Persistent Immune Activation and Chronic Inflammation: Unraveling Their Impact on Anemia in HIV Infection

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ABSTRACT
Persistent immune activation and chronic inflammation represent pivotal facets of Human Immunodeficiency Virus (HIV) infection, profoundly influencing disease progression and complications. This abstract synthesizes current knowledge to unravel the intricate interplay between persistent immune activation, chronic inflammation, and their consequential impact on the development and exacerbation of anemia among individuals living with HIV. Persistent immune activation and chronic inflammation are recognized hallmarks of HIV infection, contributing significantly to disease pathogenesis and complications. This paper aims to elucidate their intricate roles in perturbing erythropoiesis, leading to anemia, thus highlighting the pathophysiological mechanisms and clinical implications within the context of HIV. Anemia, emerging as a consequence of persistent immune activation and chronic inflammation in HIV, bears significant clinical implications. Its association with disease progression, treatment responses, and prognostic implications underscores its criticality in the comprehensive care of HIV-infected populations. Persistent immune activation and chronic inflammation intricately contribute to the pathogenesis of anemia in HIV infection. Understanding their multifaceted roles in disrupting erythropoiesis holds promise for developing targeted interventions and refining management strategies to alleviate anemia burden among individuals living with HIV.

Keywords: Immune Activation, Chronic Inflammation, Anemia, HIV

INTRODUCTION
Human Immunodeficiency Virus (HIV) infection is characterized not only by its direct impact on the immune system but also by persistent immune activation and chronic inflammation, which significantly contribute to disease progression and associated complications. Among these complications, anemia stands out as a prevalent hematologic manifestation that is increasingly recognized as intricately linked to the persistent immune activation and chronic inflammatory milieu in HIV-infected individuals [1-10]. Persistent immune activation and chronic inflammation, characteristic features of HIV infection, extend beyond the acute phase of the disease and persist throughout the course of infection, even in
individuals undergoing effective antiretroviral therapy (ART). These immune dysregulations contribute to a sustained pro-inflammatory state characterized by elevated levels of cytokines, immune cell activation, and ongoing immune system perturbations [11-20]. The impact of persistent immune activation and chronic inflammation on hematopoiesis, specifically erythropoiesis, has garnered significant attention in recent years. Disruption of the delicate balance in hematopoietic processes due to chronic inflammation and immune activation has been implicated in the pathogenesis of anemia observed in individuals living with HIV [21-25]. Anemia, marked by a decline in red blood cell production or hemoglobin levels, poses substantial clinical implications in HIV-infected populations.

Persistent Immune Activation and Chronic Inflammation in HIV

Persistent immune activation and chronic inflammation are hallmark features of Human Immunodeficiency Virus (HIV) infection that exert profound and lasting effects on the immune system, contributing significantly to disease progression and associated complications. Despite advancements in antiretroviral therapy (ART), these immune dysregulations persist and continue to impact HIV-infected individuals, influencing both viral pathogenesis and the development of various comorbidities, including hematologic complications such as anemia [33-35]. HIV infection triggers a cascade of immune responses characterized by sustained immune activation. This persistent immune activation involves the upregulation of immune cells, elevated levels of inflammatory cytokines (e.g., TNF-α, IL-6), and chronic immune cell stimulation, contributing to ongoing inflammation even in individuals receiving ART and achieving viral suppression [36-42]. The chronic inflammatory state induced by HIV involves a complex interplay between the virus, immune cells, and various tissues. Viral persistence, residual viral replication, and microbial translocation from the gut contribute to chronic immune activation and subsequent inflammatory responses. This sustained inflammation perpetuates tissue damage and contributes to systemic complications, including hematologic abnormalities [43-47]. Persistent immune activation and chronic inflammation disrupt the delicate balance of hematopoiesis, specifically affecting erythropoiesis—the process of red blood cell production. Elevated levels of pro-inflammatory cytokines interfere with the bone marrow microenvironment, impairing the differentiation and proliferation of erythroid progenitor cells, thereby compromising red blood cell production [48-51]. The dysregulation of erythropoiesis due to chronic inflammation and immune activation contributes significantly to the development of anemia in HIV-infected individuals. Reduced red blood cell production, shortened red blood cell survival, and impaired iron metabolism are among the mechanisms that link persistent immune activation and chronic inflammation to anemia in HIV [52-55]. Anemia, as a consequence of persistent immune activation and chronic inflammation, bears clinical implications in HIV care. Its association with accelerated disease progression, increased morbidity, and reduced quality of life underscores the significance of addressing...
immune dysregulation in managing hematologic complications in HIV-infected individuals.

Anemia Development Mechanisms

In the context of Human Immunodeficiency Virus (HIV) infection, the development of anemia involves intricate mechanisms influenced by persistent immune activation and chronic inflammation, contributing to hematologic complications in affected individuals [56-57]. Persistent immune activation and chronic inflammation in HIV interfere with bone marrow function, impacting erythropoiesis—the process of red blood cell production. Dysregulated cytokine signaling disrupts the bone marrow microenvironment, inhibiting the differentiation and maturation of erythroid progenitor cells and impairing their ability to produce red blood cells [58-60]. Elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), negatively impact erythroid progenitor cells, hindering their proliferation and differentiation. This suppression leads to a reduced number of functional erythroid precursors, ultimately affecting red blood cell production [61-63]. Chronic inflammation and persistent immune activation in HIV infection disrupt the erythropoietin-mediated signaling pathway. The altered balance of erythropoietin production and activity contributes to impaired erythropoiesis, diminishing the responsiveness of erythroid precursors to erythropoietin stimulation and further compromising red blood cell production [64-65]. Inflammatory cytokines impact iron metabolism by disrupting the homeostasis of iron-regulating hormones such as hepcidin. Dysregulated hepcidin levels lead to impaired iron absorption, sequestration of iron within macrophages, and reduced iron availability for erythropoiesis, contributing to the development of anemia [66]. Chronic inflammation and immune dysregulation in HIV infection may lead to increased red blood cell destruction due to various factors, including oxidative stress, autoimmune mechanisms, and alterations in red blood cell membrane integrity. Additionally, shortened red blood cell survival contributes to decreased overall red blood cell count, exacerbating anemia. HIV-infected individuals are prone to nutritional deficiencies (e.g., iron, vitamin B12, folate) that exacerbate anemia. These deficiencies, either due to malabsorption, increased utilization, or dietary insufficiency, further compromise erythropoiesis and worsen anemia in HIV-infected populations [68].

Clinical Implications

Anemia serves as a predictor of accelerated disease progression in HIV-infected individuals. Lower hemoglobin levels are associated with increased morbidity, including a higher risk of opportunistic infections, reduced tolerance to antiretroviral therapy (ART), and progression to AIDS-defining illnesses [69]. Anemia exacerabates the burden of HIV-related complications, contributing to increased hospitalization rates and poorer clinical outcomes. Individuals with anemia experience reduced quality of life due to symptoms such as fatigue, weakness, and decreased exercise tolerance, impacting daily activities and overall well-being. Anemia’s presence influences treatment responses, potentially affecting the efficacy of antiretroviral therapy. Individuals with anemia may exhibit delayed immune recovery, reduce virological suppression, and alter responses to ART, leading to challenges in achieving and maintaining optimal treatment outcomes [69]. Anemia, as a prognostic marker, aids in predicting disease severity and clinical outcomes in HIV-infected individuals. Lower hemoglobin levels or the presence of anemia are associated with increased mortality rates, serving as indicators of advanced disease stages and poorer prognoses [70]. Beyond clinical parameters, anemia significantly impacts
patients' quality of life, affecting physical functioning, productivity, and emotional well-being. Persistent fatigue, exertional dyspnea, and limitations in daily activities diminish patients' overall quality of life. Management of anemia in HIV poses challenges, including identifying and addressing underlying causes such as nutritional deficiencies, managing coexisting conditions, and balancing therapeutic interventions without compromising the effectiveness of ART. Anemia increases healthcare utilization and associated costs in HIV care due to frequent hospitalizations, increased need for medical interventions, and the management of complications arising from reduced red blood cell counts.

**Therapeutic Approaches**

In the context of Human Immunodeficiency Virus (HIV) infection, where anemia often arises due to persistent immune activation and chronic inflammation, several therapeutic approaches aim to mitigate the burden of anemia while managing the underlying HIV infection. Initiation or adjustment of ART regimens plays a crucial role in managing anemia in HIV-infected individuals. Switching to or modifying ART regimens less likely to exacerbate anemia, such as avoiding zidovudine (AZT) or other nucleoside reverse transcriptase inhibitors (NRTIs) associated with bone marrow suppression, is considered [70]. Addressing coexisting infections (e.g., mycobacterial, parasitic infections) and managing other comorbidities prevalent in HIV, which might contribute to anemia or exacerbate its effects, is essential. Treating concurrent conditions effectively may alleviate the burden of anemia. In select cases of anemia in HIV, especially those associated with inadequate erythropoiesis, Erythropoietin-Stimulating Agents (ESAs) may be considered to stimulate red blood cell production. However, their use requires careful evaluation due to potential risks and concerns regarding increased cardiovascular events [71]. Addressing nutritional deficiencies, including iron, vitamin B12, and folate, through dietary interventions or supplementation, is crucial. Correcting deficiencies can aid in improving erythropoiesis and mitigating anemia. Managing chronic inflammation using anti-inflammatory agents or therapies aimed at modulating the immune response is an area of exploration. However, caution is warranted in balancing the suppression of inflammation without compromising immune function crucial for controlling HIV. In severe cases of anemia or symptomatic patients, red blood cell transfusions may be necessary to rapidly improve hemoglobin levels and alleviate symptoms. Regular monitoring and consideration of transfusion thresholds are crucial to manage anemia without inducing iron overload.

**Implications for Health Policy Makers**

Health policy makers play a pivotal role in shaping the landscape of healthcare delivery, including the management of anemia in the context of Human Immunodeficiency Virus (HIV) infection. Addressing the implications of anemia driven by persistent immune activation...
and chronic inflammation in HIV involves several policy considerations:

**Guidelines and Recommendations:** Health policy makers can collaborate with healthcare experts to develop or update guidelines that emphasize comprehensive hematologic monitoring, including regular assessments of hemoglobin levels and related parameters, within HIV care protocols. These guidelines should integrate recommendations for managing anemia, considering its impact on treatment responses and patient outcomes.

**Resource Allocation and Accessibility:** Policymakers must allocate resources effectively to ensure access to diagnostic tools, laboratory tests, and treatment modalities necessary for managing anemia in HIV-infected individuals. Ensuring equitable access to a diverse range of antiretroviral medications with varying hematologic profiles is crucial in mitigating anemia-related complications.

**Education and Training Initiatives:** Advocating for educational programs targeting healthcare providers can raise awareness about the significance of anemia in HIV care. Policymakers can support initiatives aimed at enhancing providers' understanding of anemia monitoring, interpretation of hematologic parameters, and appropriate interventions within the context of HIV management.

**Research and Surveillance Funding:** Policymakers can allocate funding to support research programs aimed at elucidating the impact of anemia on treatment outcomes, disease progression, and overall health in HIV-infected populations. Longitudinal studies and surveillance programs can provide valuable insights into the relationship between anemia and HIV, guiding evidence-based policymaking.

**Integrated Care Models:** Policymakers can advocate for the implementation of integrated care models that incorporate hematologic assessments as an integral part of HIV care. Encouraging collaborative efforts between hematologists, infectious disease specialists, primary care providers, and other healthcare professionals ensures holistic care addressing both viral suppression and hematological health.

**Support for Innovation and Development:** Advocating for policies that incentivize research and development of novel therapies, diagnostic tools, and interventions targeting anemia in HIV is essential. Supporting innovation in this field can lead to improved treatment modalities and better outcomes for individuals living with HIV.

**Equitable Access to Care:** Policymakers play a critical role in advocating for equitable access to comprehensive HIV care, ensuring that marginalized or underserved populations have access to effective treatments addressing anemia and other hematologic complications associated with HIV.

**CONCLUSION**

In conclusion, the intricate relationship between persistent immune activation, chronic inflammation, and anemia in the context of Human Immunodeficiency Virus (HIV) infection underscores the necessity for comprehensive approaches to manage hematologic complications in affected individuals. The persistent immune activation and chronic inflammation characteristic of HIV contribute significantly to the development and exacerbation of anemia. These immune dysregulations disrupt erythropoiesis, impair red blood cell production, and contribute to hematologic abnormalities observed in HIV-infected populations. The impact of anemia on treatment outcomes, disease progression, and overall health in HIV-infected populations. Longitudinal studies and surveillance programs can provide valuable insights into the relationship between anemia and HIV, guiding evidence-based policymaking.

**Anemia:** Anemia, beyond being a hematologic abnormality, holds substantial clinical implications within HIV care. Its association with disease progression, treatment responses, and adverse clinical outcomes emphasizes the need for targeted interventions addressing immune dysregulation and hematologic complications. Health policymakers play a crucial role in shaping healthcare strategies to address anemia in HIV-infected individuals. Implementing guidelines emphasizing comprehensive hematologic monitoring, resource allocation for diagnostic tools and treatments, educational initiatives,
research funding, and advocacy for equitable access to care are essential policy considerations.

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