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REVIEW ARTICLE

IMMUNOLOGICAL CHALLENGES IN TREATING PATIENTS WITH HIV AND SICKLE CELL DISEASE: A NARRATIVE REVIEW

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Abstract

The simultaneous presence of HIV infection and sickle cell disease (SCD) poses considerable immunological and treatment difficulties, especially in areas where both conditions are very common. HIV leads to gradual immunodeficiency by depleting CD^{4+} T cells and causing chronic immune activation, whereas SCD is marked by ongoing inflammation, hemolysis, and weakened immune responses. These factors together result in a complicated immune environment characterized by increased inflammation, immune fatigue, and greater vulnerability to infections. This review examines the shared immune dysregulation in HIV and SCD, emphasizing the contributions of monocyte activation, T cell impairment, and endothelial damage in promoting disease complications. We examine how persistent inflammation and immune response worsen vaso-occlusive crises, coagulopathy, and blood-related issues, making clinical management more complex. Moreover, the effects of standard therapies including antiretroviral treatment and SCD-specific therapies like hydroxyurea and transfusions on immune balance are evaluated, emphasizing possible drug interactions and immune effects.

Keywords: Chronic inflammation, HIV, immune dysregulation, immunologic synergy, sickle cell co-infection.

INTRODUCTION

Sickle cell disease (SCD) and HIV infection are both chronic ailments that separately create considerable health challenges, particularly in sub-Saharan Africa and other areas with limited resources. SCD is an inherited hemoglobin disorder marked by ongoing hemolysis, vaso-occlusive events, and gradual organ deterioration. At the same time, HIV infection causes a slow reduction in CD^{4+} T lymphocytes, leading to immune deficiency and a heightened risk of opportunistic infections. The coinciding epidemiology of these illnesses has led to an increasing number of patients suffering from both ailments, creating intricate clinical and immunological issues that require dedicated research and specific interventions[1,2]. HIV and SCD both involve ongoing immune activation and systemic inflammation, though they are caused by different mechanisms. In SCD, hemolysis and ischemia reperfusion injury trigger a pro-inflammatory condition, activating innate immune cells like monocytes and neutrophils. This ongoing inflammatory environment leads to endothelial impairment, heightened coagulation, and tissue harm. In contrast, HIV infection leads to immune dysregulation mainly due to the virus-induced reduction of CD^{4+} T cells and ongoing activation of the immune system from microbial translocation and viral replication. This ongoing immune activation speeds up immune aging and fatigue, making immune recovery more difficult even with antiretroviral therapy (ART)[3-5].

The simultaneous presence of HIV and SCD raises distinct immunopathological issues. Does the persistent inflammation observed in SCD intensify immune activation linked to HIV, or do the immunosuppressive properties of HIV reduce the inflammatory response of SCD? These interactions carry clinical significance for the intensity of vaso-occlusive crises, likelihood of infections, hematologic issues, and treatment response. Grasping the immunological interactions between these diseases is vital for creating effective management strategies that tackle both conditions without worsening either[6-8]. Monocytes and macrophages are crucial contributors to the immunopathology of HIV and SCD. In SCD, the activation of monocytes leads to endothelial damage and plays a role in coagulopathy,

whereas in HIV infection, monocytes act as reservoirs for viral persistence and are key players in systemic inflammation. Imbalances in monocyte subsets and the cytokines they produce can affect disease advancement and the likelihood of complications in patients with co-infections. Moreover, the adaptive immune system, featuring T cell exhaustion and weakened vaccine responses, poses difficulties for infection management and vaccination approaches in this at-risk population[9,10]. Managing HIV-SCD co-infection with therapeutic approaches is challenging due to possible drug interactions, shared toxicities, and the immuno-modulatory effects of therapies. For instance, hydroxyurea, a key component in SCD treatment, has immunosuppressive effects that may impact HIV disease progression or ART effectiveness. On the other hand, some antiretroviral medications might worsen hematologic toxicities prevalent in SCD, including anemia and neutropenia. Additionally, chronic transfusions frequently utilized in SCD heighten the risk of alloimmunization and iron buildup, potentially further disturbing immune balance in patients with HIV[11,12].

This review aims to critically examine the immunological challenges and interactions arising from the coexistence of HIV infection and sickle cell disease (SCD), focusing on immune dysregulation, inflam-matory pathways, and the implications for clinical management.

Immune dysregulation in sickle cell disease

Sickle cell disease (SCD) is primarily a hemoglobinopathy marked by ongoing hemolysis and frequent vaso-occlusive episodes, yet its immune-related effects are progressively acknowledged as crucial to its pathophysiology. The ongoing breakdown of sickled red blood cells causes the release of free hemoglobin and heme into the bloodstream, functioning as strong damage-associated molecular patterns (DAMPs). These DAMPs stimulate innate immune cells, especially monocytes and neutrophils, leading to a persistent systemic inflammation that results in vascular harm and organ destruction[13,14]. Monocytes in SCD patients frequently display an activated phenotype, characterized by increased expression of adhesion molecules (like CD11b and CD62L) and elevated secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β). This hyperactivation encourages the activation and dysfunction of endothelial cells, promoting the attachment of sickled erythrocytes and leukocytes to the vascular endothelium a crucial stage in the progression of vaso-occlusive crises. Additionally, neutrophils generate neutrophil extracellular traps (NETs), which worsen inflammation and may encourage thrombosis, intensifying vascular issues[15,16]. Adaptive immunity is likewise compromised in SCD. Functional hyposplenism, often resulting from multiple splenic infarcts, reduces the body's ability to eliminate encapsulated bacteria and handle antigens efficiently. This condition of weakened immunity leads to heightened vulnerability to infections and less effective responses to vaccines. T lymphocytes in patients with SCD might show indications of exhaustion and modified cytokine production patterns, along with altered ratios of CD^{4+} and CD^{8+} T cells. Moreover, persistent inflammation in SCD promotes the growth of regulatory T cells (Tregs), which may further suppress effective immune responses, potentially raising the risk of infections[17,18]. The impaired immune system in SCD also influences coagulation pathways. Activated monocytes show elevated tissue factor levels, an essential trigger of the extrinsic coagulation pathway, fostering a prothrombotic condition. Increased levels of circulating microparticles from platelets and erythrocytes exacerbate vascular inflammation and activate coagulation, heightening the risk of thrombo-embolic incidents. The connection between inflamm-ation and coagulation is a defining feature of SCD pathophysiology and poses a notable therapeutic difficulty[19,20]. Additionally, persistent inflammation in SCD affects bone marrow activity. Inflammatory cytokines interfere with hematopoiesis, leading to anemia in addition to hemolysis and hindering leukocyte and platelet formation. This impairment of marrow function can complicate treatment plans, particularly when evaluating the use of immunosuppressive therapies or procedures for bone marrow transplantation (Table 1)[21].

Immune dysregulation in HIV infection

Human immunodeficiency virus (HIV) infection is characterized by profound immune system disruption, primarily driven by the virus's predilection for CD^{4+} T lymphocytes. The progressive depletion of these critical immune cells leads to impaired cellular immunity and heightened susceptibility to opportu-nistic infections and malignancies.

Table 1: Immune dysregulation in sickle cell disease.

Immune Component	Dysregulation	Clinical Consequences
Neutrophils	Activated phenotype, increased adhesion molecules	Vaso-occlusion, endothelial injury
Monocytes/Macrophages	Elevated pro-inflammatory cytokine production (TNF-α, IL-1β)	Chronic inflammation, endothelial dysfunction
T Cells	Skewed Th1/Th17 responses, impaired regulatory T cell function	Exaggerated inflammation, reduced immune regulation
Cytokines	Increased IL-6, IL-8, TNF-α	Systemic inflammation, coagulopathy
Complement System	Activation of alternative pathway	Vascular injury, hemolysis exacerbation
Endothelial Cells	Activation and adhesion molecule expression (VCAM-1, ICAM-1)	Promotes leukocyte adhesion, vaso-occlusion

However, beyond CD^{4+} T cell loss, HIV infection induces complex and chronic immune activation and dysregulation that persist even in the era of effective antiretroviral therapy (ART)[22-24]. The hallmark of untreated HIV is the gradual depletion of CD^{4+} T cells both in peripheral blood and within lymphoid tissues, particularly the gut-associated lymphoid tissue (GALT). Early in infection, viral replication causes massive CD^{4+} T cell loss in the gut, compromising the mucosal barrier and facilitating microbial translocation. This translocation of bacterial products such as lipo-polysaccharide (LPS) into systemic circulation is a key driver of persistent immune activation and infla-mmation, which fuel further immune cell dysfunction and tissue damage[25-27].

Chronic immune activation in HIV involves multiple cell types. Monocytes and macrophages become activated and secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), contributing to systemic inflammation. Elevated levels of soluble CD14 (sCD14) and soluble CD163 (sCD163), markers of monocyte/macrophage activation, correlate with disease progression and non-AIDS comorbidities including cardiovascular disease. Persistent activation also drives T cell exhaustion, characterized by upregulation of inhibitory receptors (e.g., PD-1, CTLA-4), reduced proliferative capacity, and impaired cytokine production, which compromise the adaptive immune response[28-31]. HIV also impairs the generation of robust vaccine responses, partly due to B cell dysfunction and altered germinal center architecture. The virus's impact on lymphoid tissue and chronic immune dysregulation hampers long term immuno-logic memory, leaving patients vulnerable to infections despite immunization (Table 1)[32,33].

Immunological intersection: Synergistic or strained?

The coexistence of HIV infection and sickle cell disease (SCD) creates a unique and complex immunological environment where the interplay between chronic inflammation, immune activation, and immunosuppression can be both synergistic and strained. Understanding this intersection is critical because it shapes disease progression, clinical outcomes, and therapeutic strategies in co-affected individuals[32,33]. Both HIV and SCD independently drive persistent immune activation but through differing mechanisms. In SCD, hemolysis-induced release of damage-associated molecular patterns (DAMPs) perpetuates monocyte and neutrophil activation, resulting in endothelial injury and vaso-occlusion. In contrast, HIV infection primarily causes CD^{4+} T cell depletion and microbial translocation-induced systemic inflammation. When these two processes converge, they may amplify systemic immune activation beyond levels seen in either disease alone. Elevated circulating pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β have been documented in both conditions and may synergize to exacerbate vascular inflammation, promote coagulopathy, and increase the frequency and severity of vaso-occlusive crises[36,37].

However, the immunosuppressive effects of HIV may also impose constraints on the hyperactive immune state of SCD. Progressive loss of CD^{4+} T cells and immune exhaustion can blunt certain inflammatory responses, potentially mitigating some complications of SCD but at the expense of increasing vulnerability to infections. This immunological strain reflects a delicate balance where immune hyperactivation and immune deficiency coexist, complicating both diagnosis and treatment. For example, impaired adaptive immunity due to HIV may reduce effective clearance of damaged erythrocytes and pathogens, worsening anemia and infection risk common in SCD patients[38-40]. Monocytes and macrophages play a central role at this intersection. In HIV-SCD co-infection, monocyte activation markers such as soluble CD14 (sCD14) and soluble CD163 (sCD163) are often elevated, indicating heightened innate immune activation. These activated monocytes contribute to endothelial dysfunction and coagulopathy by expressing tissue factor and releasing pro-inflammatory cytokines, which further potentiate thrombotic risks. Moreover, monocytes serve as reservoirs for HIV, sustaining viral persistence even in the context of ART, which may perpetuate inflammation and immune dysregulation in SCD patients[41-43]. The compounded immune dysfunction also affects vaccine responsiveness and infection susceptibility. Both diseases impair the generation and maintenance of effective adaptive immune responses, which may necessitate modified vaccination schedules and heightened infection prophylaxis. Clinically, this intersection demands a nuanced approach to managing inflammatory complications, opportunistic infections, and hematologic abnormalities in co-infected individuals (Table 1)[44,45].

Therapeutic challenges in co-treatment

Managing patients co-infected with HIV and sickle cell disease (SCD) presents numerous therapeutic challenges stemming from the complex interplay of immune dysregulation, overlapping drug toxicities, and potential pharmacological interactions. Effective treatment requires careful balancing of antiretroviral therapy (ART) to control HIV replication with SCD-specific interventions aimed at reducing hemolysis, inflammation, and vaso-occlusive complications[46]. One major challenge is the potential for drug–drug interactions between ART and SCD treatments such as hydroxyurea, chronic transfusions, and supportive care medications. Hydroxyurea, a disease-modifying agent that reduces sickling and inflammation by increasing fetal hemoglobin (HbF), also exhibits myelo-suppressive properties. This may exacerbate HIV-associated cytopenias or interfere with immune recovery, particularly in patients with advanced immunosuppression. Conversely, certain ART drugs, especially protease inhibitors and some nucleoside reverse transcriptase inhibitors, have hematologic toxicities including anemia, neutropenia, and thrombocytopenia, which can compound SCD-related marrow stress[47].

Chronic blood transfusions, often used to prevent or treat severe complications of SCD, carry risks that are amplified in the context of HIV. Transfusions increase

the potential for alloimmunization, iron overload, and transfusion transmitted infections, complicating immune management and long-term care. Iron overload may worsen oxidative stress and inflammation, further exacerbating endothelial dysfunction. Monitoring and managing iron burden while maintaining effective viral suppression is thus a critical component of co-treatment[48]. Immunizations and infection prophylaxis constitute another therapeutic consideration. Both HIV and SCD impair immune competence, reducing vaccine efficacy and increasing susceptibility to bacterial infections such as Streptococcus pneumoniae and Haemophilus influenzae[49]. Vaccination schedules may require modification to optimize protection, and prophylactic antibiotics need careful adjustment to avoid resistance and toxicity, especially in immunocompromised hosts[50].

Adherence to complex treatment regimens is often challenging for co-infected patients, compounded by socioeconomic factors, pill burden, and side effects. Multidisciplinary care models and patient-centered approaches are essential to improve compliance and outcomes. Additionally, access to comprehensive care may be limited in regions where HIV and SCD are prevalent, highlighting disparities in healthcare infrastructure and the need for resource-appropriate interventions[51]. Emerging therapies, including novel immunomodulators and gene therapies for SCD, hold promise but their safety and efficacy in HIV-positive patients remain to be fully evaluated. Bone marrow transplantation, a potential cure for SCD, is complicated by HIV-associated immunosuppression and risks of graft-versus-host disease. Nonetheless, recent case reports suggest feasibility under careful protocols, underscoring the importance of ongoing research into integrated therapeutic approaches[50].

Opportunities for immunologic synergy

Despite the considerable challenges posed by the coexistence of HIV and sickle cell disease (SCD), there are emerging opportunities to harness immunologic synergy that could improve outcomes for co-infected patients. By understanding shared immune pathways and leveraging therapies that modulate inflammation and immune activation, clinicians may optimize disease control and reduce complications[52]. One promising area is the use of hydroxyurea, the mainstay of SCD management, which has demonstrated immunomodulatory effects beyond its role in increasing fetal hemoglobin. Hydroxyurea reduces leukocyte counts and decreases pro-inflammatory cytokine production, thereby attenuating chronic inflammation and endothelial activation. Interestingly, some studies suggest that hydroxyurea may have beneficial effects in HIV by limiting viral replication and immune activation, potentially enhancing antiretroviral therapy (ART) efficacy. This dual action could be exploited to mitigate immune activation common to both diseases[52].

Antiretroviral therapy itself offers opportunities for synergy by reducing HIV viral load and partially restoring immune function. Effective viral suppression diminishes systemic inflammation and microbial translocation, which could theoretically alleviate some inflammatory stimuli that exacerbate SCD complications. Early initiation and strict adherence to ART in co-infected patients may therefore not only control HIV but also modulate the inflammatory milieu associated with SCD[49]. Immunomodulatory agents targeting key inflammatory pathways common to both diseases are another area of active investigation. Drugs that inhibit cytokines such as TNF-α, IL-6, or the inflammasome may reduce chronic inflammation, endothelial dysfunction, and coagulopathy. For example, blockade of IL-1β with agents like anakinra could potentially decrease vaso-occlusive crises and immune activation, though clinical trials are needed to assess safety and efficacy in co-infected populations[50].

Vaccination strategies also offer synergy potential. Optimizing vaccine responses through adjuvants or modified immunization schedules tailored to immune status can protect against common infections that disproportionately affect patients with HIV and SCD. Enhanced infection control reduces inflammatory triggers and hospitalizations, indirectly benefiting immune homeostasis and quality of life[51]. Advances in gene therapy and hematopoietic stem cell transplantation may offer curative potential for SCD with concomitant HIV infection. Innovative conditioning regimens and viral reservoir-targeting strategies are being explored to safely eradicate HIV and correct the sickle cell mutation simultaneously. Such integrated approaches, though still experimental, highlight the possibility of achieving durable remission of both diseases through immunologic synergy.

Future directions

The intersection of HIV infection and sickle cell disease (SCD) presents a compelling frontier for research aimed at unraveling complex immune interactions and improving clinical outcomes. Future studies must focus on elucidating the molecular and cellular mechanisms underlying immune dysregulation in co-infected patients to identify precise therapeutic targets.One promising direction is the integration of high-throughput “omics” technologies such as genomics, transcriptomics, proteomics, and metabolomics to map the immune landscape in HIV-SCD co-infection. These approaches can uncover novel biomarkers of immune activation, inflammation, and tissue damage, enabling personalized medicine strategies that tailor treatments based on individual immune profiles. Longitudinal cohort studies are essential to understand the natural history of immune dysfunction and clinical progression in co-infected patients under contemporary antiretroviral therapy (ART) and SCD management. Such studies should evaluate the impact of ART timing, adherence, and regimen composition on immune recovery and inflammatory complications specific to SCD. Therapeutic innovation remains a critical priority.

Gene editing technologies like CRISPR/Cas9 hold potential to correct the sickle cell mutation and confer resistance to HIV by targeting viral entry receptors such as CCR5. Combining these approaches may ultimately achieve durable remission or cure for both diseases but require rigorous preclinical and clinical

validation. Improved vaccine strategies tailored for co-infected patients represents another vital area. Research into adjuvants or dosing schedules that enhance immunogenicity without exacerbating immune activation could protect against infections that worsen disease outcomes. Addressing health disparities and improving healthcare access for populations disproportionately affected by HIV and SCD, especially in resource-limited settings, is paramount. Strengthening multi-disciplinary care models that integrate hematology, infectious disease, and immunology expertise will be crucial to translating scientific advances into meaningful patient benefits.

CONCLUSIONS

The simultaneous presence of HIV infection and SCD creates a distinct and complex immunological challenge characterized by interrelated mechanisms of persistent inflammation, immune activation, and immunosuppression. This intricate interaction affects disease advancement, vulnerability to infections, and treatment results, highlighting the necessity for comprehensive and detailed clinical management. In spite of the difficulties presented by drug interactions, blood-related issues, and immune system irregularities, new findings show encouraging possibilities for therapeutic synergy via focused immunomodulation and enhanced antiretroviral treatment. Progress in comprehending the common immunopathology of HIV and SCD has emphasized critical cellular components like monocytes and T lymphocytes, whose dysfunction contributes significantly to the disease burden.

Leveraging these insights via innovative treatmentssuch as hydroxyurea, cytokine blockers, and gene editing offers promise to enhance immune balance and clinical results in co-infected patients. Nonetheless, considerable gaps still exist in our understanding of the long term impacts of combined therapies and the most effective approaches to reduce negative interactions

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey. **Okafor CJ:** editing, critical review. Final manuscript is checked and approved by both authors.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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