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Research Article

When Improved Iron Nutrition Benefits the Pathogen and Adversely Affects the Host: A Review of Iron Metabolism in HIV-1 Infection

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ABSTRACT

Iron is an essential micronutrient for both host immune function and pathogen proliferation. In the context of Human Immunodeficiency Virus type 1 (HIV-1) infection, the management of iron status presents a complex clinical paradox. While iron deficiency contributes to anemia and impaired erythropoietic and immune function, excessive iron availability or inappropriate iron supplementation may exacerbate oxidative stress and support iron-dependent cellular processes that can favor viral persistence and replication. HIV-1 critically depends on host cellular machinery, including iron-dependent enzymes and pathways such as ribonucleotide reductase, deoxyhypusine hydroxylase, and redox-sensitive Nuclear Factor kappa B (NF-κB) signaling. In parallel, the host deploys nutritional immunity through the hepcidin-ferroportin axis to restrict circulating iron and promote its sequestration within macrophages. Emerging evidence also implicates iron-sulfur cluster-dependent host proteins and ferroptotic pathways in HIV-associated cellular pathology, although their broader contribution to HIV-1 pathogenesis remains incompletely defined. This review examines HIV-1 biology, viral replication, host immune interactions, and iron metabolism, with emphasis on the mechanisms linking iron dysregulation to anemia, oxidative stress, macrophage dysfunction, and viral persistence. Furthermore, we evaluate the clinical implications of iron supplementation, the importance of distinguishing true iron deficiency from anemia of inflammation, potential interactions between iron-containing supplements and integrase strand transfer inhibitors, and the emerging therapeutic potential and limitations of iron chelators as host-directed antiviral agents.

Keywords: *HIV-1, Iron metabolism, Hepcidin, Nutritional Immunity, Anemia of inflammation, Iron chelation*

INTRODUCTION

Human Immunodeficiency Virus type 1 (HIV-1) remains a critical global health challenge. Despite the widespread availability of highly active anti-retroviral therapy (ART), chronic complications such as anemia persist as major sources of morbidity and predictors of mortality among People Living with HIV-1 (PLWH) (Volberding et al., 2004). Anemia in PLWH is multifactorial, arising from opportunistic infections, bone marrow suppression, ART toxicity, and nutritional deficiencies. Historically, clinicians have responded to low hemoglobin levels by administering exogenous iron. However, an evolving body of evidence suggests that improving iron nutrition in infected hosts may paradoxically benefit the pathogen while adversely affecting the host (Drakesmith & Prentice, 2012).

Iron is biologically indispensable. Its capacity to readily accept and donate electrons (cycling between ferrous, Fe^{2+}, and ferric, Fe^{3+} states) makes it vital for oxygen transport,mitochondrial respiration, DNA synthesis, and cellular proliferation. However, this same redox capability

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renders free iron highly toxic, as it catalyzes the generation of hydroxyl radicals via the Fenton reaction (Kell, 2009). In infectious disease paradigms, competition for iron between the host and pathogen is intense, a phenomenon known as "nutritional immunity" (Weinberg, 1974). While bacterial pathogens synthesize siderophores to scavenge host iron, viruses like HIV-1 depend entirely on the host cell's metabolic machinery. HIV-1 infection systematically alters host systemic and cellular iron homeostasis to create an iron-replete intracellular environment that facilitates robust viral transcription, translation, and virion assembly (Nekhai et al., 2013).

This review critically examines the complex biological interactions between HIV-1 replication and host iron metabolism, highlighting the potential risks associated with empirical iron supplementation.

MATERIALS AND METHODS

Search strategy

A structured literature search was conducted using PubMed/MEDLINE and Google Scholar to identify relevant literature on the relationship between Human Immunodeficiency Virus type 1 (HIV-1) infection and iron metabolism. The search covered publications from 1974 to 2026, capturing both foundational discoveries in nutritional immunity and contemporary research on HIV-1 pathogenesis, iron regulation, biomarkers, and host-directed therapeutic strategies.

Search strategy and Boolean queries

To enhance search reproducibility, Boolean search strings were constructed by combining HIV-1 terminology with terms relating to iron metabolism, iron homeostasis, inflammation, and iron-dependent cellular pathways. The primary search string used in PubMed/MEDLINE was:
("HIV-1" OR "HIV" OR "Human Immunodeficiency Virus") AND ("iron metabolism" OR "iron homeostasis" OR "hepcidin" OR "ferroportin" OR "nutritional immunity" OR "ribonucleotide reductase" OR "deoxyhypusine hydroxylase" OR "DOHH" OR "anemia of inflammation" OR "ferritin" OR "iron chelation")
Supplementary targeted searches were performed in Google Scholar using combinations such as "HIV-1" AND "hepcidin" AND "ferroportin" and "HIV-1" AND "integrase inhibitors" AND "iron". Additional relevant publications were identified by examining the reference lists of retrieved articles and following citations from key publications.

Eligibility criteria

The selection of literature was guided by predefined inclusion and exclusion criteria.
Inclusion criteria were: (1) peer-reviewed original research, experimental and mechanistic studies, and clinical studies providing relevant information on HIV-1 biology, viral replication, or iron-dependent biochemical pathways; (2) studies examining inflammatory regulation of the hepcidin-ferroportin axis in HIV-1 infection; (3) studies investigating clinical biomarkers of iron status, including serum ferritin and soluble transferrin receptor (sTfR), in people living with HIV-1; and (4) studies evaluating the effects of antiretroviral therapy (ART) on iron status, iron redistribution, drug-cation interactions, or potential iron-chelation strategies. Foundational publications and authoritative reviews were also considered where they provided essential evidence for established concepts or mechanisms discussed in the review.
Exclusion criteria were: (1) publications lacking substantive relevance to HIV-1 infection and iron metabolism; (2) studies addressing general anemia without relevance to HIV-1-associated pathophysiology or iron regulation; and (3) non-English publications for which an accessible English translation was unavailable.

Screening and selection workflow

The retrieved literature was screened initially by title and abstract to identify publications relevant to the objectives of the review. Potentially relevant articles were subsequently assessed in full text against the predefined eligibility criteria. Reference lists of key publications were also examined to identify additional relevant studies that might not have been retrieved through the database searches. The eligible literature was then critically evaluated and synthesized according to the major themes of the review: HIV-1 biology and iron-dependent cellular processes, hepcidin-ferroportin regulation and nutritional immunity, clinical assessment of iron status and anemia, and therapeutic implications.

This article is a narrative review rather than a systematic review or meta-analysis. Accordingly, formal PRISMA study-selection procedures and quantitative screening counts were not applied.

HIV-1 Biology and the viral life cycle

To understand how iron influences HIV-1, one must first describe the viral life cycle. HIV-1 is a lentivirus belonging to the retroviridae family. The virion contains two copies of positive-sense single-stranded RNA, encapsulated alongside essential viral enzymes: reverse transcriptase (RT), integrase (IN), and protease (PR) (Engelman & Cherepanov, 2012).

The replication cycle initiates with the binding of the viral envelope glycoprotein (gp120) to the host CD4 receptor, predominantly on T helper cells and macrophages. This interaction induces a conformational change allowing binding to co-receptors (CCR5 or CXCR4), leading to membrane fusion and viral uncoating. Upon entry, the viral RNA is reverse-transcribed into double-stranded DNA by RT. This step requires an adequate intracellular supply of host deoxynucleotide triphosphates (dNTPs), which serve as substrates for viral DNA synthesis.

The newly synthesized viral DNA is translocated into the nucleus and permanently inserted into the host genome by integrase, establishing the provirus. Transcription of the provirus is regulated by the viral long terminal repeat (LTR) promoter, which is heavily reliant on host transcription

factors, particularly nuclear factor kappa light-chain enhancer of activated B cells (NFκB) and Specificity protein 1 (Sp1) (Schreck et al., 1991).

The resulting viral mRNAs are translated into polyproteins, which are subsequently assembled at the plasma membrane, budded off, and cleaved by viral protease into mature, infectious virions (Freed, 2001). Crucially, multiple steps in this sequence most notably reverse transcription, LTR-driven transcription, and mRNA translation are functionally tethered to host cellular iron availability (Nordlund & Reichard, 2006).

Iron-Sulfur (Fe-S) cluster machinery in HIV-1 replication and inmate restriction

Beyond bulk cellular iron, iron-sulfur (Fe-S) clusters constitute a distinct layer of regulated iron utilization. Predominantly occurring as (2Fe-2S) and (4Fe-4S) centers, Fe-S clusters function as cofactors in electron transfer, enzymatic catalysis, metabolic regulation, and nucleic-acid metabolism. Their incorporation into target proteins requires dedicated cellular biogenesis pathways. In mammalian cells, Fe-S cluster assembly and insertion into recipient proteins involve complex machinery operating in mitochondrial and cytosolic/nuclear compartments, while the cytosolic iron-sulfur protein assembly (CIA) machinery contributes to the maturation of numerous cytosolic and nuclear Fe-S proteins (Lill, 2020; Maio & Rouault, 2020). Importantly, HIV-1 reverse transcriptase (RT) is not an Fe-S protein; its polymerase and RNase H activities depend on divalent metal ions, particularly Mg^{2+} (Goldschmidt, 2006). Thus, current evidence does not establish an intrinsic Fe-S requirement for HIV-1 reverse transcription. Instead, Fe-S-dependent host proteins may influence other stages of the viral life cycle. One example is ATP-binding cassette subfamily E member 1 (ABCE1), an Fe-S protein containing two (4Fe-4S) clusters that functions in translation and ribosome recycling. ABCE1 associates with HIV-1 Gag at plasma-membrane assembly sites, and its dissociation from Gag is associated with subsequent virion maturation and production (Dooher et al., 2007; Klein et al., 2011). Although these findings link an Fe-S-containing host protein to HIV-1 assembly, the specific contribution of ABCE1 Fe-S clusters to HIV-1 assembly remains incompletely defined.

Fe-S biogenesis also supports innate antiviral defense through viperin (RSAD2), an interferon-stimulated radical SAM enzyme whose catalytic activity requires an Fe-S cluster. Viperin catalyzes the conversion of cytidine triphosphate (CTP) to the antiviral nucleotide analogue 3′-deoxy-3′,4′-didehydro-CTP (ddhCTP) through a SAM-dependent radical mechanism (Gizzi et al., 2018). CIAO1-dependent Fe-S cluster insertion is required for viperin maturation and antiviral activity (Upadhyay et al., 2017). In contrast, SAMHD1 is not an Fe-S protein; rather, it restricts HIV-1 primarily by regulating intracellular dNTP availability, thereby limiting substrates available for viral DNA synthesis (Zhang et al., 2014). Its relationship with iron metabolism is therefore indirect and occurs within the broader network governing cellular nucleotide metabolism.

Collectively, these findings indicate that the relevance of iron to HIV-1 extends beyond bulk iron availability to its regulated incorporation into Fe-S cofactors. Fe-S-dependent host proteins can influence both viral particle production and innate antiviral defense, although the contribution of altered Fe-S homeostasis to HIV-1 pathogenesis remains incompletely defined.

Immune system interaction and chronic inflammation

HIV-1 pathogenesis is characterized by progressive CD4+ T-cell depletion and chronic immune activation. The immune system's interaction with the virus initiates a profound inflammatory cascade. The presence of viral pathogen-associated molecular patterns (PAMPs) and the translocation of microbial products from a compromised gut barrier led to the continuous activation of monocytes and macrophages (Brenchley et al., 2006). Activated macrophages release pro-inflammatory cytokines, including IL-6, Interleukin-1β (IL-1β), and Tumor Necrosis Factor-alpha (TNF-α).

This cytokine storm has a direct, profound impact on systemic iron metabolism. IL-6 is the primary transcriptional activator of hepcidin, the key regulatory hormone of systemic iron homeostasis, synthesized primarily in the liver (Ganz, 2003). Recent clinical data from Western Kenya confirms this relationship, demonstrating that high viral loads and systemic inflammation are associated with a distinct triad of iron dysregulation characterized by elevated hepcidin and suppressed erythroferrone (Abonyo et al., 2025). This hormonal shift promotes iron sequestration within the reticuloendothelial system, contributing to reduced circulating iron availability and functional iron deficiency in infected individuals.

Iron metabolism and nutritional immunity

Systemic iron balance relies on homeostatic regulation due to the absence of a physiological iron excretion pathway. Humans control iron levels purely through absorption and cellular sequestration. Hepcidin functions by binding to ferroportin (FPN1), the sole known cellular iron exporter, which is highly expressed on enterocytes, hepatocytes, and reticuloendothelial macrophages. Upon binding, hepcidin induces the ubiquitination, internalization, and lysosomal degradation of ferroportin (Nemeth et al., 2004).

During HIV-1 infection, IL-6-driven upregulation of hepcidin restricts iron efflux from macrophages and reduces dietary iron absorption in the duodenum. Consequently, iron becomes sequestered within macrophages, leading to

reduced circulating serum iron and decreased iron availability for erythropoiesis in the bone marrow. This reduction in iron availability contributes to functional iron deficiency and the development of anemia of inflammation (AI) (Weiss & Goodnough, 2005).

While functional iron restriction represents an important host defense strategy against extracellular and blood-borne pathogens, its consequences in chronic intracellular infections such as HIV-1 are more complex. Hepcidin-mediated ferroportin downregulation promotes iron retention within macrophages, potentially altering the intracellular iron environment in cells that can harbor persistent HIV-1 infection. In addition, iron availability influences host cellular pathways that HIV-1 exploits for efficient replication. Under iron-restricted conditions, inhibition of deoxyhypusine hydroxylase (DOHH) impairs eIF5A hypusination and can reduce the synthesis of HIV-1 structural proteins such as Gag and Env.

Conversely, increased iron availability can restore DOHH activity and support processes required for viral protein synthesis and particle production (Park, 2006; Nekhai et al., 2013).

The pathophysiological relationship between HIV-1 infection and iron dysregulation is illustrated in Figure 1.

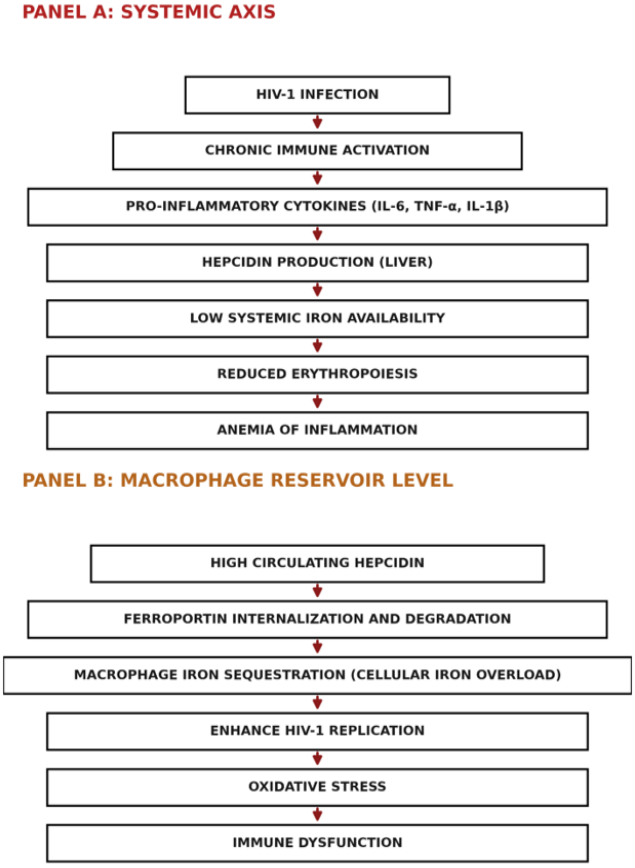


Figure 1: Pathophysiology of HIV-1-induced iron dysregulation.

Panel A (Systemic Axis): HIV-1 infection induces chronic immune activation, elevating pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) which stimulate hepcidin production in the liver. This results in low systemic iron availability, reduced erythropoiesis, and subsequent anemia of inflammation.

Panel B (Macrophage Reservoir Level): High circulating hepcidin triggers the internalization and degradation of ferroportin. This leads to macrophage iron sequestration, which enhances HIV-1 replication, increases oxidative stress, and ultimately contributes to immune dysfunction.

***Abbreviations*:** IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta.

Statistical analysis

All statistical analyses were done using simple descriptive analysis and SPSS software program (IBM SPSS v.25 Inc., Chicago Il, USA). Compiled data was analyzed using Chi square. Results were presented in frequency and percentage. P-values < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Adverse effect of excess iron on the host

While excess iron enhances pathogen replication, it simultaneously causes massive collateral damage on the host immune system. CD4+ T lymphocytes are highly susceptible to oxidative stress. Iron overload promotes the generation of hydroxyl radicals via Fenton chemistry:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-} \quad (1)$$

Where: Fe^{2+} = ferrous iron; H_2O_2 = hydrogen peroxide; Fe^{3+} = ferric iron; $OH^{\bullet}$ = hydroxyl radical, a highly reactive oxygen species; OH^{-} = hydroxide ion.

This leads to lipid peroxidation, protein denaturation, and DNA damage (Galaris & Pantopoulos, 2008; Kell, 2009). This oxidative environment enhances cellular toxicity and redox imbalance (Bresgen & Eckl, 2015). Consequently, oxidative damage contributes to immune cell dysfunction and apoptosis, accelerating CD4+ T-cell depletion in HIV-1 infection (Gordeuk et al., 2001).

Ferroptosis in HIV-1 pathogenesis

Beyond generalized oxidative injury, iron dysregulation may contribute to cellular damage through ferroptosis, a regulated form of cell death characterized by iron-dependent lipid peroxidation (Dixon et al., 2012; Stockwell, 2022). Ferroptosis occurs when the generation of oxidized membrane lipids exceeds the capacity of cellular antioxidant systems to neutralize them. A major protective mechanism involves glutathione peroxidase 4 (GPX4), which reduces lipid hydroperoxides and limits the propagation of membrane lipid oxidation (Yang et al., 2014). Consequently, disturbances in intracellular iron homeostasis, antioxidant defenses, and lipid metabolism can increase cellular susceptibility to ferroptotic injury.

Emerging evidence directly links ferroptosis to HIV-1-associated cellular pathology. In experimental studies, exposure of microglial cells to HIV-1 Tat induced several characteristic features of ferroptosis, including increased acyl-CoA synthetase long-chain family member 4 (ACSL4),

lipid peroxidation, and intracellular labile iron, together with reduced GPX4 expression (Kannan et al., 2023). Pharmacological inhibition with ferrostatin-1 or the iron chelator deferoxamine attenuated these ferroptosis-associated changes (Kannan et al., 2023). These findings were further supported by observations in HIV-1 transgenic animal models and human brain samples, suggesting that HIV-associated ferroptotic mechanisms may contribute to neuroinflammation (Kannan et al., 2023).

Importantly, ferroptotic lipid peroxidation may also amplify inflammatory signalling. HIV-1 Tat-induced ferroptosis in microglial cells was associated with increased expression and release of pro-inflammatory cytokines, including TNF-alpha, IL-6, and IL-1beta (Kannan et al., 2023). Inhibition of ferroptosis reduced these inflammatory responses, suggesting that ferroptosis may contribute to a self-perpetuating cycle involving iron dysregulation, oxidative lipid damage, cellular dysfunction, and inflammation (Kannan et al., 2023).

The relevance of ferroptosis to HIV-1 infection should, however, be interpreted cautiously. Current evidence is strongest in the context of HIV-associated neuroinflammation and microglial dysfunction, and the relative contribution of ferroptosis to systemic CD4+ T-cell depletion, macrophage dysfunction, viral persistence, and disease progression remains incompletely defined. Ferroptosis should therefore be regarded as an emerging mechanism of HIV-associated cellular injury rather than as an established explanation for all immune-cell loss during infection.

Macrophage dysfunction and opportunistic infection

While iron accumulates in macrophages due to the hepcidin mediated inhibition, this iron loading impairs the macrophage's primary defensive functions: phagocytosis and intracellular killing (Ward et al., 2002). Iron intoxication inhibits the production of nitric oxide and suppresses the oxidative burst required to destroy engulfed pathogens. This immune paralysis renders the host highly vulnerable to opportunistic infections, most notably *Mycobacterium tuberculosis* (TB) and Hepatitis C Virus (HCV), both of which also utilize host iron for their own replication (Lounis et al., 2001). Clinical studies consistently show that elevated serum ferritin correlates with poorer prognoses and shorter survival times in PLWH (Gordeuk et al., 2001).

Clinical implication: Iron supplementation versus chelation

Differentiating anemia of inflammation from iron deficiency

Administering iron to a patient with Anemia of Inflammation (AI) is generally ineffective because, although total body iron is adequate or increased, it is sequestered within macrophages and hepatocytes due to hepcidin-mediated ferroportin downregulation. Consequently, circulating iron availability for erythropoiesis is reduced despite systemic iron sufficiency. In this context, iron supplementation does not correct the underlying functional iron deficiency because continued iron loading can exceed the iron-binding capacity of transferrin and may contribute to increased non transferrin bound iron, promoting oxidative stress and potential tissue damage. By contrast, in iron deficiency anemia, iron stores are depleted, and supplementation restores hemoglobin synthesis and erythropoietic activity.

Routine iron supplementation in AI is not recommended because iron is typically sequestered in reticuloendothelial system despite adequate or increased total body iron. Iron therapy should be reserved for confirmed cases of true iron deficiency anemia, particularly when associated with ongoing iron loss such as chronic gastrointestinal bleeding, chronic hemorrhage, or parasitic infections (e.g., hookworm infestation).

To accurately distinguish iron deficiency anemia (IDA) from anemia of inflammation in people living with HIV-1 (PLWH), reliance on serum ferritin alone may be insufficient because ferritin is an acute-phase reactant. In HIV-1 infection, chronic inflammation can elevate serum ferritin independently of body iron stores, potentially masking coexisting absolute iron deficiency; therefore, ferritin should be interpreted cautiously in conjunction with inflammatory markers and other indices of iron status.

The soluble transferrin receptor (sTfR)/ferritin index can provide additional diagnostic information and is calculated as:

$$\text{sTfR–Ferritin Index} = \text{sTfR (mg/L)} / \log_{10}[\text{Ferritin (µg/L)}] \quad (2)$$

Because sTfR concentrations generally increase during cellular iron deprivation and are less directly affected by inflammation than ferritin, an elevated sTfR/ferritin index may help identify concomitant iron deficiency in patients with anemia of inflammation (Punnonen et al., 1997).

However, sTfR concentrations may also be influenced indirectly by inflammation through its effects on erythropoiesis. Values of the index <1 are more consistent with anemia of inflammation, whereas values >2 support concomitant iron deficiency, although assay-dependent variation and a diagnostic zone of uncertainty should be considered (Weiss et al., 2019).

Table 1: Comparison of Iron Biomarkers in Iron Deficiency Anemia, Anemia of Inflammation, and Coexisting Iron Deficiency and Inflammation

Biomarker/Parameter	Iron Deficiency Anemia (IDA)	Anemia of Inflammation (AI)	Mixed IDA + AI (Coexisting)
Serum Ferritin **(µg/L)**	Low (<30 **µg/L**)	Usually normal or elevated; often >100 µg/L	May be normal or elevated; due to inflammation making underlying iron deficiency difficult to detect.
Serum Hepcidin **(ng/mL)**	Low/suppressed	Elevated	Variable; may remain inappropriately elevated despite iron deficiency
Transferrin Saturation (TSAT, %)	<20%	<20%	<20%
Soluble Transferrin Receptor (sTfR, mg/L)	Elevated	Usually normal	Elevated
sTfR-Ferritin Index	Elevated	Usually normal	Elevated; may improve detection of coexisting IDA in inflammatory states
Primary Clinical Management	Targeted iron repletion	Optimize ART; resolve inflammation; assess iron status before iron therapy	Treat inflammation + careful iron repletion

Ferritin is an acute-phase reactant; normal or elevated ferritin does not exclude iron deficiency during inflammation. TSAT <20% indicates reduced iron availability but is not specific for IDA. Hepcidin and sTfR thresholds are assay-dependent. An sTfR-ferritin index >2 may support coexisting iron deficiency

Antiretroviral therapy drug interaction

The primary therapeutic strategy for HIV-1-associated anemia is effective initiation and optimization of antiretroviral therapy (ART). Suppression of HIV-1 replication can reduce chronic immune activation and inflammatory signaling, including interleukin-6 (IL-6)-mediated stimulation of hepatic hepcidin expression (Minchella et al., 2015; Obeagu et al., 2024). As inflammatory signaling and hepcidin activity decline, ferroportin-1 (FPN1)-mediated iron export from macrophages and other iron-recycling cells may increase, facilitating mobilization of sequestered iron into the circulation and improving iron availability for erythropoiesis in patients whose anemia is partly attributable to inflammation-mediated iron restriction (Minchella et al., 2015; Obeagu et al., 2024). However, because HIV-associated anemia is multifactorial, improvement in inflammation-associated iron sequestration does not necessarily correct concomitant absolute iron deficiency, which requires appropriate diagnostic assessment and, when indicated, iron replacement therapy.

An important pharmacokinetic consideration arises when iron supplementation is administered to patients receiving integrase strand transfer inhibitor (INSTI)-based ART. INSTIs such as dolutegravir, bictegravir, and raltegravir inhibit HIV-1 integrase through interactions involving the enzyme's essential divalent metal cofactors (Thierry et al., 2017; Zhao et al., 2022). These metal-binding properties also make INSTIs susceptible to pharmacokinetic interactions with orally administered polyvalent cations. Iron, calcium, magnesium, and aluminium can interact with INSTIs within the gastrointestinal tract, forming poorly absorbed complexes and thereby reducing drug absorption and systemic exposure (Scarsi et al., 2020; Zhao et al., 2022). The magnitude of this interaction varies according to the specific INSTI, cation, formulation, dosing conditions, and timing of administration.

This interaction is particularly relevant when oral iron preparations, such as ferrous sulfate or ferrous fumarate, or iron-containing multivitamins are prescribed for anemia. For dolutegravir specifically, oral iron or calcium supplements may be co-administered when taken with food; under fasting conditions, dolutegravir should be dosed at least 2 hours before or 6 hours after the supplement (ViiV Healthcare, 2024). Recent pharmacokinetic evidence for bictegravir demonstrated that simultaneous administration of ferrous fumarate under fasting conditions reduced bictegravir area under the plasma concentration-time curve extrapolated to infinity (AUC∞) by 63%, whereas administration with food substantially mitigated the interaction (Arora et al., 2026). Raltegravir is also highly susceptible to polyvalent-cation interactions. In a pharmacokinetic study of raltegravir 1200 mg once daily, concomitant administration of calcium carbonate reduced raltegravir AUC_{0-24} by 72%, Cmax by 74%, and C24 by 48% (Krishna et al., 2016).

Accordingly, management of INSTI-cation interactions should be individualized rather than based on a single separation interval for all INSTIs (Scarsi et al., 2020; Zhao et al., 2022). When iron therapy is indicated in a patient receiving INSTI-based ART, the specific INSTI, iron formulation, dosing conditions, and timing of administration should therefore be considered to minimize reductions in antiretroviral exposure. These considerations are clinically important because substantial reductions in INSTI exposure could compromise antiretroviral effectiveness. Consequently, management of HIV-associated anemia requires a balance between correcting iron deficiency and maintaining adequate antiretroviral drug exposure.

Iron chelators as host-directed therapy

Given that cellular iron availability supports several host processes required for HIV-1 replication, pharmacological iron restriction using iron chelators has been investigated as a potential host-directed antiviral strategy. Early experimental studies demonstrated that iron chelation can interfere with HIV-1 activation through redox-sensitive mechanisms, including suppression of NF-κB activation

(Sappey et al., 1995). Iron chelators may also inhibit iron-dependent cellular enzymes required for viral replication, including ribonucleotide reductase, thereby limiting processes necessary for DNA synthesis and viral replication (Boelaert et al., 1996). Subsequent studies provided more direct evidence that deferoxamine (DFO) and deferiprone (DFP) can inhibit HIV-1 replication in human peripheral blood lymphocytes and monocyte-derived macrophages (Georgiou et al., 2000).

More specifically, DFP was shown to inhibit the iron-dependent enzyme deoxyhypusine hydroxylase (DOHH), thereby interfering with the hypusination of eukaryotic initiation factor 5A (eIF5A), a host factor involved in HIV-1 gene expression and replication (Andrus et al., 1998; Hoque et al., 2009). Experimental evidence indicates that inhibition of DOHH prevents the formation of mature hypusyl-eIF5A and can suppress HIV-1 gene expression and replication (Hoque et al., 2009).

Unlike conventional direct-acting antiretroviral agents that primarily target viral proteins, host-directed strategies interfere with cellular factors exploited by HIV-1. This approach may provide a relatively higher barrier to the emergence of classical drug-resistance mutations because the targeted factors are encoded by the host rather than the viral genome. Nevertheless, host-directed therapies are not inherently resistance-proof, as viruses may potentially adapt through altered dependence on host factors, utilization of alternative cellular pathways, or changes in their interaction with targeted host factors under sustained selective pressure (Kumar et al., 2020).

The therapeutic potential of DFP has also been explored beyond cell-culture models. A proof-of-concept, double-blind, placebo-controlled, randomized exploratory trial in treatment-naïve individuals with HIV-1 investigated the antiretroviral effects of DFP and provided preliminary support for further evaluation of host-targeted approaches involving inhibition of the hypusine pathway (Saxena et al., 2016). However, these findings remain preliminary, and iron chelation has not been established as a component of standard HIV treatment.

Translation into routine clinical practice is further constrained by important safety concerns. Because iron is essential for erythropoiesis, immune-cell function, and numerous metabolic processes, excessive or prolonged systemic iron depletion may produce clinically significant toxicity. DFP carries a well-established risk of neutropenia and potentially fatal agranulocytosis, necessitating regular monitoring of the absolute neutrophil count (ANC) during treatment (U.S. Food and Drug Administration, 2025). DFO is also associated with clinically important ocular and auditory toxicities, particularly during prolonged treatment or excessive dosing, and may increase susceptibility to serious infections caused by organisms such as *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* (U.S. National Library of Medicine, 2026).

Collectively, these findings indicate that systemic iron chelation cannot presently be considered a clinically established antiviral strategy for HIV-1 management. Rather, iron chelation remains an experimental host-directed approach whose potential therapeutic benefits must be carefully balanced against the physiological requirement for iron and the risk of systemic toxicity. Future development may therefore depend on more selective targeting of iron-dependent host pathways, optimized compounds that retain antiviral activity while minimizing systemic iron depletion, or time-limited combination strategies designed to complement standard ART. Further preclinical and clinical research is required to establish the safety, efficacy, optimal dosing, and potential effects of such approaches on persistent HIV reservoirs and host immune function.

CONCLUSION

The relationship between HIV-1 and iron metabolism is a classic evolutionary arms race. Through the acute phase response and the hepcidin-ferroportin axis, the host attempts to withhold iron from the pathogen, resulting in the anemia of chronic disease. However, HIV-1 exploits dysregulated host iron homeostasis by benefiting from iron dependent cellular processes, including ribonucleotide reductase mediated deoxyribonucleotide synthesis, which supports efficient viral replication in macrophage-rich reservoirs. Consequently, empirical iron supplementation in the context of HIV-1 infection requires careful clinical consideration. Unregulated iron administration may exacerbate oxidative stress and impair macrophage immune function through iron-driven redox imbalance, while simultaneously supporting iron-dependent host enzymatic processes, including ribonucleotide reductase–mediated dNTP synthesis and DOHH (deoxyhypusine hydroxylase) dependent eIF5A activation, which can facilitate viral replication. Modern clinical management demands precision medicine: distinguishing true iron deficiency from inflammatory anemia, prioritizing ART to resolve inflammatory hepcidin blocks, and cautiously exploring iron chelation as a strategic adjunct to conquer viral latency.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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