators, and relevant comorbidities.

Ferritin and Nutritional/Iron Status

Iron deficiency and anemia remain important concerns among people living with HIV. The causes of anemia are multifactorial and may include inadequate nutritional intake, impaired iron availability, chronic inflammation, opportunistic infections, HIV-related mechanisms, and treatment-related factors. A systematic review found that people living with HIV are at substantial risk of anemia and that anemia is associated with adverse clinical outcomes, including increased mortality and incident tuberculosis. (Abioye et al., 2020)

The major challenge is distinguishing absolute iron deficiency from inflammation-associated functional iron restriction. Absolute iron deficiency refers to inadequate total body iron stores, whereas functional iron restriction occurs when iron is present in storage compartments but is insufficiently available for erythropoiesis. In inflammatory conditions, increased hepcidin promotes iron sequestration and may result in low circulating iron despite normal or elevated ferritin concentrations. (Abioye et al., 2020)

This distinction is especially important in HIV infection because a normal or elevated ferritin concentration does not necessarily exclude iron deficiency when inflammation is present. In HIV-infected Kenyan adults, ferritin was elevated and showed stronger correlations with CRP and hepcidin than with hemoglobin. Soluble transferrin receptor was more strongly associated with anemia and was considered a useful marker of iron deficiency in the setting of HIV-associated inflammation (Frosch et al., 2018).

Evidence from a high-HIV-prevalence setting further demonstrates the limitation of conventional iron markers. Among adults with severe anemia in Malawi, no routine blood test was sufficiently accurate to reliably diagnose iron deficiency in HIV-positive patients without assessment of bone marrow iron. This finding illustrates the difficulty of distinguishing absolute iron deficiency from inflammation-associated abnormalities using ferritin alone. (Lewis et al., 2007)

Therefore, assessment of iron status in people living with HIV should ideally integrate ferritin with other parameters, including hemoglobin, transferrin saturation, soluble transferrin receptor, serum iron, and inflammatory markers. A multidimensional approach may provide a more accurate assessment of iron availability than ferritin alone, particularly in the presence of chronic inflammation (Abioye et al., 2020).

Influence of Antiretroviral Therapy

Antiretroviral therapy has substantially changed the clinical course of HIV infection by reducing viral replication, morbidity, and mortality. However, suppression of viral replication does not necessarily result in complete normalization of immune and metabolic processes. Persistent immune activation and inflammatory abnormalities may remain in some individuals receiving effective antiretroviral therapy and may continue to influence iron homeostasis.

Evidence regarding the influence of antiretroviral therapy on hepcidin and iron metabolism is heterogeneous. A study evaluating iron regulation in HIV-1 infection found that hepcidin remained elevated among individuals receiving antiretroviral therapy compared with uninfected controls, although concentrations were lower than those observed in untreated HIV infection. Hepcidin elevation occurred together with increased inflammatory markers, suggesting that abnormalities in iron regulation may persist despite virological suppression (Armitage et al., 2014).

More recent longitudinal evidence from Tanzania provides additional insight into changes in iron status during treatment. Among 400 adults initiating antiretroviral therapy, the prevalence of iron deficiency increased during the first year of treatment, whereas the prevalence of elevated iron status decreased. Importantly, the estimated prevalence of iron deficiency and elevated iron status varied substantially according to whether ferritin was interpreted without adjustment or corrected for

inflammation. These findings demonstrate that changes in iron status during antiretroviral therapy are dynamic and that the interpretation of ferritin is strongly influenced by concurrent inflammation (Abioye et al., 2023).

These observations indicate that ferritin concentrations should not necessarily be interpreted as a direct indicator of treatment response. Changes in ferritin after initiation of antiretroviral therapy may reflect changes in inflammation, immune recovery, nutritional status, and iron availability rather than changes in iron stores alone. The Tanzanian study further showed that the prevalence of iron deficiency increased while elevated iron status decreased during the first year of therapy, emphasizing that iron metabolism may change substantially during treatment (Abioye et al., 2023).

The influence of specific antiretroviral regimens on ferritin and iron metabolism requires further investigation. Future studies should evaluate ferritin together with treatment duration, viral suppression, immune recovery, nutritional status, inflammatory markers, and comorbidities rather than considering ferritin as an isolated indicator of treatment response.

Clinical Interpretation and Limitations of Ferritin

The principal clinical limitation of ferritin is its lack of specificity for iron stores in inflammatory conditions. In otherwise healthy individuals, ferritin is a useful indicator of body iron stores and low concentrations generally indicate depleted iron stores. However, infection and inflammation can increase ferritin independently of iron status. The World Health Organization (WHO) therefore recommends that ferritin be interpreted together with indicators of infection or inflammation and that ferritin concentrations be appropriately adjusted when inflammation is present (WHO, 2023).

For people living with HIV, this limitation is particularly relevant because elevated ferritin may reflect increased iron stores, inflammation, concurrent infection, liver dysfunction, or a combination of these conditions. Conversely, a ferritin concentration within a conventional reference range does not necessarily exclude iron deficiency when substantial inflammation is present. WHO recommends a higher ferritin threshold for identifying iron deficiency in adults with infection or inflammation and emphasizes that ferritin should not be used alone to assess the risk of iron overload (WHO, 2023)

Clinical interpretation should therefore involve a combination of biomarkers. Ferritin may be assessed together with C-reactive protein (CRP) and, where appropriate, other acute-phase proteins to account for the influence of inflammation. Transferrin saturation and serum iron provide information regarding circulating iron availability, whereas soluble transferrin receptor may provide additional information regarding cellular iron demand and erythropoietic activity. Hemoglobin and red-cell indices remain important for identifying the hematological consequences of altered iron metabolism. Evidence from HIV populations also indicates that soluble transferrin receptor may be useful for identifying iron deficiency when ferritin is influenced by inflammation.

The use of ferritin as a biomarker in HIV should consequently shift from a single-marker approach toward an integrated biomarker framework. Combining ferritin with inflammatory markers and complementary indicators of iron availability may improve differentiation between absolute iron deficiency, functional iron restriction, inflammation-associated hyperferritinemia, and possible iron overload. This approach is particularly important in people living with HIV because multiple inflammatory, infectious, nutritional, and metabolic factors may influence ferritin concentrations simultaneously.

Research Gaps and Future Perspectives

Despite considerable evidence linking ferritin with inflammation and iron metabolism in HIV infection, several important knowledge gaps remain. First, the independent contribution of ferritin to HIV-related clinical outcomes remains uncertain because ferritin is influenced by multiple overlapping factors, including inflammation, opportunistic infections, nutritional status, liver disease, and metabolic conditions. Existing studies frequently cannot completely distinguish whether elevated ferritin reflects altered iron stores or the inflammatory burden associated with HIV and its comorbidities.

Second, there is a need for longitudinal studies evaluating ferritin before and after antiretroviral therapy while simultaneously measuring inflammatory markers, hepcidin, iron availability, immune

status, and nutritional indicators. Such studies could clarify whether persistent ferritin elevation represents residual inflammation, altered iron regulation, changes in nutritional status, or other treatment-related factors.

Third, future research should investigate whether combining ferritin with other biomarkers improves clinical classification. A multimarker approach incorporating ferritin, hepcidin, CRP, transferrin saturation, soluble transferrin receptor, hemoglobin, and nutritional indicators may provide greater biological information than ferritin alone. However, the clinical utility, cost-effectiveness, and appropriate interpretation of such multimarker approaches in people living with HIV remain to be established.

Fourth, population-specific research is needed because the interpretation of ferritin may be influenced by differences in nutritional status, infectious disease burden, tuberculosis prevalence, liver disease, sex, age, and access to antiretroviral therapy. Evidence from Indonesia and other high-burden settings is particularly valuable because concurrent infections and nutritional challenges may substantially affect iron metabolism and inflammatory biomarkers.

Finally, future studies should determine whether ferritin has practical value as a prognostic or monitoring biomarker beyond its established role in assessing iron stores. The key challenge is not simply determining whether ferritin is elevated in HIV infection, but establishing what an elevated ferritin concentration represents in a particular clinical context. Addressing this question may improve the interpretation of iron status, anemia, and chronic inflammation among people living with HIV.

CONCLUSION

Ferritin is a biologically complex biomarker in people living with HIV because its concentration reflects both iron storage and inflammatory processes. Current evidence indicates that HIV-associated immune activation, chronic inflammation, altered hepcidin–ferroportin regulation, nutritional factors, and coexisting infections may contribute to changes in ferritin concentrations. Consequently, elevated ferritin cannot be interpreted solely as an indicator of increased iron stores, particularly in individuals with active inflammation or infection. Ferritin should therefore be interpreted together with other indicators of iron status and inflammation, including hemoglobin, transferrin saturation, soluble transferrin receptor, hepcidin, and inflammatory markers. Future longitudinal studies are needed to determine the independent prognostic value of ferritin and to establish multimarker approaches that can improve the assessment of iron metabolism and inflammation in people living with HIV.

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